

**The Arkadi M. Rywlin
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- Case 2. Plasmablastic lymphoma of the oral cavity
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Adsay Case 1

CASE HISTORY: 48-year old female with a remote history of pancreatitis presented with abdominal pain. CT-scan revealed a 6 cm cyst in the tail of the pancreas. Intraoperative examination revealed a multilocular cystic lesion with a thick wall and purulent contents. Two frozen sections were submitted from the cyst wall and both were diagnosed as "pseudocyst". Despite that, the surgeon decided to resect the lesion because of the multilocular nature of the cysts. First slide shows a segment of the wall from the main cyst.

MICROSCOPIC FINDINGS: This section is taken from the papillary component of this cystic tumor. The lining epithelium of both the cystic component and the papillae display significant cytologic atypia and disorganization. The cells are cuboidal to columnar. While some cells are very bland, in some nuclei are markedly pleomorphic and hyperchromatic with clumped chromatin, and nuclear contours are irregular. Some cells have prominent nucleoli. Mitoses are easily identified. Necrosis and acute inflammation of the epithelium is evident. In some sections, the stromal tissue shows a cellular spindle cell proliferation. These stromal spindle cells are monotonous, have a wavy appearance, and occasionally show a parallel arrangement, which closely resembles ovarian stroma. No invasive carcinoma is identified.

DIAGNOSIS: MUCINOUS CYSTADENOCARCINOMA OF THE PANCREAS

DISCUSSION: Mucinous cystic neoplasms (MCNs) are seen most frequently in perimenopausal females (in their 5-6th decade, mean age=50) and patients usually present with abdominal pain or a pancreatic mass. The tumor is most often located in the tail of the pancreas, forming multilocular cysts.

Macroscopically, these tumors exhibit large cystic spaces ranging from 1 to several centimeters. Unless there is fistula formation they do not communicate with the ductal system. Typically, the cyst wall is thick. The inner lining may show velvety papillations and appear trabeculated and thickened. The cyst contents are often mucoid, but a more watery consistency may also be noted. Solid areas within the cyst should be sampled extensively, as they may harbor an invasive component.

Microscopically, the cysts are lined by tall, columnar, mucin-producing epithelium, which may exhibit gastric foveolar-type intracellular mucin or intestinal-type features with goblet cells. Scattered neuroendocrine cells can be documented immunohistochemically by neuroendocrine markers such as chromogranin and synaptophysin. Paneth cells may also be detected.

Ovarian-type stroma is characteristic and pathognomonic for MCNs. It has become an almost requirement for the diagnosis of MCNs. This stroma resemble ovarian stroma not only morphologically, but also immunophenotypically by expressing the same profile as ovarian stroma including muscular differentiation (actin, desmin positive), hormone receptors (ER and PR positive) and others (bcl2, CD99 and others). Luteal type cells may also be present. The presence of ovarian stroma, along with the occurrence of this tumor presominantly in perimenopausal females raises the suspicion of hormone-related pathogenesis in these tumors. Ovarian type stroma is also present in rare males with MCNs.

Mucinous cystic neoplasms can show a wide range of cytologic and architectural atypia: Some are histologically bland, with uniform, basally oriented nuclei and minimal architectural atypia, while others exhibit prominent papillary proliferations that form intraluminal polypoid masses with cribriform architecture and substantial cytologic atypia. The epithelial atypia may be multifocal, and there is often an abrupt transition between histologically bland epithelium and epithelium with severe atypia. Numerous sections may be required to properly evaluate these neoplasms. This may explain why the studies from the Armed Forces Institute of Pathology (AFIP), a referral center where the diagnosis is generally based on a few selected slides submitted for consultation, have failed to demonstrate that dysplasia and even the presence of an invasive cancer are prognostically relevant. For that reason, the authors from the AFIP regard all MCNs, regardless of their grade, as "low grade malignant neoplasms", i.e. cystadenocarcinoma. However, more recently, a number of studies from other authors who performed more complete examination and extensive sampling of the neoplasms concluded that grade does accurately predict the outcome. It is also our experience that patients with completely resected mucinous cystic neoplasms without atypia (mucinous cystadenomas) are almost always cured. These tend to be small as well (<3 cm). Mucinous cystic neoplasms with moderate atypia are classified as mucinous cystic neoplasms with moderate dysplasia, while those with significant architectural and cytologic atypia are classified as mucinous cystic neoplasm with carcinoma in situ. Patients with these latter two grades of non-invasive mucinous cystic neoplasms are also almost always cured if their tumors are surgically resected.

If an invasive carcinoma is present, the neoplasm should be classified as a mucinous cystadenocarcinoma. The invasive carcinomas that arise in association with mucinous cystic neoplasms are usually tubular/ductal type. These mucinous cystic neoplasms with an invasive carcinoma usually pursue a more indolent course than ordinary infiltrating ductal adenocarcinoma. It is difficult to determine whether this implies that the invasive

carcinomas arising from MCNs are biologically different (although they may look morphologically identical to ductal adenocarcinoma) or whether MCN allows for earlier diagnosis of invasive carcinoma. The same concept is also true for intraductal papillary mucinous neoplasms (see above).

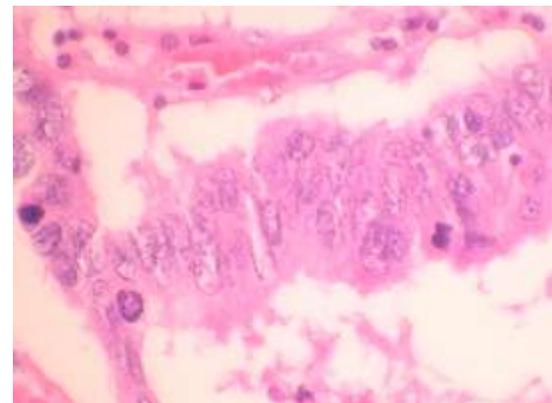
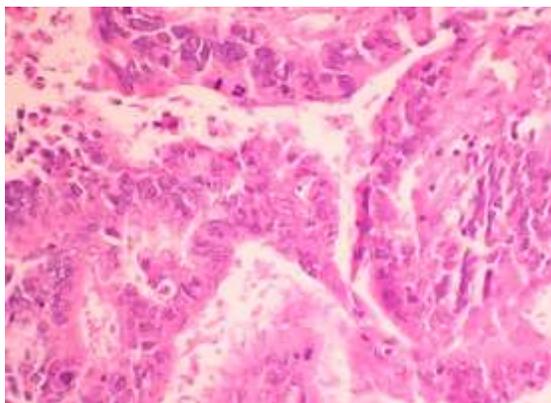
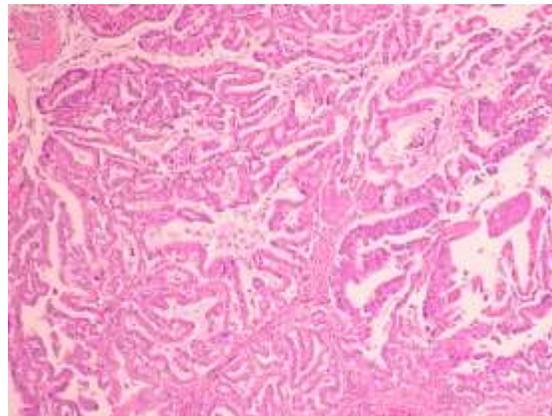
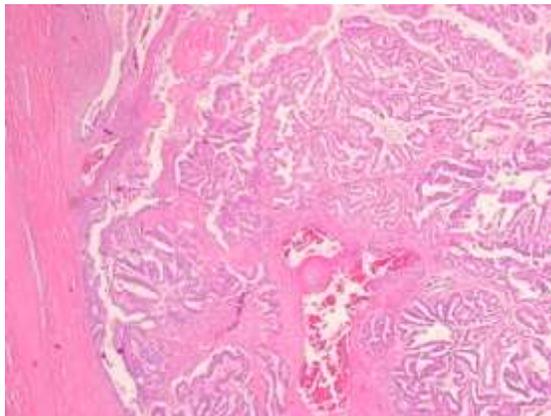
In addition to its association with invasive tubular adenocarcinomas, some MCNs may be associated with undifferentiated carcinoma with osteoclast-like giant cells, or high-grade sarcoma. Colloid carcinoma, which is the predominant invasive carcinoma in IPMNs does not appear to occur in MCNs if the latter is defined by the presence of ovarian stroma.

One of the important differential diagnosis of MCNs is with pancreatic pseudocyst. It is not uncommon for the epithelial lining of a mucinous cystic tumor to become inflamed and denuded. Thus, a small biopsy of an apparently unilocular or oligolocular cyst may show only a fibrous capsule with inflammation while other areas show typical features of mucinous cystic neoplasm.

MCNs also ought to be distinguished from other cyst-forming, pre-invasive ductal neoplasia in the pancreas, namely intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms. While MCNs are seen predominantly in perimenopausal females (mean age, 48) and in the tail of the organ, IPMNs are seen in patients two decades older (mean age, 68) and predominantly in the head. Communication with the ductal system, and thus, mucin extrusion from ampulla of Vater are characteristic features of IPMNs. In contrast, MCNs form thick-walled multilocular cystic mass that do not visibly communicate with the ducts.

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Adsay Case 2

CASE HISTORY: 35-year old female was found to have a 5 cm partially cystic and partially solid mass in the head of the pancreas.

MICROSCOPIC FINDINGS: There is sheet-like growth pattern without any intervening desmoplastic stroma. The degeneration (and cleavage) of cells located away from the fibrovascular stroma is associated with the typical pseudopapillary and rosette-like formations. The cells are uniform, round and evenly spaced. Immunohistochemical stains showed diffuse and strong nuclear labeling of the cells for beta-catenin.

Diagnosis: SOLID-PSEUDOPAPILLARY TUMOR OF PANCREAS

Discussion:

Solid-pseudopapillary tumor (SPT) is a tumor of indeterminate origin, which is reflected in the various descriptive names used for this tumor including "solid and cystic", "cystic and papillary", "papillary-cystic", and "solid and papillary epithelial neoplasm". Interesting enough, this tumor is neither cystic (cystic change is a degenerative phenomenon) nor papillary (no true papilla; though *pseudopapilla* is characteristic) nor a conventional epithelial neoplasm (keratin is sometimes negative or focal). Dr. Virginia Kneeland Frantz is credited to be the first to recognize this lesion as a distinctive neoplasm. In the first AFIP pancreas fascicle published in 1959, she recorded two examples of this lesion as "papillary tumor, benign or malignant?" and included them under the category of cystadenoma.

Essentially, SPTs are solid tumors which often undergo cystic degeneration. Solid areas grossly appear brown-hemorrhagic. They may appear deceptively well circumscribed; however, histologically they often prove to be infiltrative, sending projections to the normal pancreatic tissue, often without any intervening stroma (usually, no capsule is seen).

Microscopically, they are characterized by sheet-like growth pattern without any desmoplastic (scirrhous) tissue. In many cases, the cells are round and uniform and may form nested appearance closely mimicking endocrine neoplasia. In most cases, however, if searched carefully, the typical areas of pseudopapillary formation can be identified. These pseudopapillae are secondary to the degeneration of cells located away from the fibrovascular stroma. Often, there are clusters of foamy macrophagic-appearing cells in these degenerative areas; this finding is quite characteristic for this tumor type. In some cases, pseudopapillary pattern associated with fibrillary appearance of the stroma imparts the tumor an "ependymoma-like" morphology. Although in most cases the nuclei are round and uniform, in some, more elongated cells with nuclear grooves can be predominant. When present, eosinophilic intracytoplasmic globules are also quite characteristic. Some cases may have vacuolar degeneration in the cytoplasm.

Although deceptively round and demarcated on macroscopic examination, many SPTs do show tongue like projections into the adjacent pancreas, sometimes with no intervening stroma. For this reason, one often finds islets, ducts and acinar units, individually or in clusters, within the boundaries of the main lesion. In fact, entrapped pancreatic tissue may be found even in the inner aspects of the lesion, blending imperceptibly with the neoplastic cells. Conversely, tumor cell clusters in the pancreas away from the lesion may mimic islets.

The cystic degeneration in SPT may be so extensive that it may present like a pseudocyst. On the other end of the spectrum, some cases are markedly sclerotic. Calcifications may be prominent.

Immunophenotype of this tumor is most puzzling in regards to its possible origin and differentiation; however, it is very helpful in terms of achieving the correct diagnosis. Despite its epithelioid morphology, keratin immunolabeling is lacking in some SPTs, and is focal in some others. In contrast, vimentin is uniformly and diffusely present. CD56 is also commonly positive. In our experience, chromogranin is *not* expressed; a tumor with diffuse chromogranin expression should be classified as a pancreatic endocrine neoplasm. Recently, CD10 and APC/ β -catenin expression were also found to be consistent in SPTs. Another marker that is uniformly present is progesterone receptors. This is of interest, especially considering that these patients are, almost exclusively, young females (mean age 30; male to female ratio: 1-9).

The main differential diagnosis of SPT is with the other stroma-poor (non-scirrhous) cellular neoplasia; i.e pancreatic endocrine neoplasia, acinar cell carcinoma, pancreatoblastoma, metastatic tumors and the small blue cell tumors. In cases with a sheet-like growth pattern and those that lack the characteristic pseudopapillae, grooves, hyaline globules or clusters of macrophages, the following clues may help in the differential. Acinar cell carcinomas often have a distinct basophilia and the nucleoli are prominent. Pancreatoblastomas often show foci of acinar or ductal differentiation, and more importantly, if present,

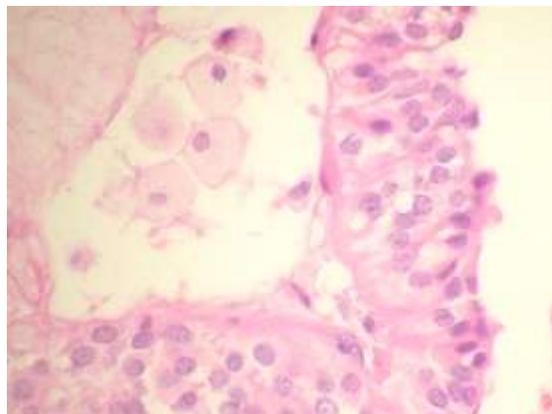
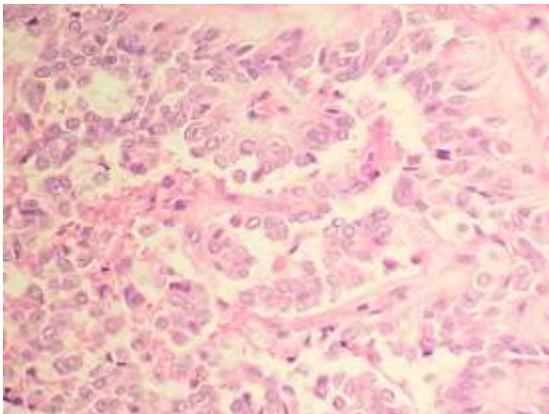
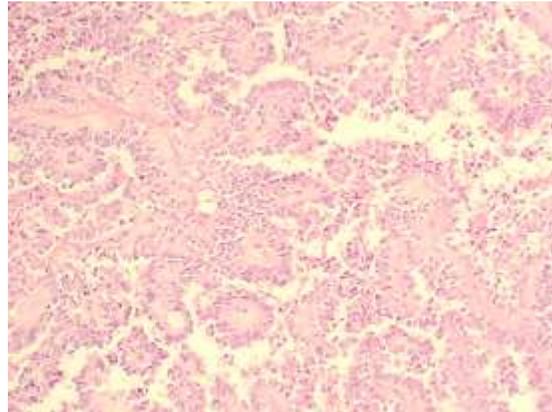
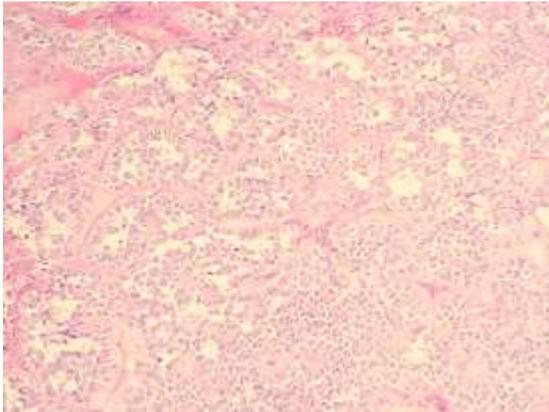
squamoid corpuscles are diagnostic. Small blue cell tumors such as primitive neuroectodermal tumors/Ewing sarcoma, desmoplastic small cell tumors do rarely involve the pancreas.

SPTs are often mistaken for pancreatic endocrine neoplasia (PEN) and vice versa. In SPT, the nuclei tend to be more ovoid than those in PEN. Overlapping of nuclei is also more typical, possibly owing to its non-epithelial characteristics, in contrast to endocrine tumors. Immunohistochemistry is very helpful in this distinction, since PENs are commonly positive for keratins and chromogranin.

SPTs are regarded as low-grade malignant neoplasia. Metastases occur in only 10-15% of the cases, mostly into the liver or peritoneum, and are usually detected at the time of diagnosis. Those that metastasize do not seem to be different than non-metastatic ones morphologically. Frank anaplasia, high-grade sarcomatoid change and abundant necrosis are the only findings that may be helpful in suspecting a more malignant behavior. Infiltrative appearance and perineurial invasion can be seen even in ordinary (non-metastatic) SPTs. Interestingly, even patients with metastatic disease often survive for many years (even decades) with few symptoms. In fact, only rare deaths have been attributed to direct effect of solid-pseudopapillary tumors.

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Adsay Case 3

Clinical history: 62-year old male presented with back pain and weight loss. He had history of alcohol abuse and possible pancreatitis. An abdominal CT-scan was performed as a part of the work-up, and a 3.5 cm ill-defined lesion was found in the head of the pancreas which was interpreted as cystic. The clinical diagnosis of pseudocyst was rendered. FNA was inconclusive. Pancreatoduodenectomy with frozen sections was performed.

Microscopic findings: Although the surgeon was convinced that this was a cystic neoplasm, the frozen sections showed that on the wall of a necrotic mass, there were invasive well-formed tubular elements characteristic of an invasive ductal adenocarcinoma of the ordinary type. The glandular units had irregular, angulated contours, and they were lined by fairly atypical cells with foamy or clear cytoplasm also characteristic of invasive ductal adenocarcinoma. The surgeon sent multiple frozen sections to affirm that this is indeed an adenocarcinoma, not a pseudocyst.

DIAGNOSIS: (PSEUDO-PSEUDOCYSTIC) INVASIVE DUCTAL ADENOCARCINOMA OF THE PANCREAS

Discussion:

Invasive ductal carcinoma (pancreatobiliary type adenocarcinoma; DA) constitutes the vast majority of pancreatic neoplasia. Virtually all DA are solid tumors; cystic examples are very uncommon. This case exemplifies the one of several mechanisms in which a DA can present as a (or with a) cystic mass.

1. Centrally necrotic/cystic DA

As seen in this patient, ordinary ductal adenocarcinoma of the pancreas may undergo degenerative cystic change which generally occur in larger tumors with central necrosis. The clinical presentation and radiologic findings may be mistaken for a pseudocyst or a true cystic neoplasm. Microscopic examination of the cyst wall in such cases reveals the viable cells of invasive ductal cancer. The biologic behavior of ductal adenocarcinomas with cystic change does not seem to be any different from ordinary ductal carcinomas.

2. Microcystic (large-duct type) invasive carcinoma.

Most invasive pancreatic ductal adenocarcinomas are composed of small tubular units. Occasionally, however, they achieve a focal microcystic appearance simply due to marked ectasia of the infiltrating neoplastic glands. This phenomenon may be particularly pronounced in regions of the tumor infiltrating the overlying duodenal muscularis propria. When this appearance is predominant, some authors refer to it as "Large-duct- type" invasive carcinoma (LDA). Although these microcystic glands may be detected grossly, cystic change is generally not a pronounced feature and has not been detected radiographically in these cases. Each small cyst is composed of an invasive neoplastic gland with marked dilatation. The cytologic findings of the lining epithelium may be deceptively bland. Tumors with this microcystic change appear to be a well-differentiated form of invasive ductal adenocarcinoma with only slightly longer survival rates than the ordinary ones. It is important, however, not to mislabel a tumor with simple cystic dilatation of invasive glands as a mucinous cystadenocarcinoma, a lesion with a much better prognosis. The features that favor LDA are clustering and irregularities in the contours of the ducts, and if present, the desmoplastic stroma.

3. Ductectasia secondary to compression of ductal carcinoma

Another mechanism with which invasive ductal adenocarcinoma may lead to "cyst" formation is by causing obstruction of the ducts and subsequent dilatation of the upstream ductal system. This can be confused with intraductal papillary mucinous neoplasms which are characterized by primary cystic dilatation of the ducts occurring due to a proliferation of mucinous and papillary neoplastic cells. Macroscopic examination and proper dissection of the specimens are crucial in making this distinction.

4. Invasive ductal (tubular-type) carcinomas associated with intraductal papillary mucinous neoplasms (IPMNs)

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by a proliferation of neoplastic cells within the pancreatic ductal system, commonly in a papillary configuration, and typically associated with cystic dilatation of the native ducts. IPMNs usually present as a cystic mass. Although they are defined by an "intraductal" process, they can be associated with invasive carcinomas. Most invasive carcinomas associated with IPMNs are of the colloid type (muconodular type), however, a small percentage also has a tubular-type invasion that is virtually indistinguishable from ordinary DA.

5. Large epithelial-lined cysts amidst ductal carcinoma without characteristics of IPMNs

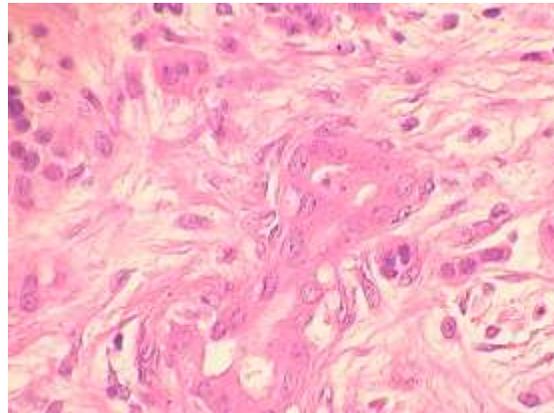
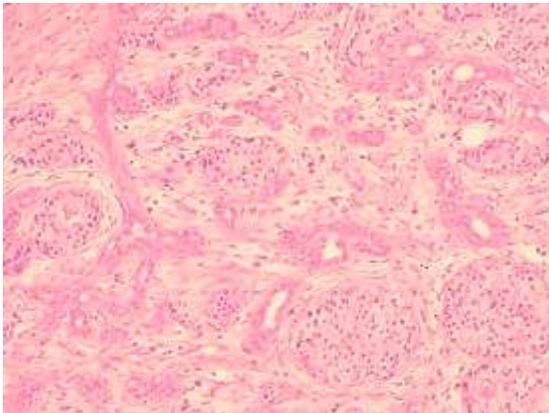
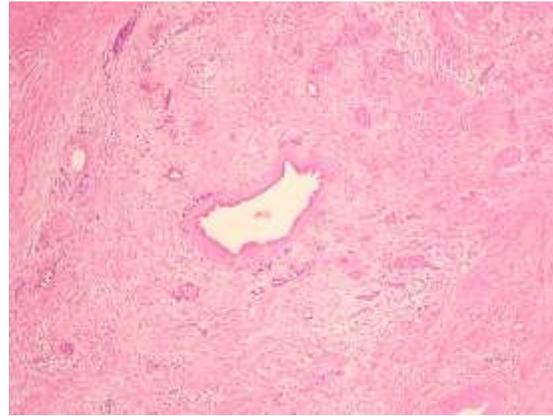
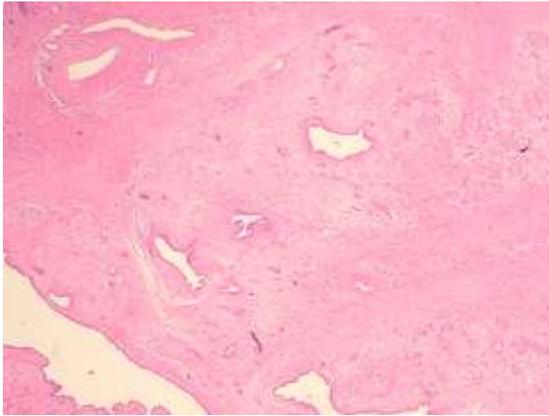
Rarely, an invasive ductal carcinoma of the pancreas is associated with large (several centimeter size) cysts with grossly smooth lining showing the same cyto-morphology as the small tubular infiltration of the same tumor. It can be difficult to determine whether these cysts represent an attenuated IPMN, a passive

(secondary) ductectasia with pagetoid extension of cancer cells, or an unusual mega version of microcystic (large duct type) DA.

In conclusion, an invasive ductal carcinoma of the pancreas may occasionally present as a (or with a) cystic mass. It is important to be aware of this occurrence to avoid misdiagnoses.

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BenDor- Case 1

Clinical history: this 71 year old woman who was discovered on mammography to have atypical calcifications in both breasts underwent needle biopsies diagnosed at an outside laboratory as infiltrating ductal carcinoma and intermediate grade ductal carcinoma in situ in the right breast and high grade ductal carcinoma in situ in the left breast. She was referred to our hospital for continuation of treatment, and bilateral wire guided lumpectomies with right axillary sentinel lymph node biopsy were performed. The material submitted to you is from the right breast.

Pathological findings: the specimen measured 11x7x1 cm. No gross mass was identified and sections were taken from mammographically suspicious areas.

Low power histological examination shows distended lobular units containing discohesive cells with moderate amounts of cytoplasm (focally demonstrating vacuolization positive for mucins with PAS/diastase in some cases with signet ring cell morphology) and prominent nuclear atypia not seen in classical cases of lobular carcinoma in situ. These same cells also infiltrated to varying extents the epithelial lining of the adjacent small ducts. Scattered mitoses and small foci of cellular necrosis were found. Focally lobules filled with small monotonous cells more in keeping with classical lobular carcinoma in situ (LCIS) were found.

While in many places the involved lobular units were well defined, with a regular round shape, in others the architecture showed marked distortion, with the neoplastic lobules seeming to break up into small irregular units. However foci of sclerosing adenosis were seen in non-tumor areas, and these irregular groups of atypical cells were found to be delineated by myoepithelial cells using immunohistochemical staining for **actin, p63, and calponin**. No evidence of invasive tumor was found in any of the sections examined. The separately submitted sentinel lymph node was negative for tumor.

In subsequent studies ER was positive, and PR and HER negative.

DIAGNOSIS: PLEOMORPHIC LOBULAR CARCINOMA IN SITU WITH INVOLVEMENT OF AREAS OF SCLEROSING ADENOSIS.

Discussion: This case raises several interesting points which will be discussed separately.

First: concerning the rare diagnostic entity. Lobular carcinoma is a well established entity which pathologists are made familiar with early in their training. While the histological features of lobular carcinoma in situ were first described earlier in the (twentieth) century, it was only in the landmark paper by Foote and Stewart from 1941 that this along with the invasive variant was proposed as a distinct entity unique in the fact that its origin was proposed to be the lobular apparatus of the breast and not the ducts. It is composed of uniform small discohesive (reflected in the absence of e-cadherin) cells with modest amounts of cytoplasm which can have a small internal lumen. In the in-situ form the proliferation takes place in the lobules with distension of the acini and spreading into the ductal epithelial lining in a pagetoid fashion (in contrast to the usual filling of the lumen in ductal carcinoma in situ). In the invasive form these same cells form rows of cells ("Indian filing") which are dissociated and do not form tubules or aggregates. In the years following the formulation of this entity it was realized that both types of lobular carcinoma can show deviation with regard to its cytological features. In the seventies, Haagensen divided cases of lobular carcinoma in situ into types A and B, type A referring to the classical type as previously described composed of small monomorphic cells, with the cells in type B being larger and more atypical. About 20 years later, cases of lobular carcinoma in situ with severe atypia were first described and named *pleomorphic lobular carcinoma in situ*. With regard to the invasive type, myoid, histiocytoid, or pleomorphic forms, including an apocrine type of the latter, were recognized, these behaving more aggressively than the classical type. About 45% of cases of infiltrating pleomorphic lobular carcinoma showed pleomorphic lobular carcinoma in situ (Middleton et al).

Recently Sneige et al studied a large collection of cases of pleomorphic lobular carcinoma in situ (alternatively denoted as ductal-lobular carcinoma in situ, reflecting the less clear cut distinction between this variant and ductal carcinoma in situ as compared with classical LCIS), with and without an invasive component, noting that all previously reported cases of pleomorphic lobular carcinoma in situ were accompanied by invasive carcinoma. When present the invasive tumor was pleomorphic lobular type. The constituent cells showed extensive discohesion, had eccentric nuclei described as being several times (3-6) larger than a lymphocyte, with moderate to marked pleomorphism, and the cytoplasm was moderate to abundant in quantity. Other features mentioned included necrosis, calcifications, and pagetoid ductal spread in many cases. Foci of classical lobular carcinoma in situ were identified adjacent to the pleomorphic type. In their conceptualization this entity is a progression from the classical type on a spectrum starting with type A classical LCIS, passing through type B, and terminating in the pleomorphic type under discussion (alternatively one can refer to these stages as grades 1, 2, and 3). But in reviewing previous publications on classical LCIS illustrating Haagensen's conception, Sneige et al admit that "some of the LCIS lesions having type B cells had a higher level of nuclear

pleomorphism similar to that observed in our cases". Rosen, on the other hand, in the first edition of his textbook (p. 515) states, in describing the cytomorphology of cells in LCIS, that "considerable cytologic pleomorphism may be encountered.... *and the more varied cells have been classified as type B or pleomorphic LCIS*" (italics mine) (note: I was informed by a friend who has the second edition from 2001 that this same formulation was retained. I do not know what phrasing will appear in the soon to be published third edition). Biologically in comparison with classical LCIS, the authors state that the pleomorphic cases show greater aggressive potential manifested by a greater degree of positivity for p53 and a higher proliferation index (Ki-67) than do classical LCIS, while similar to the classical type the pleomorphic type shows ER positivity and HER negativity.

Fadare presented a unique case of pleomorphic lobular carcinoma in situ composed wholly of signet ring cells (focally seen in this case). Their case showed lobular architecture only focally but the diagnosis was substantiated by negative staining for e-cadherin.

A different paper by Fadare et al explored another manifestation which previously was considered to be absent from LCIS and when if present in an in-situ process was an indication of ductal differentiation: necrosis. These authors collected a number of cases of lobular carcinoma in situ which showed comedo necrosis but which were otherwise morphologically typical of LCIS. All cases were e-cadherin negative; in fact some cases originally included in the group on the basis of histological examination alone were later disqualified when they were shown to be e-cadherin positive. There was no mention of any cytological atypia. Calcification of the necrotic material in some of the cases led to their detection mammographically. Like LCIS cases in general and the pleomorphic LCIS subset, these cases were positive for ER and PR and negative for HER. These cases also showed a relatively marked incidence of associated invasive carcinoma. The invasive tumor in many of the cases was either lobular or at least had a lobular component without pleomorphism. No mention was made of other possible biological indices of aggressivity in this group such as those studied by Sneige et al.

In a study from the AFIP (Bratthauer and Tavassoli), a large number of LCIS cases were stratified into three groups, equivalent to atypical lobular hyperplasia (LIN1), classical LCIS (LIN2), and pleomorphic LCIS (LIN3). Overall 18% of the cases were associated with invasive carcinoma, divided equally between lobular and ductal types. These values reflect the behavior of the predominant classical LCIS group (LIN 2). However on close examination it was observed that the percentage of cases with invasive carcinoma differed significantly among the groups, with the proportion rising with the degree of atypia. Similarly if the invasive carcinomas in the LIN 1 group were predominantly ductal, this decreased with increased atypia along with a concomitant increase in the number of invasive lobular cases, which predominated in the pleomorphic (LIN 3) group.

Second: the question of invasion brought on by the involvement of areas of sclerosing adenosis by tumor. This can create a pitfall in that the architectural distortion inherent in this lesion can be mistaken for invasion when the involved lobular units fill up and distend with neoplastic cells. This can be especially confusing when the neoplastic cells are pleomorphic as in this case. This problem was discussed by Rasbridge and Millis among others. One clue is the presence in the background of sclerosing adenosis uninvolved by the in-situ process. When studied from this vantage point with an appropriate index of suspicion some of the "invasive" foci will be better delimited than true invasive tumors, the individual constituent cell groupings will tend to be rounder with smoother shapes, and the stroma while spindly will not show the fibrotic/edematous features of invasion- in many places it looked more hyalinized than reactive.

However to prove the point conclusively, one will need to resort to immunohistochemical study, the **third** issue to be discussed. Proving or disproving invasion in situations in which the architecture is confusing relies on the demonstration of myoepithelial cells which are not always apparent on routine histology. Immunohistochemistry necessitates markers that preferentially react with myoepithelial cells to the exclusion of other constituents. With the advent of immunohistochemical staining it was found that markers such as actin and S100 could be helpful in this matter. However these markers have disadvantages in that they can cross react with other cells that are not myoepithelium, such as, in the case of actin, myofibroblasts which are especially numerous in invasive tumors and can be confounded with myoepithelium. Recently Werling et al, in a paper co-authored by Allen Gown, a member of the AMR group, and colleagues investigated the application of markers which have become available in the past few years, namely smooth muscle myosin heavy chain (SMM-HC) and p63, in comparison with calponin which was previously demonstrated by them to be superior to actin markers. They found that SMM-HC showed much less cross-reactivity with stromal myofibroblasts than did calponin, with both staining vascular smooth muscle to the same extent. p63 failed to stain either of these two tissues, though on occasion it might stain a few carcinoma cells. p63 is also a nuclear stain, and as such it doesn't form a complete ring around the non-invasive epithelium as would the smooth muscle markers, which can be detrimental in cases such as sclerosing adenosis in which the glands are closely approximated. They recommend using p63 and SMM-HC in tandem with one complementing whatever deficiencies are shown by the other. In my work up I used actin, calponin, and p63- I found all to be convincing in ruling out invasive carcinoma.

Further comments: I made the diagnosis of pleomorphic LCIS wholly on morphological grounds- the lobulocentric pattern in the absence of anything I would consider consistent with ductal carcinoma in situ (ductal involvement is seen only as pagetoid involvement of the lining epithelium by the neoplastic cells characteristic for LCIS), and the cytology, namely, extensively discohesive cells which while pleomorphic are still rather uniform in size with intracytoplasmic vacuoles and mucin drops to the extent of signet ring cell formation, are diagnostic for lobular carcinoma and are not seen in the only other differential diagnostic possibility, lobular cancerization by ductal carcinoma in situ (DCIS). I'm not

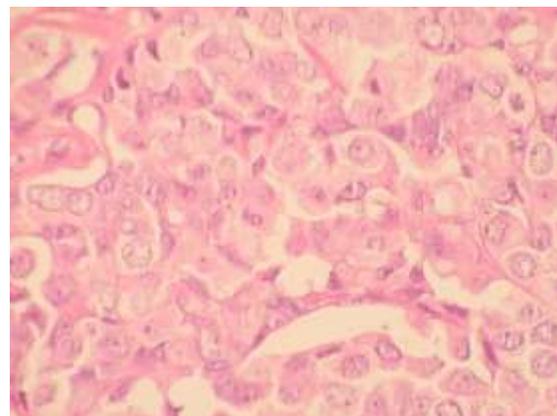
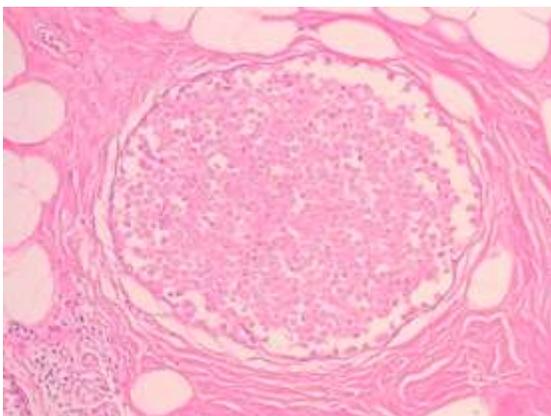
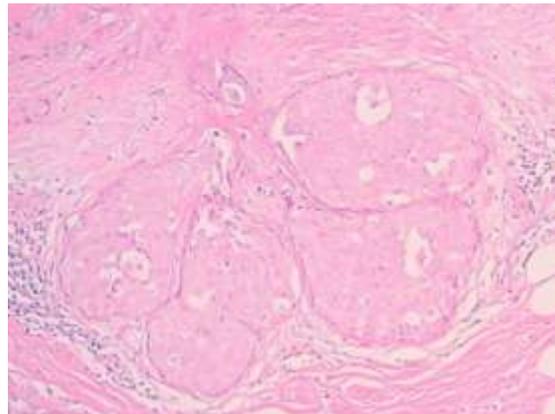
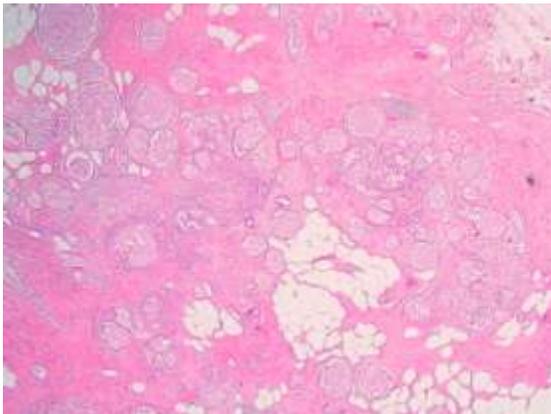
sure that the discohesion in of itself rules out DCIS but then I would expect the tumor cells to be larger and more pleomorphic – as an aside I think that the term “pleomorphic” as used in the context of LCIS should be considered relative to the monomorphism characteristic of LCIS as originally delineated and does not make the cells cytologically comparable to those of DCIS.

In the interest of completing the case presentation, the operative specimen from the contralateral (left) breast showed high grade ductal carcinoma in situ also with involvement of areas of sclerosing adenosis. However one small focus was found of invasive ductal carcinoma- sentinel lymph node biopsy was subsequently performed and was negative for tumor.

Sneige et al recommend that patients such as with pure pleomorphic LCIS be treated as DCIS (this point reinforced in an email communication from the author) which is what I recommended to the clinicians).

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BenDor- Case 2

Clinical history: the slide you received is from a subcutaneous mass excised from the left cheek of a 72 year old female in September 2003. Surgical procedures were previously performed at the same location (at a different hospital) with flap reconstruction and the specimen was submitted with a clinical suspicion of fat necrosis.

Pathological findings: on initial examination especially at lower magnifications one can make out an extensively sclerosing process infiltrating into the fat and containing multiple lymphoid nodules. On higher power there are reactive lymphoid follicles and scattered lymphocytes and spindle cells are found amidst the dense collagen bundles. However on continued close examination, one becomes aware of the fact that there is atypia in the stromal cells, which in places form bundles displacing the collagen fibers and in other foci round up and form nests. S100 shows a good many positive cells infiltrating the specimen while keratin stains are negative.

DIAGNOSIS: DESMOPLASTIC MALIGNANT MELANOMA.

Discussion: Before proceeding to discuss the diagnostic entity from the academic point of view, I need to set the record straight on several points of fact:

- A. Regarding *previous patient history* from the other hospital (as subsequently provided): **lentigo malignant melanoma** was previously excised *twice* from the left cheek: the *first* time in *December 2000*, with invasion to a depth of 0.4 mm. and involvement of margins- no tumor found on subsequent re-excision; in a *second* excision performed in *November 2002* the tumor was invasive to a depth of 0.3 mm. and the margins were positive. In addition, malignant melanoma in situ was excised from a different location, the left arm, in March 2002. The patient was also diagnosed with infiltrating ductal carcinoma of the breast in July 2000. I elected *not* to disclose these exact details at the onset for the purposes of the diagnostic exercise and in order not to prejudice your examination of the slides, though knowledge of them could obviously facilitate the diagnosis.
- B. In addition to the biopsy you have, a small biopsy which included skin was taken in my hospital in *July 2003* two months previously, and a third specimen consisting of a re-excision from the same site was subsequently sent in *March 2004* (in total, three biopsies performed at my hospital). All of these specimens show the findings as described above. The clinician informed me of the fact that melanoma was previously excised from the site (though not necessarily detailing the multiple recurrences) in submitting the specimens.
- C. In *August 2005*, the patient returned to the other hospital for an additional extensive excision from the left cheek area. This time **invasive spindle cell malignant melanoma** was revealed. Submitted lymph nodes were negative.
- D. And now for the final disclosure: the materials from the three biopsies taken at my hospital which were reviewed by me, including the biopsy you have, were all originally *misdiagnosed* at the time they were received as **inflammation and fibrosis**. It was only after the plastic surgeon informed me in late Sept. 2005 that malignant tumor was found at the procedure recently performed at the other hospital and thereupon reviewing all three of the biopsies with that in mind that I immediately perceived what I had previously overlooked: the spindle cell proliferation in the subcutis in all three biopsies showed cytologic atypia and the atypical melanocytic proliferation in the epidermis of the first biopsy that I didn't pay attention to or maybe didn't see (there was no epidermis in the other two biopsies). Only then did it dawn on me that this patient in fact had recurrent desmoplastic malignant melanoma (which could have been present when the lesion was first discovered in 2000).

Excellent comprehensive reviews of desmoplastic malignant melanoma (DMM) were published by McCarthy et al in 2004 and by Busam in 2005. I will review some of the salient points presented in these papers. This condition is uncommon (between 2-4% of all melanoma cases) and is defined by the tumor infiltrating as spindle cells between collagen bundles. It usually appears on sun damaged skin and in most cases there is an associated lentigo malignant melanoma in the overlying epidermis. It is thought that the neoplastic melanocytes adopt fibroblast characteristics though there are true fibroblasts amongst the tumor cells. The tumor is characteristically amelanotic and paucicellular and may appear deceptively cytologically bland, creating the potential for misdiagnosis, though upon searching cytological atypia is noticed. Patchy lymphoid aggregates are often found and the authors state that this can be helpful in the differential diagnosis with scar. Most cases are deeply invasive (Clark level IV-V) at the time of diagnosis. These tumors are prone to neurotropism, manifested by actual penetration into nerves or growth around them; the *neurotropic variant* consists of cases in which this feature is prominent. These latter may be more aggressive, possibly by virtue of the fact that neural involvement may extend beyond the main tumor, making surgical management difficult. Immunohistochemically the tumor spindle cells are S100 positive and for the most part negative with other

markers characteristically positive in melanomas. These tumors are reputed to be "stubbornly recurring"- this behavior may reflect the presence of cutaneous metastases or neurotropic growth beyond the confines of the original tumor mass which can explain recurrences following excision with negative margins reported. Because of the seeming innocuousness of the cells immunohistochemical staining for S100 might be necessary for confirmation of margins. Lymph node involvement is infrequent.

Busam recently (2004) proposed that tumors with extensive paucicellularity and desmoplasia (>90%- pure DM) be segregated from cases which are more cellular and less fibrotic (mixed DM), claiming that the former have a better prognosis.

The *differential diagnosis* includes sclerotic nevi, scar tissue, and other spindle cell tumors. DMM usually appears on sun damaged skin of elderly people (on the average these tumors are diagnosed 10 years later than conventional melanomas) while sclerotic nevi are often found in younger people on undamaged skin. The presence of an associated lentigo maligna in the overlying skin is helpful in identifying this condition and ruling out mimickers. The presence of atypia, the orientation of the spindle cells (which may be vertical, diagonal, whorled, or storiform), and S100 positivity help distinguish DMM from scar tissue, which lacks atypia, and in which the spindle cells are in parallel orientation and should be S100 negative. Appropriate immunohistochemistry panels help rule out other possible spindle cell tumors, such as sarcomatoid/spindle cell squamous cell carcinoma, and smooth muscle neoplasms, which are not expected to be S100 positive. Here also the presence of melanoma in the overlying skin is a useful indicator, especially in ruling out malignant peripheral nerve sheath tumor, which is also S100 positive (though not as diffusely as in DMM).

It is well known that the diagnosis of this entity is often missed (as it was by me). This point is stressed in articles on this topic, as is shown by the title of one of the cited reviews (see references), and can have medico-legal repercussions. This may be due to the extensive fibrosis which renders the neoplastic cells inconspicuous when they are dispersed singly and do not form groups, especially in light of the fact that while atypia is always found when looked for it is not necessarily ubiquitous and the more deceptively bland cells may "blend in" with their surroundings and not attract attention. Personally I think that the lymphoid aggregates may also be a source of confusion when there is a history of previous surgery, which can reinforce an initial bias that the lesion is "reactive".

Summary: DMM is a "stealth lesion"- it has deceptively bland features which can distract the pathologist from its true nature and which can make management difficult. I think that the vicissitudes shown by this particular case are characteristic of this entity and illustrate the difficulties it poses.

To avoid missing this diagnosis it is important to have an adequate index of suspicion in the appropriate circumstances.

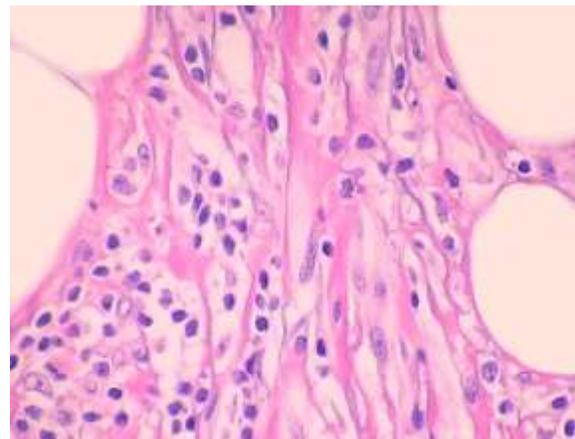
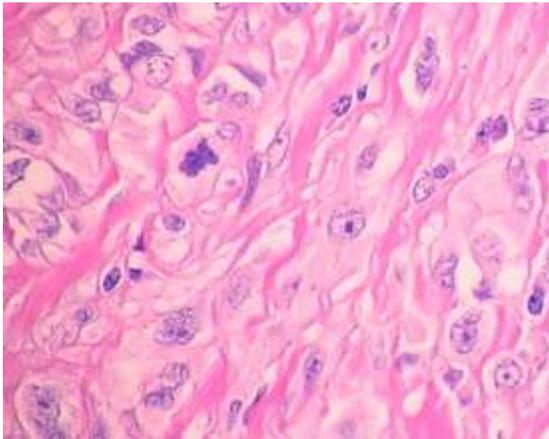
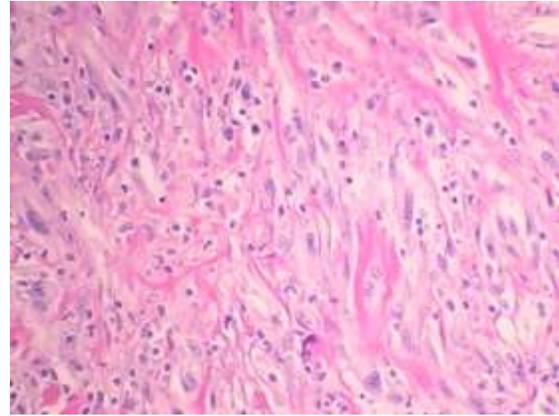
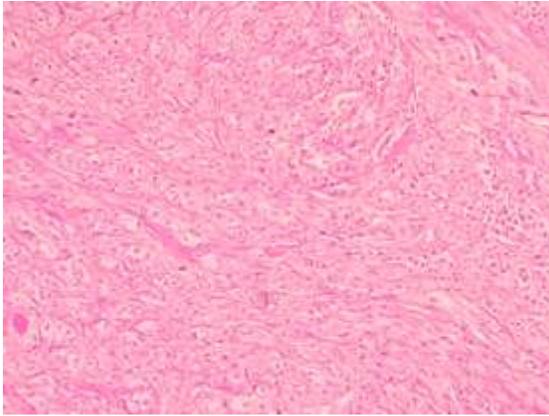
Based on the lessons learned from this case this is the strategy I recommend:

1. all skin biopsies from sun-damaged skin of elderly patients should be scrutinized carefully for atypical melanocytes;
2. in the presence of lentigo maligna the underlying tissues must be rigorously examined for the presence of spindle cells (note that the tumor cells in DMM do not produce melanin). S100 staining should be performed if needed;
3. any fibro-inflammatory lesion or unexplained tumefaction underlying the sun-damaged skin of an elderly person (even in the absence of melanoma but more so if there is) should raise the suspicion of DMM, *especially if recurrent or persistent* (note: if repeated surgeries were performed this should *raise* the index of suspicion in this context rather than provide an alibi for the fibro-inflammatory changes) and should not be summarily dismissed as reactive unless the possibility of tumor was ruled out after careful examination (note: the clinical presentation is often *not* that of a melanocytic lesion: the biopsy may be submitted under a variety of guises (Wharton et al).

In retrospect in examining the biopsies I attached too much weight to the history of previous surgeries and assumed that what I saw was simple scarring and associated inflammation. The history of melanoma (which was in fact provided at the time by the clinician) should have induced me to examine the specimen more carefully.

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Ben Dor Case 3:

Clinical description: the enlarged right lobe of the thyroid from an 82 year old woman was removed after a small piece was sent for frozen section.

Pathologic description: the lobe measured 5x4x9 cm. and was completely replaced by grayish tumor tissue which was contained by the thyroid capsule (thus the tumor cannot be considered encapsulated). Histological examination from the frozen section showed mostly solid architecture. The appearance on sections from the lobectomy varies from place to place. In some areas the tumor cells are organized in groups or islands separated by fibrous septae. The individual cells are for the most part small and monomorphic, with round regular nuclei. While at first glance these groups appear solid, on closer examination small abortive follicular spaces can be discerned containing material consistent with colloid. In other places there is frank well developed follicular architecture. Some groupings appear to be transitional between these two patterns, with semi-solid collections showing small to medium sized follicular spaces. The proportion of these two patterns varies between slides and in different areas on the same slide, though they tend to be segregated. Vascular invasion is focally prominent, there are scattered mitotic figures, and there is no evidence of necrosis. While in places the nuclei appear to be a bit larger and paler, no diagnostic inclusions or grooves were seen. The left lobe also removed showed colloid adenomatous nodules without evidence of tumor.

DIAGNOSIS: FOLLICULAR CARCINOMA OF THE THYROID WITH WIDESPREAD INSULAR/POORLY DIFFERENTIATED ARCHITECTURE.

Discussion: In 1907 Langhans described a thyroid tumor with an insular pattern, which he termed "wuchernde struma". As depicted in the third series AFIP fascicle on thyroid tumors (p.123), this shows tumor cells in rather solid looking islands showing retraction from the stroma, as is seen in the slides from this case. This insight seems to have been unacknowledged for succeeding decades (as witnessed by the fact that in the thyroid fascicle from the first series, reference is made to a "compact (small cell) variant of undifferentiated

carcinoma", without specific reference to Langhans' contribution) until it was rescued from oblivion by Carcangiu et al in 1984, who used this morphologic construct as the linchpin for an entity they called "poorly differentiated carcinoma" of the thyroid, which was to provide a prognostic and structural middle ground of thyroid tumors between the well differentiated follicular and papillary carcinomas on the one hand, which often have a good prognosis, and anaplastic carcinomas on the other, with a dismal one. Besides the insular architecture, the tumors they included in this rubric also showed mitotic activity and necrosis, the latter, when extensive and sparing the cells surrounding the blood vessels, forming a "peritheliomatous" pattern. At about the same time, Sakamoto et al published *their* conception of poorly differentiated carcinoma, consisting of tumors showing "non-glandular"-solid, trabecular, and scirrhous- growth patterns as distinct from well differentiated carcinomas (papillary or follicular) which show only "glandular" architecture. From that point on, much effort has been expended by pathologists expert in the field to refine this idea, engendering much controversy in the process. Part of the problem seems to result, in my opinion, from the fact that the morphological criteria used to compose the "poorly differentiated" group varies among the different authorities and may differ from those of the original authors. Aside from the tumors or tumor types originally suggested, others have included different distinct entities such as tall cell and columnar cell carcinomas by virtue of their more aggressive behavior though they do not necessarily demonstrate the distinctive morphological patterns previously defined.

The main questions are:

1. to what extent is the insular growth pattern to be regarded as a path of differentiation totally separate from the classical types (follicular and papillary) or is it to be regarded as a progression or outgrowth from them?
2. as it often co-exists with other types, to what extent do tumors with the insular pattern constitute a separate entity or can they be considered subtypes of these tumor groups (i.e. follicular and papillary)?
3. does the presence of the insular pattern have any independent clinical significance or should the aggressive potential of a tumor be judged on the basis of other factors (size, mitotic activity and necrosis, extra-thyroidal spread) already recognized as negative prognostic omens?

Personally I found the literature on this topic which was available to me to be confusing with conclusions appearing to vary between different authorities.

This problem was a topic of discussion at the USCAP meeting in 2004 (Endocrine Pathology Society), and the presentations were later published in 2004 in the journal Endocrine Pathology. Rosai admits that the title of the original paper by Carcangiu et al created confusion in implying that insular was synonymous with poorly differentiated, saying that it is only a "type of poorly differentiated carcinoma" (though earlier on he says that the term was used by Carcangiu et al to describe an *entity* and not "a grouping of morphologically diverse tumors on the basis of architectural similarities"). He goes on to say that there is "not a single PDTC (poorly differentiated thyroid carcinoma) but rather poorly differentiated forms of either papillary or follicular carcinomas". Albores Saavedra and Carrick state that tumors with an insular component are either follicular carcinomas or follicular variants of papillary carcinomas. They claim that the mere presence of the insular pattern in of itself does not impact on prognosis, which is related to other factors, though they acknowledge other papers which come to the opposite conclusion (see also Decaussin et al, who showed that thyroid tumors with distant metastases have a relatively high degree of insular morphology in comparison with tumors without metastases). These authors have seen insular morphology in the context of cases of minimally invasive follicular carcinomas which showed long term survival, and also claim that the pattern may be seen even outside the tumor setting in non-neoplastic conditions such as dys-hormonogenetic goiter. Thus these authors would seem to downplay the uniqueness or significance of the insular pattern. They do describe a tumor showing large vesicular nuclei with prominent nucleoli and rhabdoid inclusions which they feel better merits the title of "poorly differentiated carcinoma". Some papers (such as one by Volante et al from 2004) have included tumors with trabecular, insular, and solid patterns (TIS) under the rubric of poorly differentiated carcinoma, thus combining the criteria used originally by Sakamoto in 1983 and Carcangiu. They conclude that the behavior of these tumors is intermediate between that of pure follicular/papillary and anaplastic carcinomas, but also go on to point out that within this group aggressive behavior correlated with scores formulated on the basis of necrosis, mitotic activity, and age. Interestingly, Sakamoto in a later publication says that "some cases of poorly differentiated (insular) carcinoma that are completely composed of cribriform like components must also be classified as well differentiated carcinoma". But he goes on to say in the next sentence that "most insular carcinomas have a non-glandular appearance" (thus apparently meriting their inclusion in the poorly differentiated category). Hiltzik et al define poorly differentiated carcinomas as those showing necrosis and mitotic activity rather than on the basis of architecture and demonstrated that tumors with these features did indeed show intermediate behavior. However 79% of the tumors they included in their study group were of the TIS type (whether this was by design or results from this architecture coexisting with the other features measured is hard to say).

More recently an international group of pathologists gathered and formulated a consensus opinion as to the definition of poorly differentiated thyroid carcinoma (the Turin proposal- 2007). To begin with all tumors to be considered for this category must show solid/insular/trabecular architecture, but to be included in the poorly differentiated category they need to show in addition either necrosis, mitotic activity (greater than 3>10 h.p.f.) or convoluted nuclei. Tumors with clear cut nuclear features diagnostic for papillary carcinoma were classed as *solid variants* of papillary carcinoma, and those without any of the additional aspects mentioned above would be considered *follicular or well differentiated NOS carcinoma*.

Summary: this case is distinctive by virtue of the widespread insular architectural pattern, which would make it a candidate to be included in the category of *poorly differentiated carcinoma* (per various definitions). The insular pattern as a morphologic construct is not controversial but the diagnostic implications it has given rise to are, with the differences being at least in part semantic. I signed the case out as above in an attempt to skirt some of these minefields. Based on the other findings in this case which include prominent vascular invasion and the total replacement of the lobe by tumor, even without consideration of the insular component the tumor would still be diagnosed as *widely invasive* type of follicular carcinoma, which in of itself has a known aggressive potential. I did not think on the whole that the nuclear morphology justifies the diagnosis of papillary carcinoma, though based on focal findings one might disagree with this.

References:

The following are the first papers to propose the entity of *poorly differentiated carcinoma of the thyroid*:

- Carcangiu et al. Poorly differentiated ("insular") thyroid carcinoma. Am J Surg Pathol, 8: 655-668, 1984.
- Sakamoto et al. Poorly differentiated carcinoma of the thyroid. A clinicopathologic entity for a high risk group of papillary and follicular carcinomas. Cancer 52: 1849-1855, 1983.

Note: I did not have access to the above articles at the time I composed this handout and thus do not claim to have read them. Information regarding their content is based on references made to them in other publications, some subsequently written by the authors or co-authors of the original articles themselves.

Tumors of the Thyroid Gland, Atlas of Tumor Pathology, Third Series (5), Armed Forces Institute of Pathology, Washington D.C., 1990.

Articles from the Endocrine Pathology Society proceedings:

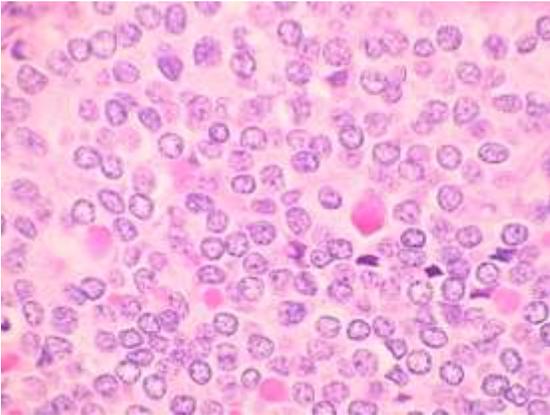
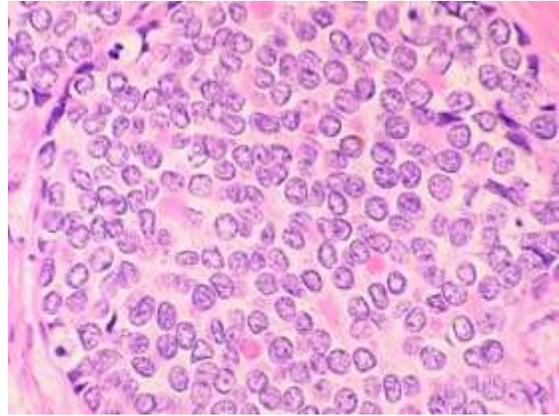
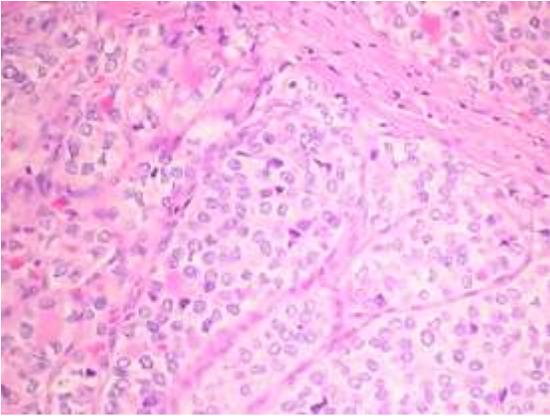
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Decaussin M. et al. Thyroid carcinoma with distant metastases. Am J Surg Pathol. 26: 1007-1015, 2002

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Volante et al. Poorly differentiated thyroid carcinoma: the Turin proposal for the use of uniform diagnostic criteria and an algorithmic diagnostic approach. Am J Surg Pathol. 31: 1256-1264, 2007.



THOMAS COLBY, M.D.
MAYO CLINIC
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Colby-case 1 (tv02-494)

Clinical History:

A 64-year-old man presented with consolidation of the left lower lobe. Cytology was considered suspicious for malignancy and a left lower lobectomy was performed. Grossly there was extensive consolidation.

Mucin-producing epithelial cells were confirmed with histochemical and immunohistochemical stains (EMA, panCK). CEA, MOC31, and CK 7 were positive. CK20, TTF-1 and CDX-2 were negative.

Diagnosis: CONSOLIDATING ADENOCARCINOMA (DIP-LIKE) WITH SOME SIGNET RING CELLS.

Discussion

Lung cancers exhibit many unusual patterns. Some of the unusual patterns of adenocarcinoma are:

1. Signet ring change in lung adenocarcinomas – in any such case one should consider a gastrointestinal primary but is a pattern that may be encountered in lung carcinoma.
2. Mucinous cystic tumors simulating mucoid impaction, including mucinous cystadenoma (very rare), and colloid carcinoma/mucinous cystadenocarcinoma.
3. Well-differentiated adenocarcinoma with fibrosis and inflammation mimicking honeycomb change and inflammatory lung disease.
4. Highly discohesive tumors mimicking an alveolar filling process such as DIP (“malignant DIP”).
5. Sarcomatoid change

The case presented is unusual from a number of points of view. Because of the production of a focal mass rich in mucin, one could consider this a variant of colloid carcinoma. It also illustrates diffuse flooding of airspaces by mucus and cells with preservation of the underlying architecture. Some of the cells are sufficiently bland that they mimic histiocytes and one could consider this “malignant DIP.” Finally, this case illustrates signet ring change, which may be occasionally found in primary lung cancers.

Signet ring cell change is an uncommon, but well-described phenomenon in lung cancer. Typically it is seen as a focal change in a moderate to poorly differentiated adenocarcinoma. In the study by Tsuta et al, signet ring cell lung cancers frequently expressed MUC-1, cytokeratin 7, and TTF-1 with low expression of MUC-5AC and MUC-6. Those authors consider this change something encountered in peripheral lung adenocarcinomas rather than central carcinomas related to submucosal glands.

Colloid carcinoma of the lung is among the group of mucin-rich tumors that has also been called mucinous cystic tumors; three categories have been described:

1. Mucinous cystadenomas are described as localized tumors with massive pooling of mucus, comprising a unilocular cyst with a wall encompassing the entire lesion. The lining epithelium is tall, columnar goblet cells with absent or minimal cytologic atypia.
2. Pulmonary mucinous cystic tumors of borderline malignancy are partially encapsulated lesions with massive mucin production, few neoplastic cells, focal epithelial papillae, stratification and cytologic atypia, and focal dissection of mucus into the surrounding parenchyma where there is an associated inflammatory infiltrate.
3. Colloid (mucinous) carcinomas (also known as cystadenocarcinomas) show massive mucus accumulation with mucin and scant numbers of neoplastic columnar mucinous cells extending into surrounding lung parenchyma, often in a lepidic fashion. The neoplastic cells may be seen floating in the mucin, and cytologically the cells show variable but often mild atypia. Focal areas of invasive adenocarcinoma (with desmoplastic stroma) may be identified.

Moran believes all mucinous cystic tumors should be considered low-grade carcinomas in view of their potential to metastasize. Complete but conservative surgical excision of the tumor and long term follow-up appears to be the most appropriate treatment.

Rossi et al. have described 13 primary mucinous carcinomas of the lung. These represented 0.24% of their lung cancers. The clinical features were similar to those studied by Moran et al. Two of the 13 cases were composed entirely of signet ring tumor cells. The remaining 11 were the goblet cell type. Both patients with signet ring cancers died, whereas all 11 with goblet cell type carcinomas were alive.

The study by Rossi et al illustrates the vagaries of immunostaining of lung cancers rich in mucus.

| | Goblet-Cell-Type MC | Signet-Ring Cell-Type MC | m-BAC | MCRA* | MGA* |
|--------|---------------------|--------------------------|-------|-------|------|
| TTF-1 | +/- | + | -/+ | - | - |
| CDX-2 | + | - | - | + | -/+ |
| CK7 | +/- | + | + | - | +/- |
| CK20 | + | - | + | + | -/+ |
| MUC2 | + | - | - | + | -/+ |
| MUC5AC | - | + | + | -/+ | + |
| SP-A | -/+ | +/- | -/+ | - | - |

MC, mucinous carcinoma of the lung; m-BAC, mucinous bronchioloalveolar carcinoma; MCRA, mucinous colorectal adenocarcinoma; MGA, mucinous gastric adenocarcinoma; CK7, cytokeratin 7; CK20, cytokeratin 20; SP-A, surfactant apoprotein A.
 *According to previous literature (references 3,5,6,16,17,19,20,24,27,29,33,34,47,56,57).

The diagnosis of colloid carcinoma can often be suspected grossly on the basis of a mucinous mass lesion. The key histologic findings are mucinous flooding of airspaces (and its presence alone should alert one to search for neoplastic epithelium) and the identification of uniform, well differentiation mucinous cells that are similar one to the next and lack cilia. In some cases, moderate cytologic atypia, nuclear stratification, and mitotic figures may be present.

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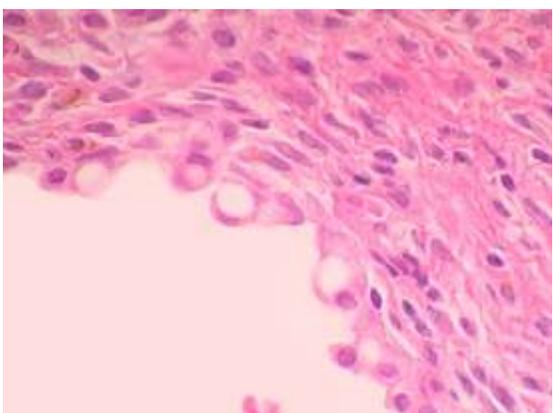
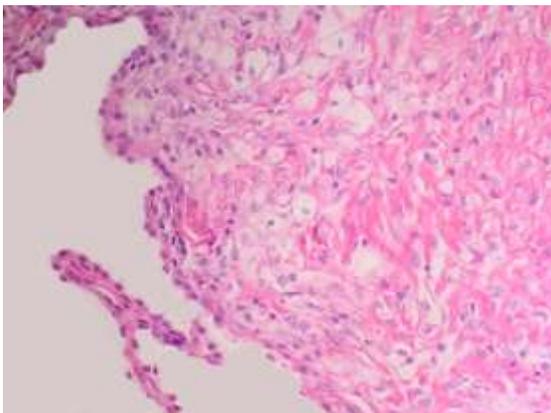
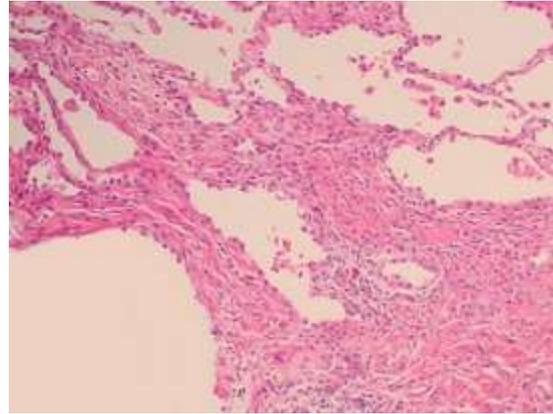
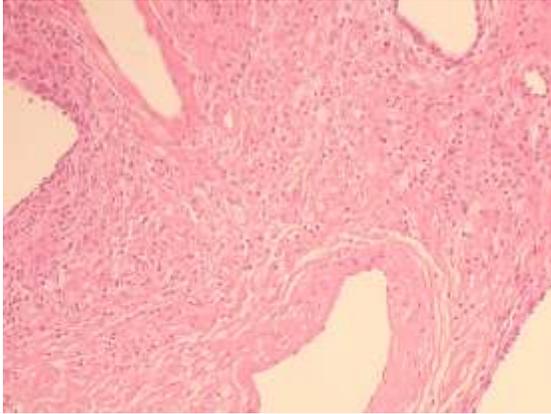
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Colby- Case 2 (TV98-279)

Clinical History (Case courtesy of R. Sobonya, Tucson, AZ):

A 49-year-old man presented with progressive interstitial lung disease and restriction on pulmonary function testing. He ultimately underwent orthotopic lung transplantation and the sections are from the explanted lung tissue.

Diagnosis: ERDHEIM-CHESTER DISEASE WITH PULMONARY INVOLVEMENT.

Follow-up: Radiologic studies of the extremities confirmed the typical radiologic features of Erdheim-Chester disease. The patient developed recurrent Erdheim-Chester disease in the allograft one year after transplantation.

Discussion:

The most important aspect of this case is to recognize why it is not a fibrosing interstitial pneumonia, especially usual interstitial pneumonia (UIP) and fibrosis associated with emphysema. While the emphysema is prominent the most obvious feature is fibrous thickening of the interstitium, however on careful examination the cellular infiltrate and fibrosis are limited to the lymphatic routes. In addition the character of the inflammatory reaction, rich in histiocytes, would be unusual for UIP. UIP tends to produce patchy fibrosis and honeycomb change involving subpleural and paraseptal lung tissue rather than the pleura and septa themselves.

The disease now known as Erdheim-Chester disease was described by Erdheim's pupil Chester in 1930 under the name "lipoid granulomatose." Erdheim-Chester disease is a rare, non-familial, sometimes multifocal, histiocytosis of unknown etiology. There are no serum lipid abnormalities. The characteristic and defining lesions are symmetrical, bilateral, metaphyseal, and diaphyseal cortical sclerotic lesions of the long bones. Most patients are over 40 years of age. About half have extraskeletal manifestations.

Extraskeletal lesions may involve or present in the lung, central nervous system, orbit, kidney, retroperitoneum (where xanthogranulomatous inflammation may be misdiagnosed), breast, skin, skeletal muscle, heart, pleura, pericardium, mesentery, aorta, and sinonasal region. Systemic cases have been described. Traditional hematolymphoid sites such as lymph nodes, bone marrow, liver, and spleen are spared.

The clinical aggressiveness of some cases, recurrence in allografts, and widespread involvement all call to mind a neoplastic process, and while the precise histogenesis remains elusive, clonal cytogenetic abnormalities have been described (see Vencio ref)

The histologic findings of Erdheim-Chester disease are nondescript. This has been described as a "lipid storing histiocytosis" when foam cell change is prominent. Touton-type giant cells may be seen. There may be a sprinkling of lymphocytes, eosinophils, and plasma cells. The degree of fibrosis and cellularity vary from field to field as shown in lung case presented. The involvement of lymphatic routes in the lung for this hematolymphoid disorder of histiocytes. The histiocytes are typically positive for histiocyte markers and rarely positive for S-100. Electron microscopy shows an absence of Birbeck granules. Rare cases share features of both Erdheim-Chester disease and Langerhans' cell histiocytosis suggesting the possibility of a relationship between the two diseases.

The morbidity in the disease is generally not related to the bony involvement. The extraosseous involvement seems to determine mortality, and about 60% die of the disease, the majority due to respiratory failure or CNS involvement. Among those who die, one-third survive less than six months after initial diagnosis. There is no known effective treatment.

The differential diagnosis in this case includes two groups of lesions: 1) fibrosing interstitial pneumonias, and 2) histiocytic proliferative and infiltrative processes.

The fibrosing interstitial pneumonias that would enter into the differential diagnosis include usual interstitial pneumonia and nonspecific interstitial pneumonia. Conceivably healed sarcoidosis could leave a residue of fibrosis along lymphatic routes but the histiocytes and other inflammatory cells would generally be lacking and healed sarcoid often has rounded hyalinized fibrotic nodules.

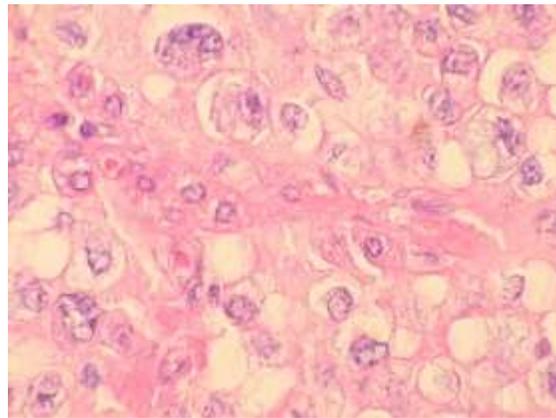
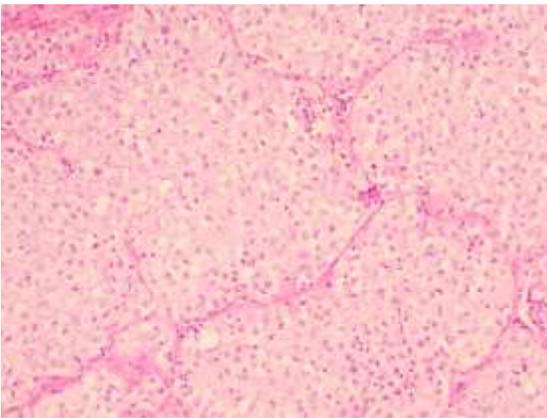
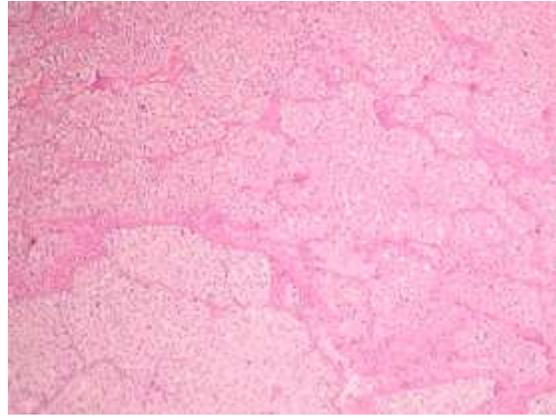
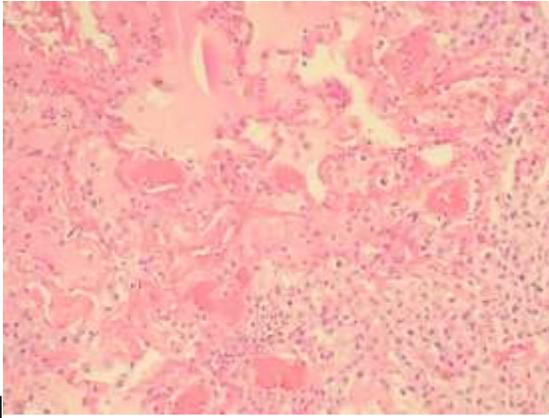
Among histiocytic infiltrates that would enter into the differential are including Langerhans' cell histiocytosis and Rosai-Dorfman disease. Langerhans' cell histiocytosis is generally associated with smoking and produces stellate centrilobular fibrosis described elsewhere in this seminar. Even Langerhans' cell sarcoma and disseminated forms of Langerhans' cell histiocytosis in children should be readily differentiated on the basis of the history, the larger number of histiocytes, their characteristic cytology, and their positivity for both S-100 and CD1a. Rosai-Dorfman disease has histiocytes that tend to be larger with nuclei with more prominent nucleoli and lung involvement is even more rare than with Erdheim-Chester disease.

The recurrence of disease in the lung allograft following transplantation is an interesting phenomenon that has obvious clinical significance. I know of two cases of Erdheim-Chester disease with lung involvement that have undergone transplantation and in both cases there was recurrence in the allograft. Other conditions that have been documented to recur in the allograft include the following:

- Lymphangiomyomatosis
- Pulmonary Langerhans' cell histiocytosis
- Desquamative interstitial pneumonia
- Bronchioloalveolar carcinoma
- Cobalt pneumoconiosis (GIP)
- Alveolar proteinosis
- Diffuse panbronchiolitis
- Sarcoidosis
- Usual interstitial pneumonia
- Idiopathic pulmonary hemosiderosis

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Colby- Case 3 (TV98-323)

History: A 78-year-old man underwent decortication for what was described as a “trapped right lung and clinical diagnosis of empyema.” There was no history of exposure to asbestos.

Diagnosis: **SARCOMATOID/DESMOPLASTIC MESOTHELIOMA.**

Follow-up/Additional Information: No follow-up is available. The neoplastic cells were diffusely positive with cytokeratin, and focally with calretinin. Cytokeratin 5/6 was negative.

Discussion/Comments: The WHO defines:

A sarcomatoid mesothelioma is “A pure spindled pattern resembling a fibrosarcoma or a malignant fibrous histiocytoma. (synonyms: sarcomatous, spindled, or diffuse malignant fibrous mesothelioma).”

A desmoplastic mesothelioma is “A sarcomatoid mesothelioma with a predominant (>50%) dense collagenous stroma and haphazardly arranged slit-like spaces made up of cells with slightly atypical nuclei.”

Clinical features of mesothelioma:

Males >> females

Age: 7th and 8th decades (with broad range)

Signs and symptoms – shortness of breath, chest pain, recurrent effusions

Sites: Pleura >> peritoneal >> other sites

Majority associated with asbestos exposure

Treatment: None proven; recent interest in extrapleural pneumonectomy and chemotherapy
 Prognosis: Survival 6 to 18 months (epithelioid greater than sarcomatoid/desmoplastic)
 Survival over five years is rare

The differential diagnosis of malignant mesothelioma depends on whether one is dealing with: 1) an epithelial/epithelioid proliferation or, 2) a spindle cell/fibroblastic proliferation and the approach to these two settings is entirely different. The basic questions are whether the process is reactive or neoplastic, and if neoplastic is it mesothelioma or some other neoplasm mimicking a mesothelioma?

The case under discussion was a spindle cell proliferation with abundant fibrous tissue and those questions would be addressed as follows:

Is this fibrous pleuritis or a neoplastic process?
 If neoplastic, is this desmoplastic/sarcomatoid mesothelioma or some other sarcoma?

For the epithelial/epithelioid proliferations, the questions would be as follows:

Reactive mesothelial hyperplasia vs. neoplasm
 If neoplastic, is this carcinoma (or melanoma, sarcoma, lymphoma) or mesothelioma?

The diagnostic approach, criteria of malignancy, and ancillary tests, particularly immunostains, for these two groups are entirely different. These two basic diagnostic problems were extensively reviewed in the Churg reference (2000).

Separation of Desmoplastic Mesothelioma from Fibrous Pleurisy (Churg et al., 2000)

| Fibrous Pleurisy | Desmoplastic Mesothelioma |
|---|--|
| Cellularity greatest immediately under effusion; becomes more fibrotic away from effusion (ie, shows "sidedness" or "zonation") | No zonation; bulk of lesion is paucicellular; may have abrupt transitions to cellular, frankly sarcomatous foci anywhere in the lesion |
| Cells immediately under effusion may be very atypical | Cytologic atypia often hard to discern |
| Capillaries perpendicular to pleural surface | Capillaries inconspicuous |
| No stromal invasion | Stromal invasion |
| No necrosis | Bland necrosis |
| No sarcomatous foci | Sarcomatous foci |
| No nodular expansion of stroma | Nodular expansions of stroma |

The series by Mangano et al. nicely showed that desmoplastic mesothelioma could be separated from fibrous pleurisy on the basis of the presence of a diffuse storiform proliferation of the pleura and one or more of the following features:

Invasion of the chest wall or lung

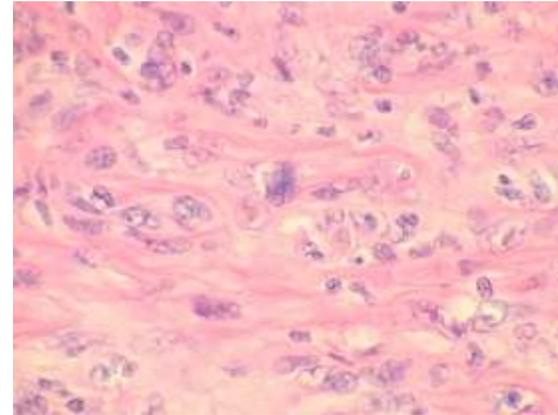
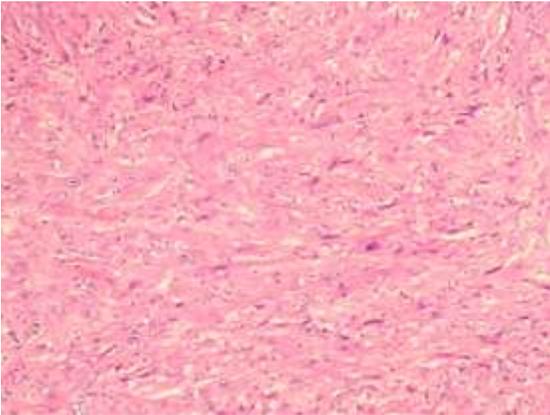
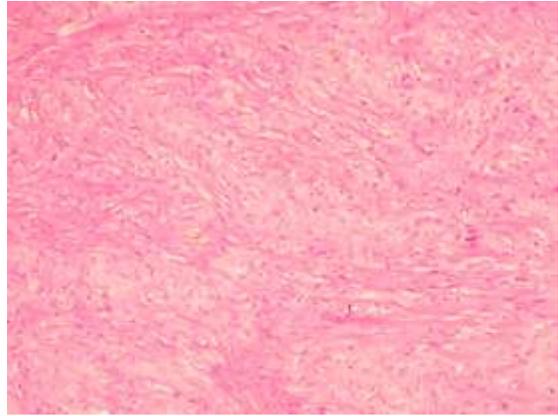
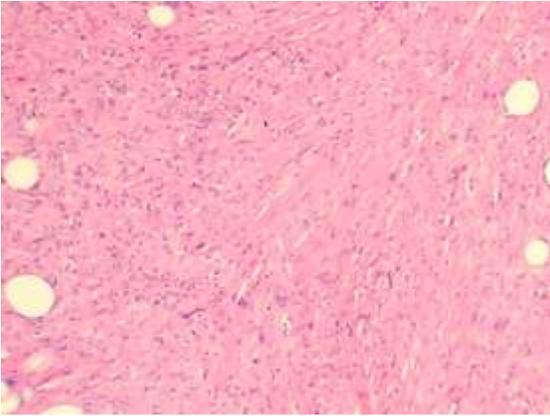
Foci of bland necrosis
 Frankly sarcomatoid foci
 Distant metastases

Immunostaining in the setting of desmoplastic mesothelioma vs. fibrous pleurisy is helpful in highlighting invasion of cytokeratin positive cells into structures adjacent to the pleura such as lung or chest wall. Distinguishing sarcomatoid mesotheliomas from other sarcomas involving the pleura is such an uncommon scenario that it is rarely encountered by the surgical pathologist. In such cases careful attention to any prior history of sarcoma, the pattern of growth in the pleural space (sarcomas tend to be multiple nodules rather than more diffuse growth) and selected immunostains based on the histology of the process should allow resolution of most cases. "Carcinoma markers" in this setting are irrelevant.

The only sarcomas seen in the pleura with any frequency, and ones which not uncommonly closely mimics a mesothelioma, are malignant vascular tumors which may manifest as epithelioid hemangioendothelioma or frank angiosarcoma (epithelioid or spindle).

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KUMARSEN COOPER, M.D.
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Cooper Case 1

Clinical History:

A 93-year-old man presented with progressive left-sided weakness and paralysis. A large soft tissue mass with bone destruction involving T3 was detected on CT scan of the thoracic spine. There was considerable extension of tumor into the spinal canal with marked canal compression. Surgery was undertaken to decompress the pressure on the spinal cord with several fragments (largest 1.2 x 0.5 cm) of tumor tissue being submitted for histological examination.

Microscopic Examination:

The tumor displays a distinctive lobular architecture with invasion of soft tissue and bone. A mixed solid and reticular or trabecular arrangement of tumor cells is evident. In some areas, the tumor cells are arranged in cords and nests. The cells are largely composed of epithelioid morphology with eosinophilic cytoplasm. Focal squamoid and clear differentiation is also present. Typically the stroma is variably myxoid or hyalinized stroma.

Whilst mild cytologic atypia (low-grade) was evident in much of the tumor, foci of moderate atypia as evidenced by vesicular chromatin, prominent nucleoli and nuclear pleomorphism was also present.

Immunohistology:

Cytokeratin (AE1/AE3, Chemicon International), epithelial membrane antigen (E29, Dako) and S-100 (polyclonal, Dako) were all diffusely positive. Focal immunopositivity was noted for glial fibrillary acidic protein (GFAP, polyclonal, Dako) and smooth muscle actin (SMA, 1A4, Sigma). To rule out metastases, the follow immunohistochemistry was performed, all of which were negative: prostatic specific antigen (polyclonal, Dako), thyroid transcription factor (TTF-1, 8G7G3/1, Dako), HepPar-1, OCH1E5, Dako), cytokeratin 7 (OV-TL, Dako), and cytokeratin 20 (K₅20.8, Dako). Desmin (33, Biogenex) and muscle specific actin (HHF35, Dako) were also negative.

Diagnosis: SOFT TISSUE MYOEPITHELIOMA

The characteristic morphology and immunoreactivity for keratin and EMA, in conjunction with the detection of S-100, GFAP and SMA, confirms the diagnosis of myoepithelioma of soft tissue. The presence of infiltration and focal moderate cytologic atypia best classifies this as **myoepithelial carcinoma**.

Discussion:

Mixed tumors have been defined by the WHO Classification of Soft Tissue Tumors (2002), as well circumscribed lesions displaying epithelial and/or myoepithelial elements in varying proportions, within a hyalinized to chondromyxoid stroma. Tumors comprising myoepithelial cells resembling those observed in pleomorphic adenoma and lacking ductal differentiation are designated myoepitheliomas.

Although well characterized in salivary glands, myoepitheliomas and mixed tumors (pleomorphic adenomas) were only recently recognized to occur primarily in soft tissue. Difficulty in recognizing these tumors has been ascribed to the plasticity of myoepithelial cells with the resultant broad heterogeneous morphologic spectrum of myoepithelial tumors. In the salivary gland, the diagnosis of myoepithelioma has been expanded to include tumors composed of spindled, plasmacytoid (hyaline), epithelioid or clear myoepithelial cells with myxoid or hyalinized stroma and a solid, reticular or trabecular architecture.

In the salivary gland, the criteria for malignancy has been widely accepted as being invasion beyond the tumor capsule with cytologic atypia and mitotic rate being useful. In soft tissue, tumors with benign cytology or mild cytologic atypia (low-grade) have been classified as myoepithelioma or mixed tumor; whereas tumors with moderate to severe atypia (high-grade) have been classified as myoepithelial carcinoma (epithelioid or spindle cells with vesicular or coarse chromatin, prominent large nucleoli or nuclear pleomorphism) or malignant mixed tumor (cytologically malignant cartilage or bone). In a recent study of 101 myoepithelial tumors of soft tissue, 18% of benign/low-grade cytology recurred (mean follow-up 36 months) and none metastasized. There were no clinical or histologic features that predicted or correlated with recurrence. Significantly, about half of these cases showed microscopic infiltrative margins, which was not associated with

recurrence nor metastasis. Among cytologically malignant cases, 42% recurred locally and 32% metastasized, illustrating the potential to pursue an aggressive clinical course. Clearly, myoepithelial tumors of soft tissue with high-grade cytologic atypia are malignant and should be treated accordingly. Alternatively, moderate cytologic atypia (prominent nucleoli, vesicular or coarse chromatin, nuclear pleomorphism) should warrant classification as myoepithelial carcinoma with significant risk for aggressive behavior and propensity for metastasis.

The majority of myoepithelial tumors arise in the extremities and limb girdles with fewer occurring in the head, neck and trunk. They may be situated in subcutis or deep soft tissue and range in size from 0.7-20 cm (mean 4.7 cm). There is no sex predilection and the mean age is 38 years (range 3-83 years), with a peak in the third to fifth decades.

An awareness of the heterogeneous morphology of myoepitheliomas is essential to perform confirmatory immunohistochemical stains to arrive at the correct diagnosis. A basic requirement would include immunoreactivity for either keratin or EMA in conjunction with detection of S-100 protein or myogenic markers. Keratin (AE1/AE3 or MNF116) and S-100 protein is detected in nearly all soft tissue myoepitheliomas, whilst about half are immunoreactive for GFAP. Neoplastic myoepithelial cells of all morphologic types often express myogenic markers, with Calponin being the most sensitive; whereas SMA and desmin are positive in about a third and fifth, respectively. The basal cell/myoepithelial (prostate/breast) marker p63 is detectable in only about a quarter of soft tissue myoepitheliomas. However, p63 is not specific for myoepithelial tumors and has been reported in other tumors, viz squamous cell and urothelial carcinomas.

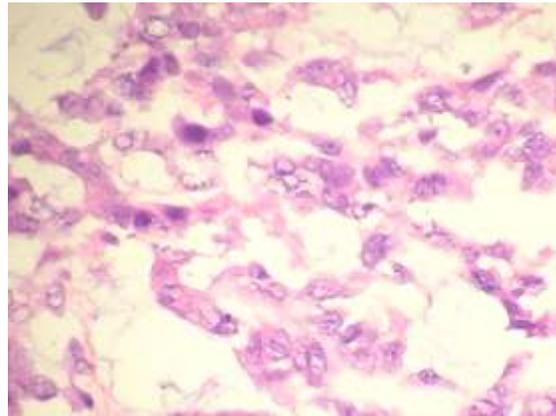
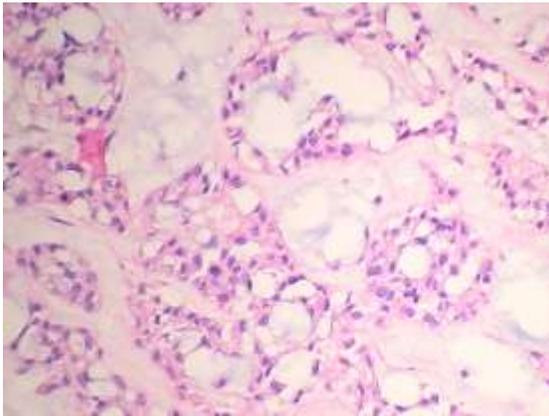
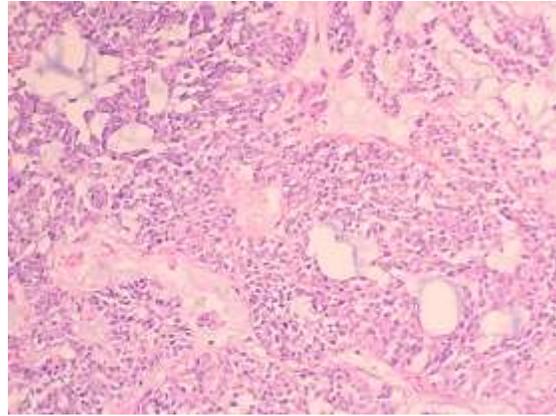
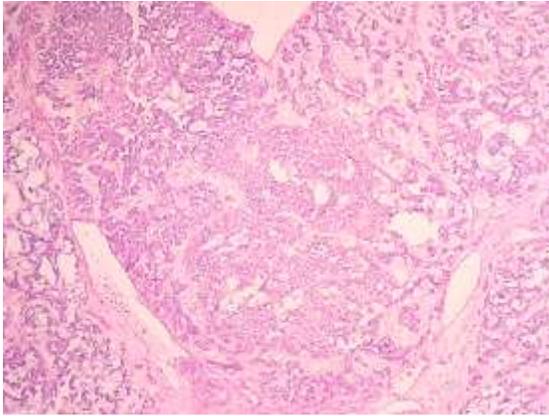
Myoepitheliomas that display a reticular architecture with chondromyxoid or hyalinized stroma entertain the differential diagnosis of extraskeletal myxoid chondrosarcoma (EMC) and ossifying fibromyxoid tumor (OFMT). EMC typically demonstrates a multinodular growth pattern with interlacing cords of spindled cells in a myxoid or chondromyxoid matrix. In contrast, myoepitheliomas are more epithelioid (or mixed with spindle cells) and often show intratumoral heterogeneity with reticular areas merging with solid areas. A minority of EMC express S-100 protein with epithelial and myogenic markers rarely positive; in contrast to myoepitheliomas, which are almost always S-100 protein and keratin positive. OFMT is a lobulated proliferation of pale-staining ovoid to round cells in cords or nests set in a variably myxoid or hyalinized stroma with a peripheral rim of metaplastic bone. Typical OFMT demonstrates a combination of S-100 protein (70%) and desmin (50%) immunopositivity with GFAP and keratin being rare. Myoepitheliomas are usually keratin positive with about a half being GFAP positive.

Although less common, the spindle cell myoepithelioma may resemble smooth muscle and nerve sheath tumors. Leiomyomas containing broad cigar-shaped nuclei are positive for desmin but negative for GFAP; whilst myoepitheliomas (with more tapered nuclei) are rarely desmin positive but are consistently S-100 protein positive and frequently GFAP positive. It should be noted that approximately 40% of smooth muscle tumors are keratin positive. Schwannomas demonstrate alternating cellular zones with nuclear palisading and hypocellular myxoid zones with hyaline vessels; and share S-100 protein and GFAP positivity with myoepitheliomas. The latter, however, lacks the zones of alternating cellularity and shows no nuclear palisading.

The differential diagnosis of high grade myoepithelial carcinomas of soft tissue includes metastatic carcinoma (as in the present case) and metastatic melanoma. Metastatic carcinoma generally lacks the myxoid stroma and multinodular architecture of myoepithelial carcinoma. Immunoreactivity for S-100 protein, GFAP and myogenic markers supports the latter diagnosis. Similarly, GFAP, keratin and myogenic immunoreactivity is exceptionally rare in metastatic melanoma.

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Cooper Case 2

Clinical History:

The excised lesion is from a mass on the right foot in a 28-year-old woman. Her history was that of a slowly growing painless mass.

Pathological Findings:

The tumor was received as multiple tan-yellow to white firm fibrous soft tissue fragments measuring 5.0 x 3.0 x 1.5 cm. The cut surfaces were tan-yellow and focally gelatinous.

Microscopically, this tumor is characterized by nodules of myxoid tissue surrounded by cellular to hyalinized stroma, variable inflammatory cells and large atypical cells with prominent nucleoli. On low power, the regional variation between myxohyaline areas and cellular granulation tissue-like areas with inflammation is notable. The bizarre atypical cells are interspersed throughout non-myxoid stroma and the paucicellular myxoid tissue. The appearance of the bizarre-shaped nuclei spans the spectrum from ganglion-like cells to Reed-Sternberg-like cells to cells mimicking lipoblasts. The ganglion-like cells have a large, vesicular, irregularly shaped nucleus and a huge nucleolus. The cytoplasm is prominent and spindled forms are also present. The binucleated forms of these cells resemble Reed-Sternberg cells. The multivacuolated lipoblast-like cells are found in the myxoid areas and feature hyperchromatic, enlarged, sometimes indented nuclei in addition to cytoplasmic vacuoles. Occasional scattered multinucleated giant cells are identified. The stroma outside the myxoid nodules alternates between cellular and hyalinized areas. Within the myxoid nodules the cells vary from being spindled to epithelioid with mild to moderate nuclear atypia (except for the bizarre cells). The hyalinized areas are prominent and contain only a few tumor cells with thick-walled vessels. Mitoses, including atypical forms, are present but difficult to find.

The inflammatory cells are most prominent in the non-myxoid cellular areas and complete the histologic picture. The composition is that of lymphocytes, plasma cells, polymorphonuclear leukocytes (especially within the myxoid areas), and eosinophils. Occasionally the intense inflammation may partially obscure the large atypical cells. In summary, the essential criteria for a diagnosis of IMHT is the location on distal extremities, myxoid nodules scattered about hyalinized to cellular stroma, large bizarre ganglion-like cells or lipoblast-like cells and a mixed inflammatory cell infiltrate.

Diagnosis: INFLAMMATORY MYXOHYALINE TUMOR OF DISTAL EXTREMITIES
(Acral Myxoinflammatory Fibroblastic Sarcoma)

Discussion:

Inflammatory myxohyaline tumor of distal extremities is a neoplasm of low malignant potential. It is characterized by large ganglion-like cells, myxoid nodules and a stroma that varies from being cellular to hyalinized, with associated inflammation.

This tumor was first published in 1998 with the appearance of three simultaneous reports comprising significant numbers of patients. The descriptive labels used by these authors were remarkably similar: "Inflammatory myxohyaline tumor of distal extremities" (Weiss), "Acral myxoinflammatory fibroblastic sarcoma" (Kindblom) and "Inflammatory myxoid tumor of soft parts with bizarre giant cells" (Michal). Although the term "sarcoma" was used by one of the authors, distant metastases have not been demonstrated in the 63 patients with follow-up; and only 1 patient developed regional lymph node metastasis. Nevertheless, two-thirds of patients in one series and one-fifth in the other developed one or more recurrences. Hence, the authors of the AFIP fascicle on soft tissue tumors assign this tumor to the intermediate group of neoplasms, rather than the sarcoma group; hence the label "inflammatory myxohyaline tumor" (IMHT) is preferred.

A total of 75 cases have been reported to date. The age of patients has ranged from childhood to the ninth decade. The majority are in the fifth and sixth decades. These tumors affect the sexes equally. Almost all tumors occurred in the hands/fingers (two-thirds), feet/toes, ankle/wrists, whilst a few involved the arms/lower legs. Significantly, no tumors developed on the trunk, head/neck, or within body cavities. Patients present with a history of a slowly growing painless mass, most often in the subcutaneous tissue. The lesions ranged in size from 1 to 8 cm (median, 3 to 4 cm). They frequently infiltrate synovium, subcutaneous fat and dermis. However, epidermal and bone invasion has not been reported. Clinically these lesions were suspected to be ganglion cysts, tenosynovitis, or giant cell tumors of tendon sheath. A single case report with cytogenetic analysis showed t(1;10)(p22;q24) in addition to the loss of chromosomes 3 and 13.

Immunohistochemistry:

Immunohistologic examination of a total of 35 cases from both series demonstrated vimentin positivity in all atypical cells. A variable number of atypical cells was also immunopositive for CD68 and CD34. Weak, focal smooth muscle actin and keratin immunopositivity were also demonstrated in a few cases. The inflammatory infiltrate comprised a mixture of both B and T cells, especially the latter. The S-100, HMB-45 and epithelial membrane antigen were negative in the neoplastic cells.

Differential Diagnosis:

- Tenosynovitis may be considered, especially when the heavy inflammatory infiltrate obscures the large atypical cells and when the tumor growth involves the synovial lining of a tendon sheath. The finding of the bizarre cells should avoid this error.
- Inflammatory myofibroblastic tumor (IMT) (inflammatory pseudotumor) enters the differential diagnosis due to the presence of a spindle cell component and the inflammation in IMHT. However, the bizarre cells of IMHT are not present in IMT. Further, IMT practically never occurs in the distal extremities.
- Ganglion cysts and juxta-articular myxomas do not contain the large atypical cells found in IMHT. Further, juxta-articular myxomas involve larger joints and do not exhibit the increased focal cellularity of IMHT.
- Proliferative fasciitis is also characterized by ganglion-like cells. However, the ganglion-like cells of IMHT are much more atypical than those of proliferative fasciitis, which also lacks marked inflammation.
- Neural tumors with enlarged nuclei and myxoid stroma are S-100 positive; whilst the cells in IMHT are negative.
- Myxoid liposarcoma enters the differential diagnosis as a result of the lipoblast-like cells. However, myxoid liposarcoma does not feature the large atypical nuclei and never occurs in the distal extremities. The characteristic plexiform vasculature and signet ring lipoblasts are not features of IMHT.
- Pleomorphic liposarcoma is rare in acral locations and the large multivacuolated cells in IMHT are not true lipoblasts.
- Extraskeletal myxoid chondrosarcoma is not characterized by the marked inflammation, fibrosis and cellular atypia of IMHT.
- Atypical lipomatous tumors contain atypical cells but primarily comprise adult fat.
- Epithelioid sarcoma can have significant inflammation, contain scattered atypical polygonal and spindle-shaped cells and often originates in the superficial tissue of the distal extremities.

However, the majority of the cells in epithelioid sarcoma are round cells with eosinophilic cytoplasm. When large atypical cells are present, they are usually cytokeratin positive, whilst similar cells are cytokeratin negative in IMHT. Even when positive in the latter, it is focal and weak.

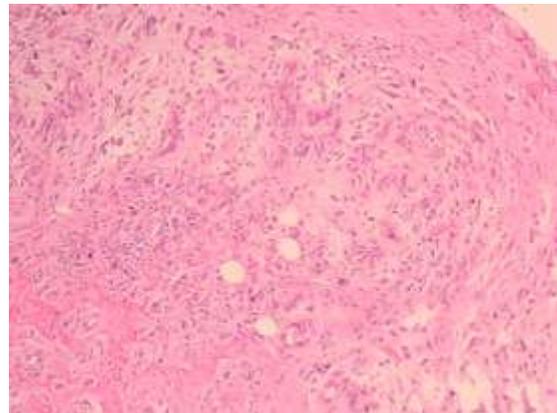
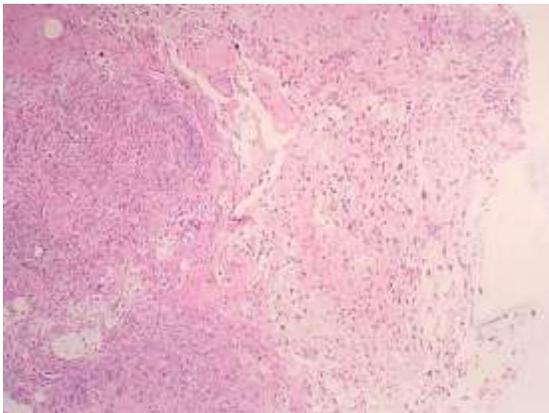
-Myxofibrosarcoma (myxoid MFH) on purely histologic evidence is fraught with difficulty. However, the clinical presentation on the distal extremity, paucity of mitotic figures, ganglion-like or Reed-Sternberg-like cells, and marked inflammation are useful features to recognize IMHT.

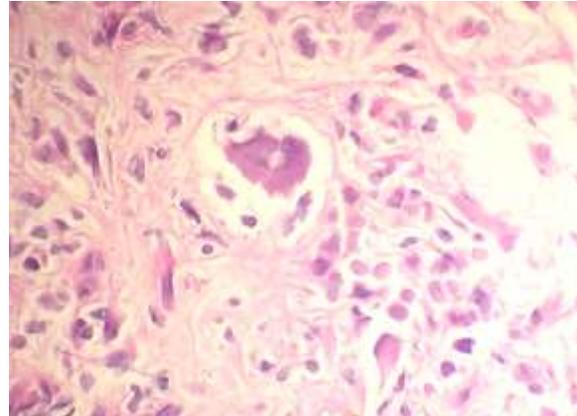
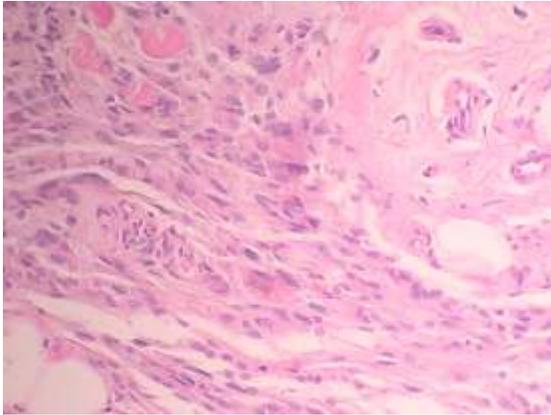
Treatment and Prognosis:

The recurrence rate in the follow-up of the patients in the two published series of IMHT was 22 percent and 67 percent. Some of the recurrences were multiple and aggressive enough to warrant amputation. In one patient, the recurrence extended up the arm. Recurrences may also occur more than a decade after the initial excision. The efficacy of post-operative radiation is difficult to assess given the prolonged course of many of these tumors. Although spread to a regional lymph node has been documented in one case, distant metastases has not been reported to date. Hence, IMHT appears to have a recurring potential but its metastatic capacity (to date) is very low. In the Kindblom series, 31 percent persisted with disease, 64 percent were alive without disease, and 5 percent were dead of other causes. No patient had died of IMHT at the last follow-up.

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Cooper Case 3

Clinical History

A 59-year-old woman underwent a total abdominal hysterectomy for a pelvic mass detected on ultrasound examination.

Gross Examination

The uterus weighed 510 grams with an unremarkable cervix, bilateral fallopian tubes and ovaries. The uterine cavity was completely replaced with an exophytic, 12.0 x 8.0 x 5.9 cm, pale tumor that arose from the posterior endometrium. The tumor invaded the posterior uterine wall and extended to the posterior serosa, without perforation. The cut surface of the tumor was pale to pink with areas of necrosis and hemorrhage. An omental mass measuring 2.2 x 1.8 x 1.6 cm was also received along with pelvis and para-aortic lymph nodes and excisional biopsies from the peritoneum, cul-de-sac and serosa of the rectum.

Microscopic Examination

The microscopic appearance of this tumor was dominated by a high-grade malignant small round blue cell tumor, with a high mitotic activity and foci of necrosis. A vaguely organoid/lobular arrangement alternating with sheets of tumor was evident. This neuroectodermal component consisted of small, round to oval cells with round hyperchromatic nuclei and scant cytoplasm. These areas merged with larger cells with more amphophilic cytoplasm, vesicular chromatin and discernible nucleoli. In scattered focal areas, these undifferentiated cells matured into distinct “neurofibrillary balls” (neuropil) with cells showing ganglionic differentiation, confirming the ganglioneuroblastomatous nature of this tumor. Other rare foci of a background of Schwannian stroma was also evident.

The second rhabdomyosarcomatous component of this tumor comprised foci of scattered rounded rhabdomyoblasts with abundant eosinophilic cytoplasm and concentric fibrils. These myoid cells were discernible especially in the background of the undifferentiated large cell neuroblastomatous component. This combination of ganglioneuroblastoma with focal rhabdomyosarcomatous differentiation supports the diagnosis of malignant ectomesenchymoma.

Following examination of several blocks of tumor, rare foci of adenocarcinoma were identified in sections from the posterior uterine wall. This supported the notion that whilst the malignant ectomesenchymoma dominated the microscopic picture, the uterine tumor most probably arose in an endometrial adenocarcinoma or a malignant mixed Mullerian tumor (MMMT), with subsequent obliteration (overgrowth) by the former.

Metastatic deposits were also demonstrated in the omentum, pelvic/para-aortic lymph nodes, and recto-vaginal cul-de-sac. The patient died six weeks following surgery with disseminated malignancy.

Immunohistochemistry

The immunohistology essentially confirmed the morphological interpretation. The undifferentiated neuroblastomatous component and scattered ganglionic cells were diffusely immunoreactive for both synaptophysin and chromogranin. S-100 immunopositivity was demonstrated in the “neurofibrillary balls” (neuropil) and the Schwannian stroma, whilst GFAP was negative. The skeletal differentiation of the

rhabdomyosarcomatous component was confirmed with myogenin, desmin and muscle specific actin immunoreactivity. Focal CD99 immunoreactivity was noted in the undifferentiated (neuroectodermal) areas of the tumor. All cytokeratins (AE1/AE3, CAM 5.2, MNF116) were negative in the malignant ectomesenchymoma. CD10 was non-contributory.

Diagnosis: UTERINE NEUROECTODERMAL TUMOR WITH RHABDOMYOSARCOMATOUS DIFFERENTIATION (MALIGNANT ECTOMESENCHYMOMA OF THE UTERUS).

Discussion

Ectomesenchyme is the term used for neural crest tissue that shows mesenchymal differentiation during embryogenesis. Divergent differentiation is a well-recognized phenomenon in neural crest tumors with a consistent rhabdomyoblastic component in ectomesenchymoma.

Malignant ectomesenchymoma (MEM) is an exceptionally rare multiphenotypic tumor featuring mesenchymal and neuroectodermal tissues, arising predominantly in soft tissue in infancy and very occasionally in adults. (MEM differs from teratomas, which arise from totipotential stem cells in gonads, midline or para-axial location.) About 25 cases of MEM have been reported in the literature, with a marked male predominance. The tumors have usually been located in the retroperitoneum, pelvis or paratesticular regions. Histologically they are characterized by an admixture of rhabdomyosarcoma with either ganglioneuroma, neuroblastoma (as in the present case), or malignant peripheral nerve sheath tumor (MPNST). Approximately 50% have pursued a fatal course.

The present case of MEM is highly unusual and unique in that it presents as a uterine tumor in an adult and probably arose in association with an endometrial adenocarcinoma or an MMMT. In this context, the differential diagnosis of malignant ectomesenchymoma would include tumors with both muscle and neural elements. In this regard, the main diagnostic considerations would include malignant triton tumor and malignant mesenchymoma. Malignant triton tumor (MTT) usually occur in older patients (as opposed to the majority of MEM presenting in infancy, with the present case being an exception) and are usually (but not always) associated with von Recklinghausen's disease (neurofibromatosis type 1). MTT are composed of stroma typical of MPNST (malignant peripheral nerve sheath tumor) with the additional component of scattered rhabdomyoblasts, the latter appearing as round cells with eosinophilic cytoplasm. The frequency of rhabdomyoblasts is uneven, with a variable cellular distribution even within the same tumor. However, the MTT should not be mistaken for MEM, since the latter comprises neuroblasts and ganglion cells.

Malignant mesenchymoma (MM) are rare tumors which by definition show at least two distinct types of frankly malignant mesenchymal differentiation in addition to "fibrosarcomatous" (undifferentiated) areas (Stout, 1948). The most common lines of differentiation are rhabdomyoblastic, lipoblastic and osteocartilaginous. MM arising in the uterus is extremely rare – there are three cases reported in the literature to date. All tumors in this setting arose from a leiomyoma, with abrupt transitions between pleomorphic areas and benign smooth muscle areas. Heterologous differentiation with malignant cartilage, osteoid and rhabdoid areas complete the picture of MM.

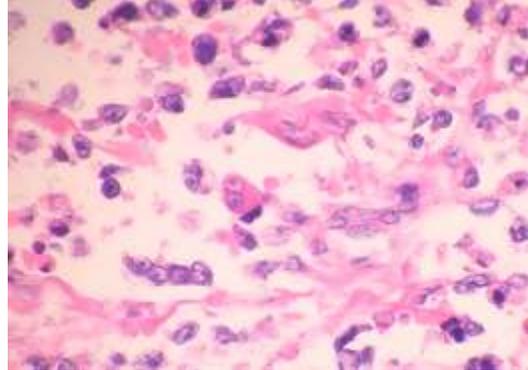
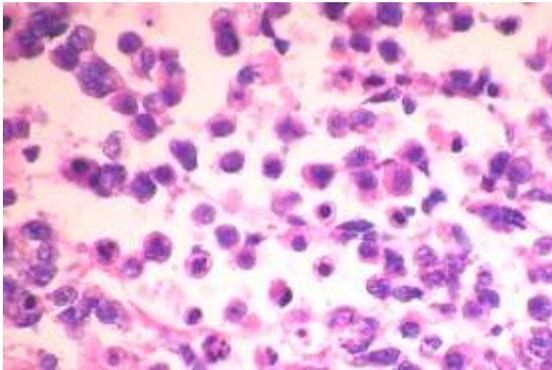
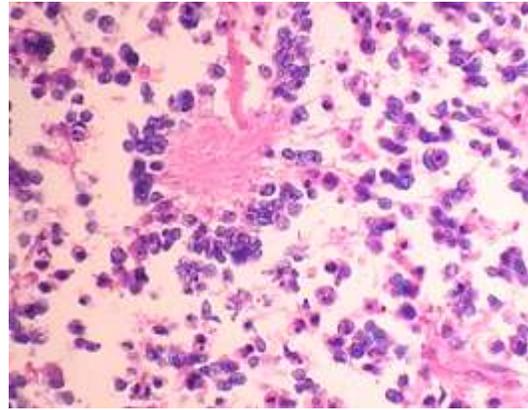
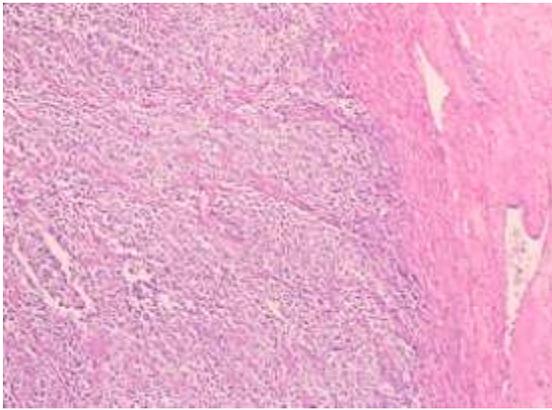
A recent study from the MD Anderson experience documented 17 cases of neuroectodermal tumors of the uterus, with 10 cases comprising pure neuroectodermal components. The remaining 7 cases were admixed with varying amounts of unclassified sarcoma, rhabdomyosarcoma, endometrioid carcinoma, adenosarcoma or MMMT. The neuroectodermal component was positive for synaptophysin, chromogranin and/or CD99. The majority presented as advanced stage cancers in post-menopausal women with an ultimate aggressive course, although prolonged survival was achieved with aggressive surgery and/or chemoradiation.

Interestingly, 12 of the MD Anderson cases were negative for EWSR1 gene rearrangement by FISH analysis, avoiding confusion with peripheral PNET. Hence, these authors prefer the term uterine tumor with neuroectodermal differentiation (akin to the central type of PNETs), occurring in postmenopausal women. They suggest an immunohistochemical panel of cytokeratin, neurofilament, synaptophysin and CD99 to highlight the neuroectodermal differentiation; with testing for EWSR1 gene rearrangement to rule out true peripheral PNETs (which have been described in the uterus).

Several theories have been proposed regarding the origin of neuroectodermal tissues in the uterus. A long held popular theory is that ectopic migration of neural crest cells was responsible for the cell of origin for neuroectodermal tumors. More recent plausible theories suggest a "neometaplastic" process of cells of Mullerian origin, i.e. the alteration of a neoplastic cell to another type not normally resident within the tissue of origin. The latter is supported by case reports of neuroectodermal tumors admixed with MMMT, suggesting a one-sided neuroectodermal differentiation in an MMMT.

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Damjanov- Case 1

Clinical history:

A 56 year-old man with cirrhosis of the liver and a pancreatic mass. Numerous peripancreatic and periaortic lymph nodes that were infiltrated with tumor.

Pathological findings: The tumor was a ductal adenocarcinoma composed of irregular glands and solid nests. In addition to this adenocarcinoma component, the original tumor as well as the lymph node metastases contained nests of hepatic cells. Between the liver cells there were clearly visible intercellular bile canaliculi filled with brownish yellow bile.

Diagnosis: HEPATOID ADENOCARCINOMA OF THE PANCREAS.

Discussion:

Adenocarcinomas with hepatoid differentiation have been described in many parts of the gastrointestinal tract, the ovary and several other sites (recently reviewed by Hameed et al, 2007). Hepatoid differentiation of these tumors can be focal or extensive, and in some cases the entire extrahepatic tumor may be completely composed of cells resembling neoplastic hepatocytes.

Tumors composed almost exclusively of liver like cells are justifiably called hepatoid carcinomas. The same term is used by some authors for adenocarcinomas containing liver cells, although it would be probably better to call them adenocarcinoma with hepatoid differentiation. In my opinion such distinctions are only of semantic significance since almost all extrahepatic carcinomas showing hepatoid differentiation proved to be highly malignant neoplasms and prone to early metastasis.

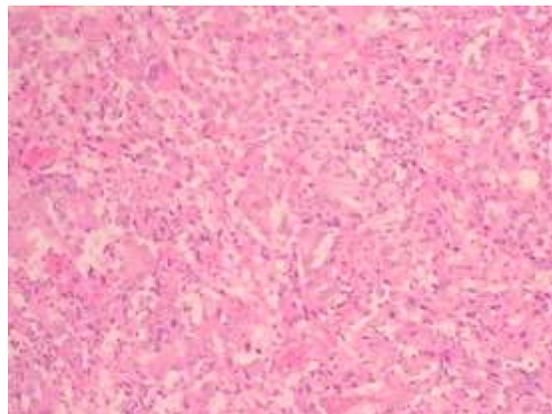
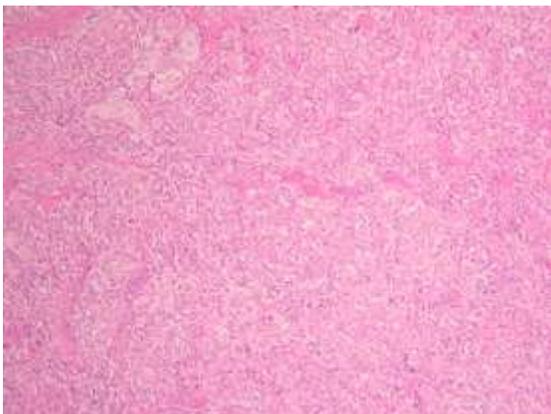
Hameed et al., 2007 reviewed the literature and found only 6 pancreatic carcinomas with hepatoid differentiation (1). It is of interest that some of these tumors were ductal carcinomas, some were pure hepatocellular carcinomas and in some tumors the hepatoid component originated in an endocrine insular neoplasms. Endocrine pancreatic tumors showing hepatoid differentiation had a somewhat better prognosis than those originating in adenocarcinomas, or those presenting as pure hepatocellular carcinomas.

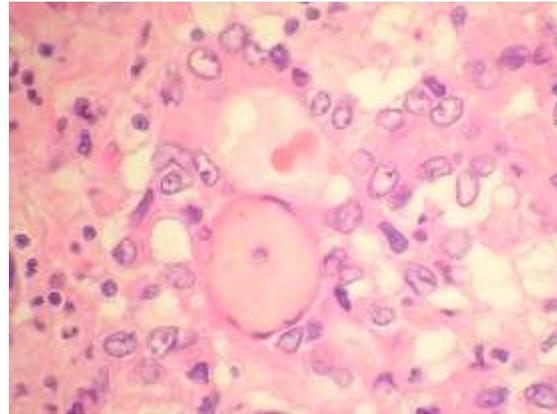
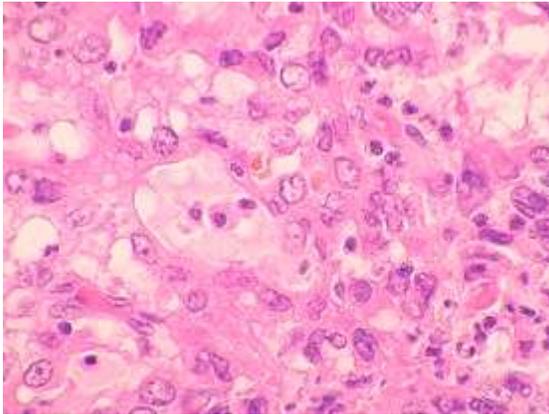
For pathologists it is important to recognize extrahepatic adenocarcinomas with hepatoid differentiation for the following reasons:

- To realize that hepatoid differentiation can occur in extrahepatic tumors and not to mistake such tumors for metastases of hepatocellular carcinoma.
- To remember that AFP is not only produced by hepatocellular carcinoma but also by extrahepatic adenocarcinomas showing hepatoid differentiation.
- To notify the clinician that this diagnosis has almost invariably a poor prognosis.

Reference:

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Damjanov-Case 2

Clinical history:

A 16 year-old girl complaining of menstrual irregularities was referred to a gynecologist who noticed that she has a tumor of the right ovary. The tumor was removed and the patients recovered completely.

Pathological findings:

The tumor was a 26 cm multicystic mass completely replacing the right ovary. It weighed 1366 g and contained 800 ml of serous fluid. On cross-sectioning the tumor was found to be multilocular, but also contained a few solid areas.

Microscopically, most cystic spaces were devoid of a lining. Focally, the internal surface of the cysts was covered with loosely arranged cells forming 2 to 6 cell thick layers. These cells had round to oval euchromatic nuclei and indistinct eosinophilic or clear cytoplasm. The thickened wall of some cysts contained focally nests of similar cells. Some of these cellular nests contained a fluid filled central area. Immunohistochemistry revealed that the tumor cells are positive for vimentin, inhibin, calretinin and CD99, and negative for cytokeratin.

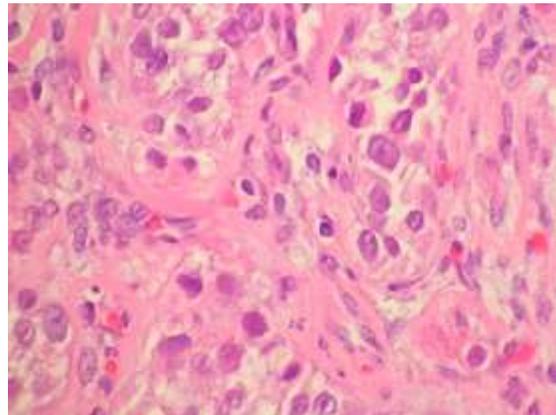
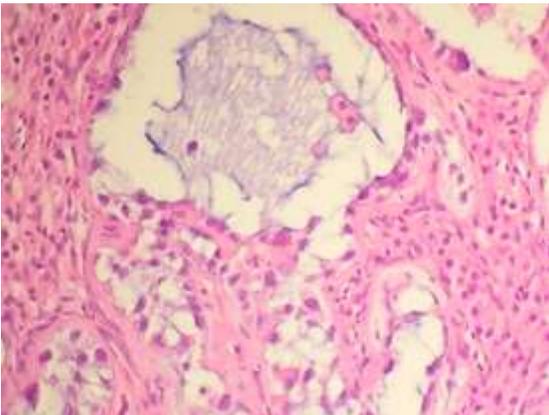
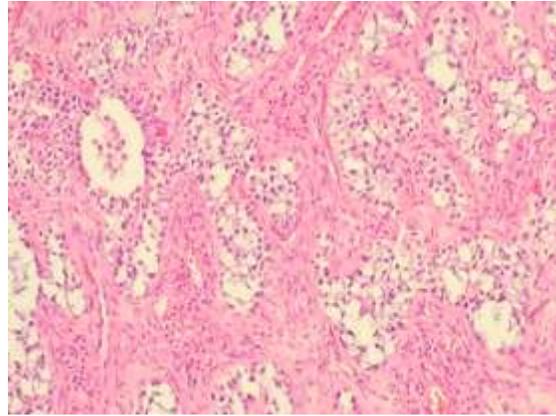
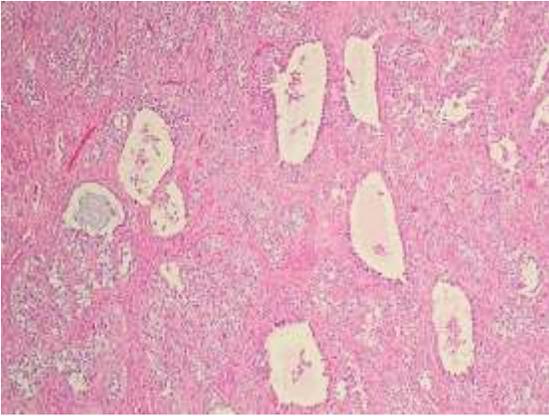
Diagnosis: JUVENILE GRANULOSA CELL TUMOR OF THE OVARY.

Discussion: Juvenile granulosa cell tumors (JGCT) account for 5% of all granulosa cell tumors. More than 90% of all JGCT are found in women under than age of 30 years, and most of them are hormonally active (1). According to Clement and Young (1) uncommon findings include rupture (10%), ascites (10%) and malignancy. Most tumors are benign, but 2-3% are malignant. Malignant tumors typically recur during the first year after surgery. Late recurrence is uncommon (2).

The microscopic diagnosis is relatively straight forward. In our case the diagnostic problem arose in part from the multicystic nature of the tumor—most JGCT are namely solid and initially we thought that the tumor was a serous cystadenoma. The fluid in the cystic spaces led to the detachment of the cells and thus, most of the cyst were devoid of diagnostic granulosa cells. Once we noticed the nests of granulosa cells, we searched for the same cells along the cyst lining, and sure enough we found them there. Immunohistochemistry confirmed that these were sex cord cells allowing us to make the final diagnosis of JGCT.

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Damjanov- Case 3

Clinical history:

A 63 year-old woman with a pathologic fracture of the left femur. Subsequently it became known that the patient had brain surgery 3 years ago.

Pathological findings:

The tumor was highly cellular and showed prominent vascularity. The vascular spaces were irregularly shaped, often angulated and had a staghorn-like appearance. The cell tumor cells were relatively uniform, with elongated hyperchromatic nuclei and indistinct cell borders. Mitotic figures were prominent and overall there were 5-7 mitoses per high power field. Reticulin stain disclosed a dense pericellular distribution of reticulin fibers. Immunohistochemistry revealed that the vascular cells are positive for vimentin, CD31 and CD 34, whereas the perivascular cells were positive for vimentin only. MIB-1 labeling index was 15%. The staining for cytokeratin and EMA gave negative results. The review of the meningeal tumor removed 3 years ago revealed that it had the same composition as the present bone tumor. Hence it was concluded that the bone tumor was a metastasis from the meningeal primary.

Diagnosis: HEMANGIOPERICYTOMA, METASTATIC FROM THE MENINGES TO THE BONE.

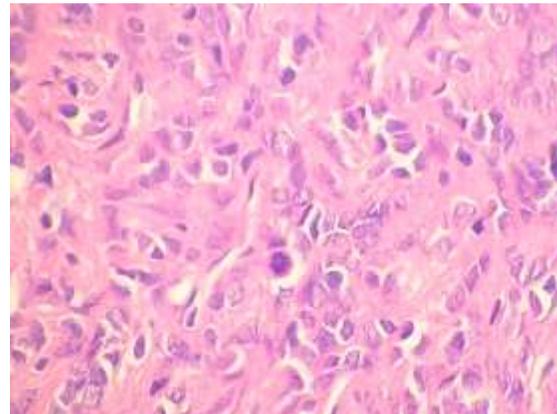
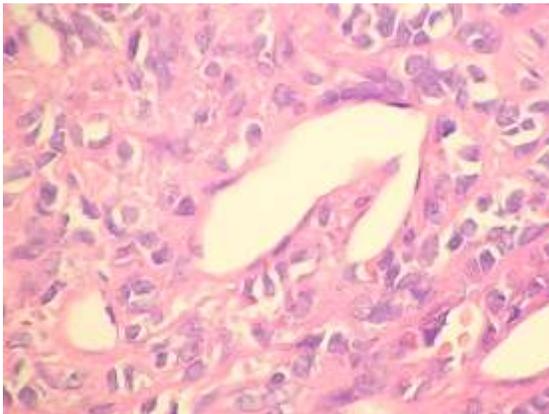
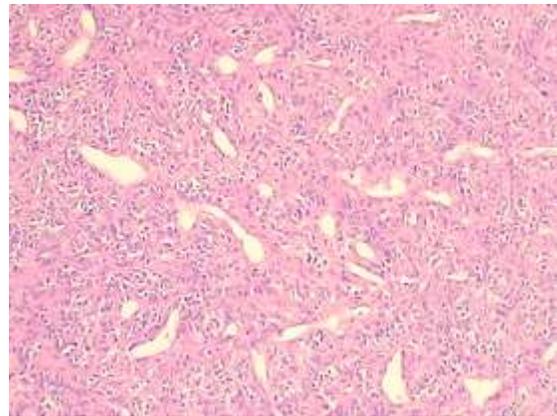
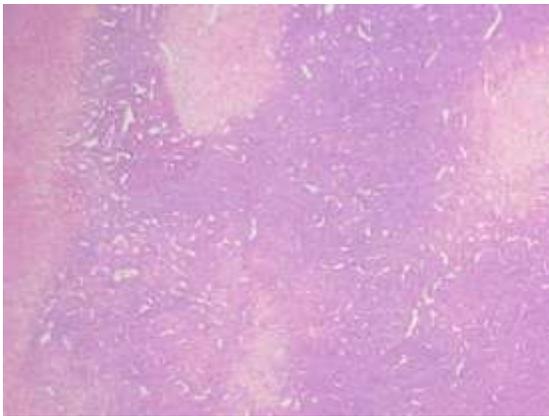
Discussion: Hemangiopericytomas (HPC) are malignant tumors of the meninges with a tendency to recur and metastasize to extracranial sites. It accounts for less than 0.5% of all intracranial tumors. The mean age at the time of diagnosis is 43 years, but the tumors may be found between 10 and 75 years of age. Approximately 60 % of tumors recur and 30 % have extracranial metastases. Such metastases are found in bones and solid organs.

HPC was initially considered to be a variant of meningioma. The potential malignancy of HPC has made it imperative that these two entities be separated one from another. HPC should also be distinguished from hemangioblastoma. HPC of the meninges resembles solitary fibrous tumors. In contrast to solitary fibrous

tumors which are benign and CD34 negative, HPCs are low grade malignancies and CD34 negative. Authorities cannot agree whether meningeal HPCs are a distinct entity or just a malignant or cellular form of solitary fibrous tumors(3). For clinical and historical purpose, and until these controversies are solved, HPC of meninges deserves to be treated as a unique tumor of low malignant potential, with a predisposition for extracranial bone and solid organ metastases.

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Damjanov- Case 3

Clinical history:

A 56 year-old man with cirrhosis of the liver and a pancreatic mass. Numerous peripancreatic and periaortic lymph nodes that were infiltrated with tumor.

Pathological findings : The tumor was a ductal adenocarcinoma composed of irregular glands and solid nests. In addition to this adenocarcinoma component , the original tumor as well as the lymph node metastases contained nests of hepatic cells. Between the liver cells there were clearly visible intercellular bile canaliculi filled with brownish yellow bile.

Diagnosis: HEPATOID ADENOCARCINOMA OF THE PANCREAS.

Discussion:

Adenocarcinomas with hepatoid differentiation have been described in many parts of the gastrointestinal tract, the ovary and several other sites (recently reviewed by Hameed et al, 2007). Hepatoid differentiation of these tumors can be focal or extensive, and in some cases the entire extrahepatic tumor may be completely composed of cells resembling neoplastic hepatocytes.

Tumors composed almost exclusively of liver like cells are justifiably called hepatoid carcinomas. The same term is used by some authors for adenocarcinomas containing liver cells, although it would be probably better to call them adenocarcinoma with hepatoid differentiation. In my opinion such distinctions are only of semantic significance since almost all extrahepatic carcinomas showing hepatoid differentiation proved to be highly malignant neoplasms and prone to early metastasis.

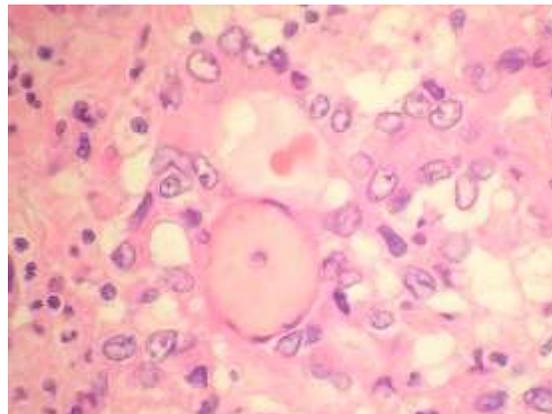
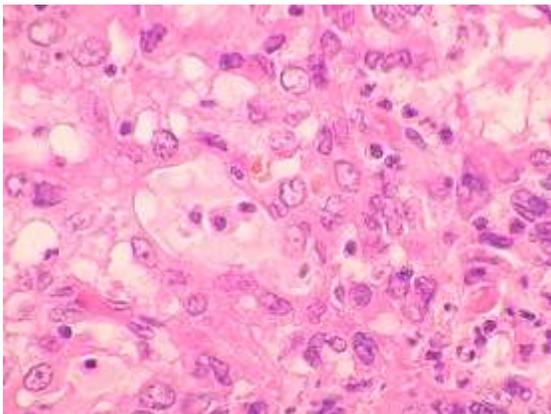
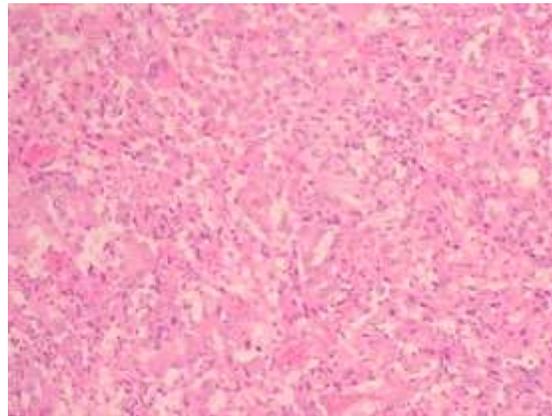
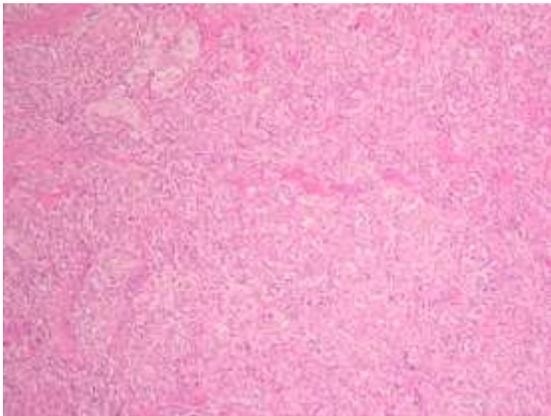
Hameed et al., 2007 reviewed the literature and found only 6 pancreatic carcinomas with hepatoid differentiation (1). It is of interest that some of these tumors were ductal carcinomas, some were pure hepatocellular carcinomas and in some tumors the hepatoid component originated in an endocrine insular neoplasms. Endocrine pancreatic tumors showing hepatoid differentiation had a somewhat better prognosis than those originating in adenocarcinomas, or those presenting as pure hepatocellular carcinomas.

For pathologists it is important to recognize extrahepatic adenocarcinomas with hepatoid differentiation for the following reasons:

- To realize that hepatoid differentiation can occur in extrahepatic tumors and not to mistake such tumors for metastases of hepatocellular carcinoma.
- To remember that AFP is not only produced by hepatocellular carcinoma but also by extrahepatic adenocarcinomas showing hepatoid differentiation.
- To notify the clinician that this diagnosis has almost invariably a poor prognosis.

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Dominguez-Case1

(IC07-9375, IC08-822) Exp. 51345

Clinical History

A 37 year-old male was seen in 1998 with a Germ cell tumor of the mediastinum, he received neo-adjuvant cis-platinum based chemotherapy and the tumor was resected in 1999.

After 8 asymptomatic years he developed hemoptysis, imaging studies disclosed metastasis in lung, spleen, liver, and bone. He received additional chemotherapy and the lung tumor was excised.

Diagnosis: LUNG, METASTATIC TELANGIECTATIC OSTEOSARCOMA, ORIGINATED IN A MEDIASTINAL GERM CELL TUMOR.

Discussion.

Development of sarcomatous components (SC) in germ cell tumors (GCT) is an uncommon phenomenon that has been described in gonadal and extragonadal GCT mostly in the mediastinum.

When SC overgrows the original tumor may pose a diagnostic dilemma, and therapeutic problem because of resistance to the usual chemotherapy regimes.

Most GCT/SC appear in males, usually in an advanced clinical stage and have a dismal prognosis, especially in mediastinal location. The SC portends more aggressive behaviour and have the characteristics of an independent tumor.

Most GCT with SC have a component of teratoma but any GCT may develop SC. The most frequent SC is rhabdomyosarcoma and angiosarcoma but other types of sarcoma have been described.

The SC may be present in the primary tumor, in the recurrences and in metastasis, or may appear only at the metastatic site. The histological type of sarcoma may be the same in both sites or change the phenotype in the metastasis, perhaps representing a de-differentiation phenomenon.

In the present case the primary tumor had extensive areas of angiosarcoma (low grade) and a single microscopic focus of osteosarcoma.

The pathogenesis for the development of SC is unclear, theories by several authors that have been published in the past include: 1) Dedifferentiation phenomenon, similar to the transformation of certain tumors like liposarcoma and chondrosarcoma of soft tissue. 2) Malignant transformation of certain components of teratoma. 3) Arousal from totipotential primitive germ cells. 4) Transformation of the blastematos stroma (magma reticularis) of YST.

In the pulmonary metastasis the only component is osteosarcoma with features of aneurismal bone cyst as occurs in tumors arising in the bones (telangiectatic osteosarcoma), this kind of tumor in a lung metastasis has not been described in the literature.

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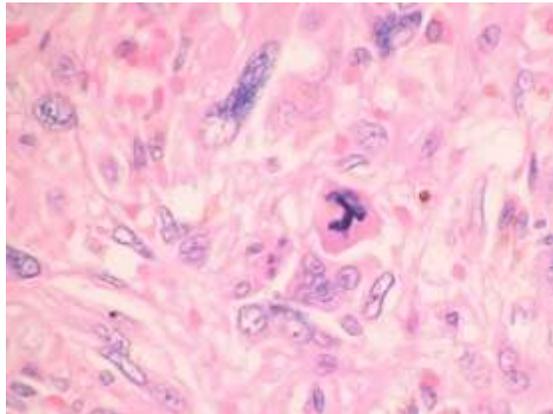
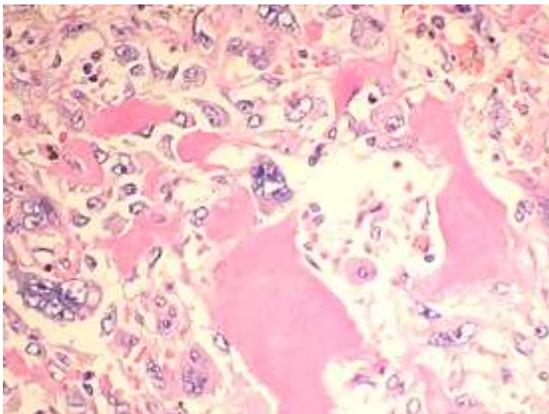
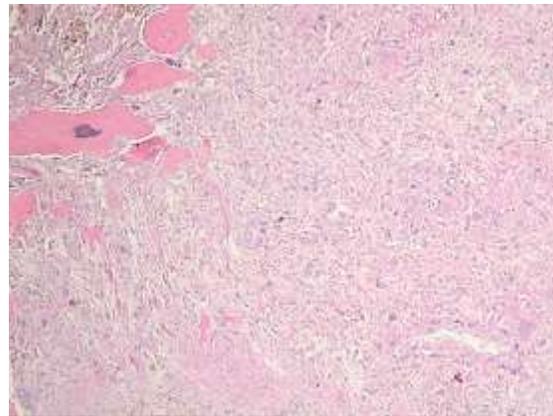
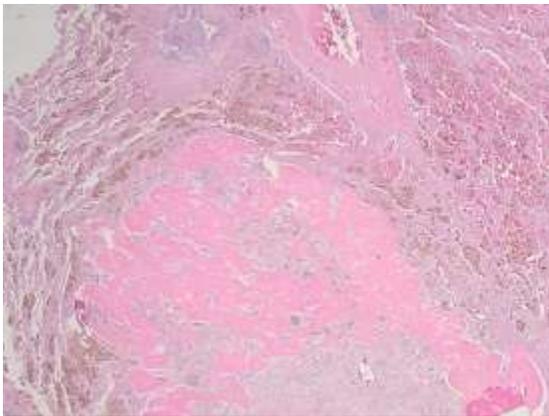
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Dominguez -Case 2
SJ08-300

Clinical history.

A 27 year-old male was admitted with chest pain and shortness of breath, on physical examination there was jugular ingurgitation and other signs of superior vena cava syndrome. Image studies revealed a large mediastinal mass. Lymph nodes at the neck base were palpated and excision of one of these nodes was done.

Histological findings.

Proliferation of oval to spindle cells in a vague storiform pattern forming nodules surrounded by fibrosis bands. The cells have large nucleus with delicate membrane and small nucleolus, the cytoplasm is pale and the cell borders imprecise. A population of reactive cells including B lymphocytes, T lymphocytes and many eosinophiles is mixed with de neoplastic cells.

Immunohistochemistry.

The cells are negative for: CD45, vimentin, cytokeratin, EMA, CD45, S100, CD20, CD3, CD45RO, CD21, CD68. They were positive for CD35 only.

Diagnosis: FOLLICULAR DENDRITIC CELL SARCOMA OF THE ANTERIOR MEDIASTINUM.**Discussion.**

In 1986 Monda et al. described four patients with primary lymph node tumors showing differentiation towards follicular dendritic cells (FDC), all four cases were misdiagnosed as lymphoma, metastatic malignant fibrous histiocytoma, and metastatic hemangiopericytoma. After this original description several case reports of "follicular dendritic cell tumors" were published until two larger series appeared: one with 13 cases by Perez-Ordoñez et al in 1996, and the other with 17 cases reviewed by Chan et al. in 1997 who considered it as a low-grade sarcoma, and proposed the name of follicular dendritic cell sarcoma (FDCS). Despite the fact that the original description was published more than a decade ago, FDCS is still considered as a new entity, frequently misdiagnosed because of its diverse histological patterns.

Reactive proliferations of FDCs are found in several benign conditions, such as reactive follicular hyperplasia, progressive transformation of germinal centers, hyaline-vascular Castleman's disease (HVCD), Kimura's disease, and HIV-associated lymphadenopathy. Reactive proliferation of FDCs have been also associated to some neoplasias, like follicular lymphoma, mantle cell lymphoma, angioimmunoblastic T-cell lymphoma, and Hodgkin's lymphomas [4,9].

A proportion of FDCS grow simultaneously with HVCD, while in others the latter condition precedes the tumor for many years. In HVCD there is diffuse and nodular proliferation of atypical FDCs in the interfollicular region, suggesting a pathogenic relationship between both diseases, there is spectrum that starts in reactive proliferation, evolves to dysplasia and ends in neoplasia of FDCs [3,4,19-21]. Chan et al [19] documented these changes by sequential biopsies showing progressive FDCs proliferation in the setting of HVCD. FDCs proliferation was observed initially limited to the follicles followed by overgrowth in the interfollicular areas, and finally evolved into a FDCS. This hyperplasia-dysplasia-neoplasia sequence is also favored by the findings of Pauwels et al [22], who demonstrated clonal karyotypic abnormality in stromal elements in a case of HVCD in absence of FDCS. More recently, clonal proliferation of FDC has been confirmed by Cokelaere and coworkers [23], who studied a case of HVCD, and demonstrated a clonal cytogenetic aberration involving the long arm of chromosome 12, with rearrangement of the High Mobility Group protein I-C (HMGIC) gene in CD21-positive cells. This gene has been implicated in mesenchymal tumorigenesis, providing a molecular pathway explaining stromal overgrowths and stromal neoplasms in HVCD. In our three cases HVCD was ruled out on clinical and histological grounds.

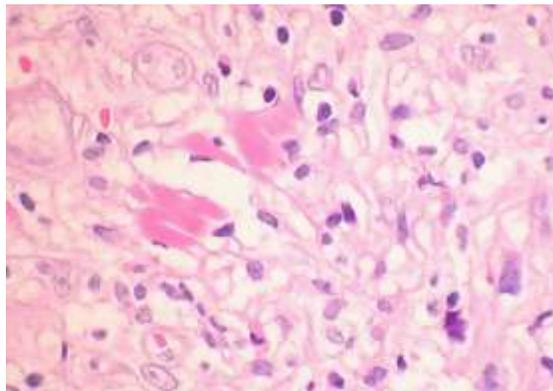
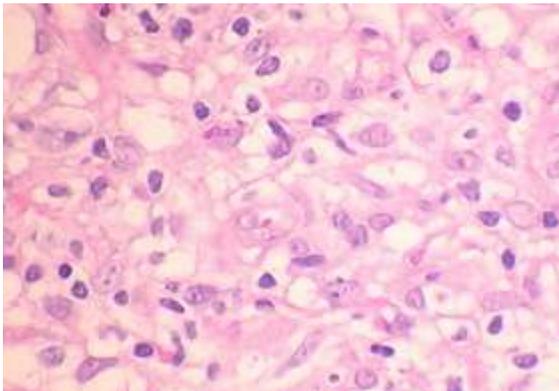
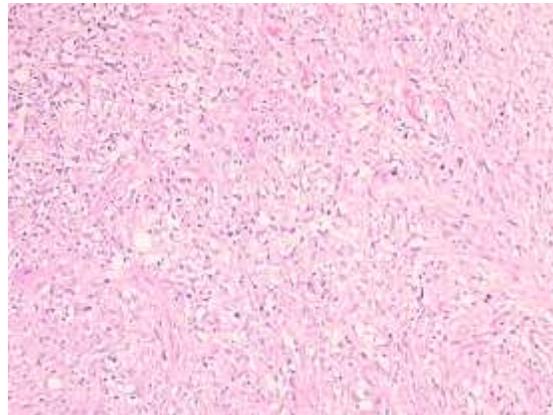
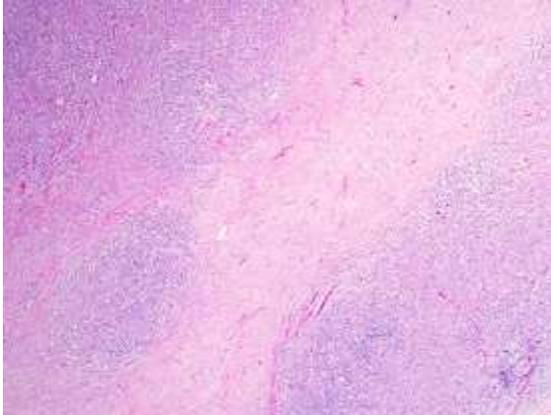
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**GORAN ELMBERGER,
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Elmberger- Case 1 (080219)

Clinical history:

70 year old woman with long-standing problems with fatigue and multiple skeletal fractures. A hypophosphatemic osteomalacia was diagnosed and after extensive evaluation finally an increased serum level of fibroblast growth factor 23 (FGF-23) was detected on selective catheterization of left jugular vein. MR and CT then revealed a 45 mm sized tumor in left ethmoid sinus with an intracranial component. Patient developed epistaxis and was approached with a left lateral rhinotomy in attempt to resect the intrasinusoidal part of the tumor.

Morphological findings:

The sections revealed a subepithelial infiltrative soft tissue tumor that was well-delineated but not encapsulated. Higher power showed a spindle cell tumor with varying cellularity. Occasional cells showed a more rounded "glomoid" appearance. The nuclear grade was generally low with a discrete chromatin pattern and minimal nucleoli. Nuclear size and shape were focally somewhat pleomorphic interpreted as a "symplastic" feature. Some cells demonstrated prominent intranuclear pseudonucleoli. Occasional cells showed pseudosignetringcell-like features suggesting local production rather than metastatic deposition of calcified stroma. Mitotic activity was minimal (<1/10HPF) and no necrosis was demonstrated. Generally, the tumor cells were not arranged in a specific pattern. Some sections showed a thin shell of osteoid – like material surrounding tumor growth. Woven bone was not identified. The intrinsic microvasculature was very rich with vessels ranging from capillary-sized hemangioma like areas to thicker walled myxoid - myopericytoid and HPC-like areas in other parts of the tumor. Classical HPC staghorn branching pattern was not typically identified. Some small vessels contain fibrin thrombi. Widespread haemorrhage with hemosiderin deposition was also documented. The stroma revealed the most characteristic deposition of a rich myxoid to myxochondroid partly hyalinized matrix with sometimes confluent amyloid-like pattern. The matrix was not heavily calcified at the light microscopical level and osteoclast-like reaction was typically not seen.. Microcystic stromal change was focally present. Multiple foci of mature fat were present and those areas appeared to represent adipose differentiation within the tumor rather than submucosal fat.

Result of ancillary studies

Routine histochemistry showed no signs of amyloid (Kongo-) or heavy calcium deposition (von Kossa-).

Immunohistochemistry revealed positive staining for vimentin and neuroendocrine markers; NSE+, SV2 -/+, synaptophysin +/-, CD56 +, chromogranin A -.MNF116-, desmin-, actin-, actin SM-, osteonectin-, CD30-, CD34-, CD68-, serotonin-, PP-, F XIIIa-. Proliferation fraction < 2% (MIB-1).

Ultrastructural studies showed polygonal tumor cells with highly irregular indented nuclei. A rich cytoplasm with interdigitating pseudopodia-like processes was presents. Some suggestive NE dense core granules were noted. The background revealed a granular matrix with sparse collagen fibrils. Multilamellated myelin-like bodies were seen. Dilated RER with dark even dense granular material were characteristically seen.

Diagnosis: PHOSPHATURIC MESENCHYMAL TUMOR MIXED CONNECTIVE TISSUE VARIANT (PMT-MCT)

Follow-up:

Serum levels of FGF-13 dropped from 2092 to 270 pg/ml after operation. Residual intracranial tumor under consideration for gamma knife radiotherapy.

Discussion

Oncogenic osteomalacia (OO) is a paraneoplastic syndrome that is usually induced by some bone or soft tissue tumors. Among the soft tissue tumors phosphaturic mesenchymal tumor of mixed connective tissue type (PMT-MCT) seems to be the most common lesion inducing this symptom. Patients generally present with bone pain and osteomalacia due to a phosphateuric factor secreted by the tumor and acting on the kidney tubules , now known to be fibroblast growth factor 23 (FGF-23). The OO can precede tumor dx by up to 20 years. Localization of the tumor causing secreting the FGF-23 can sometimes be very difficult. Octreotide

scintigraphy, high-resolution CT and PET can sometimes be of value. In this case only selective venous catheterization with biochemical analyses could help to indicate the location of the tumor to the ENT in our present case. The tumor is distinctly rare and today roughly 50 cases have been published. Many of the PMT-MCT had been previously diagnosed as other tumors like hemangiopericytoma, osteosarcoma, giant cell tumors, hemangioma, osteoblastoma and others. Tumor progression to high grade sarcoma after several recurrences over a 16 year period has been noted. Expression of FGF-23 were seen by the majority of the tumors (17/21) with IHC. In one large series approximately 10% of the tumors were considered malignant on a histological basis. 1/32 showed biological evidence for malignancy with pulmonary metastases. Tumors were generally located to soft tissue or bone of the extremities but localization to groin, deltoid, abdominal wall and the vertebra have also been documented. H&N is the second most common location of these tumors with cases localized to the temporal bone, skull, maxillary sinus, ethmoid sinus, nose, mandible and pharynx described. Retroperitoneum and parenchymal organs have not been described as sites of origin. Most cases occur in middle-aged individuals but cases have been reported from 3-73 years age. No sex predilection has been reported.

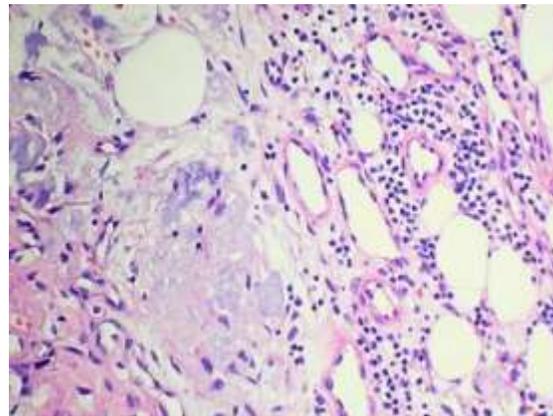
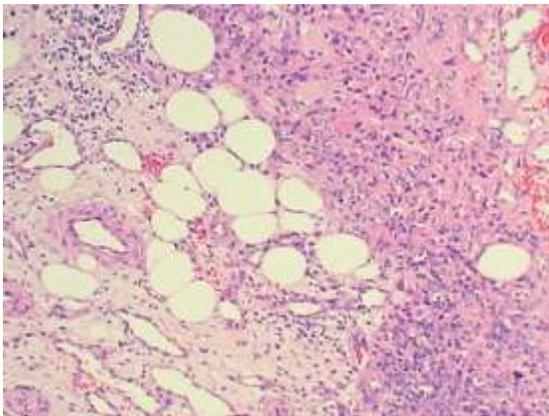
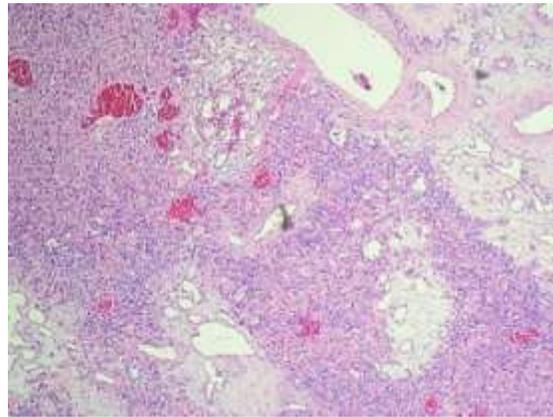
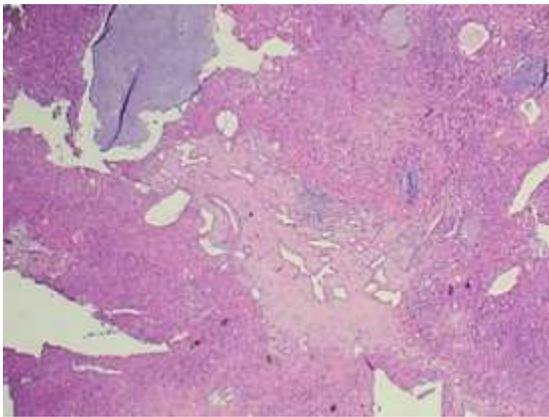
Differential diagnosis of PMTMCT is broad depending on site and predominant histopathological features. Typical soft tissue HPC and glomangiopericytoma of SN tract have often been preliminary diagnosed. Staghorn branching vessels and CD 34 + and the lack of distinctive matrix helps differentiating. Chondromas of soft parts, giant cell tumors, mesenchymal chondrosarcomas and osteosarcomas are other entities that on occasion can be difficult to sort out. The juxtaposition of typical PMTMCT to sarcomatous foci may allow distinction of malignant PMTMCT from other pleomorphic sarcomas such as MFH or leiomyosarcoma.

The present case seems to represent a well documented and fairly typical case of PMTMCT. The presentation of neuroendocrine differentiation by IHC and EM seems to be not previously reported and raises the possibility of PMTMCT being a neurally or possible neuroendocrine differentiated tumor. Further studies confirming this observation could be of interest. Recognition of PMTMCT is critical since complete removal of tumor cures the OO.¹⁻¹⁵

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Elmberger-Case 2 (080219)

Clinical history: 59 year old female patient resected for right sided 7 mm sized invasive lobular breast cancer Elston G II (3 + 2 + 1 = 6) with associated LCIS 1993. ER positive. Axillary dissection with 12 nodes without metastasis. Radiotherapy.

2002 tumor metastases in 2 of 15 axillary nodes. Maximal metastasis size 18 mm. ER positive. PgR negative. Cyclin A 8%. Periglandular growth. Adjuvant therapy FEC and Arimidex. Also suffering from chronic active hepatitis and fibromyalgia. Smoker. II para. Menopause at 50. No hormonal replacement.

Six months history of gradually increasing tumor in lower abdomen. CT reveals a 13 x 12 cm sized ovarian tumor left side. CA125 = 36. Patient underwent hysterectomy, bilateral salpingo oophorectomy and omental resection.

Morphological findings: Left ovary with tumor weighing 1177 g measuring 10x6x4 cm. Right ovary mildly enlarged measuring 3x3x3 cm. Uterus, uterine tubes and omental tissues normal. Grossly both ovaries revealed an irregular and nodular cut surface without cysts. Microscopical examination of both ovaries revealed a diffuse-solid tumor growth with a dominant insular –alveolar pattern. In other areas linear parallel cords of one to two cells dominated. At the tumor periphery a minor duct forming component was seen. No targetoid formations noted. Some sections showed clearly infiltration of residual ovarian cortex where the tumor cells closely approached but not disrupted the lining hyperplastic mesothelial cell lining. At the tumor centre degenerative edematous change and focal necrosis were seen. In high-power the tumor cells were of intermediate size with an eccentrically located nucleus. Nuclear features were rather bland but with distinct eosinophilic nucleoli. The cytoplasm was somewhat granular with frequent intracytoplasmic mucin filled neolumina. Occasionally, a signet ring cell-like character was noted. The stroma was generally sparse with collagenous character. No light microscopical evidence of stromal luteinization. Sections from uterus, tubes and omentum without tumor.

Review of previous slides from the breast cancer including lymph node metastases revealed a similar tumor morphology.

Result of ancillary studies: PAS+D highlighted positive mucinous material within some tumor cells. MNF 116 +, CK 7 +, CK 20 -, ER +, PGR +/-, mammaglobin +, GCDFP 15 +, CEA +/-, CB11 -, A485 -, E-Cadherin -, CDX2 -, Synaptophysin -, Chromogranin A -, SV2 -, villin -, WT-1 +, CA125 -. Proliferation rate 15% (MIB-1). Inhibin α indicate reactive hyperplasia of interstitial stromal cells.

Diagnosis: METASTASIS OF LOBULAR BREAST CARCINOMA TO THE OVARIES - 15 YEARS LATENCY.

Follow-up: 4 months post-op ok.

Discussion: Ovarian cancers constitute about 2.3% of all cancers. Cancer of the ovary constitutes about 25% of the gynaecological cancers. Up to 7% of the ovarian cancers, however, comprise metastases from various other locations. Tumors may spread to the ovary via a blood-borne or lymphatic route, transperitoneally or by direct extension. About 40% of ovarian secondary tumors originate from the colon and the second most common source of ovarian metastasis is the breast. Although the histological pattern is often suggestive of a metastasis from the breast, the growth pattern of the tumour can mimic that of a primary carcinoma of the ovary. Moreover, the history of a prior tumour in another organ may be remote or not known. Because of the different therapeutic approaches to metastatic carcinomas from colorectum, and breast, it is important to discriminate between metastases of these tumours.

Features favouring a metastatic rather than a primary ovarian neoplasm include bilaterality, a nodular pattern of ovarian involvement, an infiltrative pattern of stromal invasion, microscopic surface deposits of tumour, marked lymphovascular invasion (especially in the hilum and outside the ovary), single cell infiltration and signet ring forms, cells floating in mucin and variation in growth pattern from one nodule to another.

Patients with breast cancer are at increased risk of developing ovarian cancer and vice versa. This is especially so in the subset of patients with a hereditary predisposition to breast and ovarian cancer because of BRCA1 or BRCA2 mutations. Ovarian involvement is seen at autopsy in about 10% of cases of breast cancer and in therapeutic oophorectomy specimens in about half the cases but practical diagnostic issues in these circumstances are virtually nonexistent. Given this propensity for ovarian spread, it is perhaps surprising that symptomatic ovarian spread and issues in differential diagnosis with primary ovarian tumors have received such limited attention.

Breast cancer metastatic to the ovary may be of ductal or lobular type. Although ductal carcinoma is the most common type of ovarian metastasis, lobular carcinoma is proportionally more likely to spread to the ovary.

Ovarian metastasis from the breast tends to be bilateral in most cases. The ovaries are usually enlarged, but only mildly so, with a smooth surface and a bosselated nodular appearance. Lobular carcinoma within the ovary may be relatively subtle and not obvious at scanning magnification. However, high-power examination usually reveals the characteristic growth patterns, including indian-file arrangements, and the characteristic cytological features including intracytoplasmic lumina. Signet ring cells may be present.

Immunohistochemically, metastatic breast carcinoma is usually positive with CK7 and negative with CK20. Oestrogen receptor (ER) and progesterone receptor (PR) are often positive. This may be useful both in diagnosis and in determining the likely response to adjuvant therapy. Hormone receptor positivity is, of course, not specific for a metastatic breast cancer since many primary ovarian and other gynaecological malignancies are commonly positive. Gross cystic disease fluid protein-15, CEA, mammoglobin and HER2 is also commonly positive, but again these markers are not specific for a breast primary. Negative staining for WT-1 and CA-125 is of supportive value. In the end a multidisciplinary approach integrating clinical, radiological, serological and pathological features is invaluable in problematic cases.

Differential diagnosis

Patients with breast cancer have an increased frequency of ovarian carcinoma such that an ovarian cancer in a patient with a history of breast cancer is statistically more likely to be a new ovarian primary. The odds in favour an ovarian primary in this situation were as much as 10 to 1. The differential diagnosis of metastatic breast carcinoma is diverse, a reflection of the overlap of the patterns that may be seen with those of other tumors. Predominantly glandular tumors may suggest primary ovarian surface epithelial tumors, particularly those of endometrioid type. An insular pattern may mimic a carcinoid tumor, and a diffuse pattern or cords may suggest such diverse neoplasms as lymphoma, granulocytic sarcoma, undifferentiated carcinoma, and granulosa cell tumor.

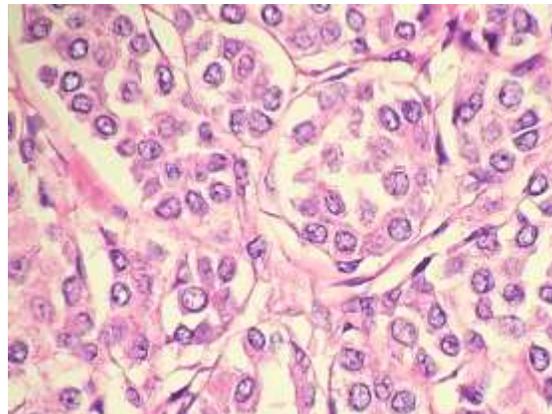
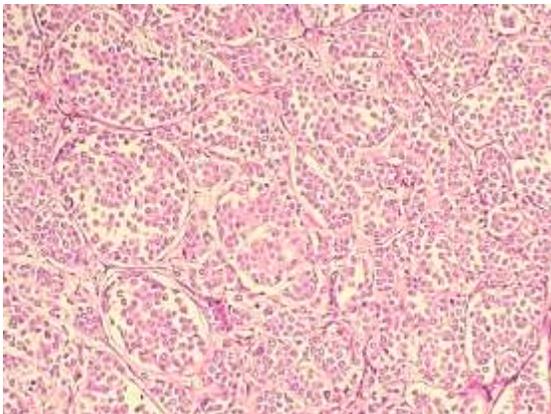
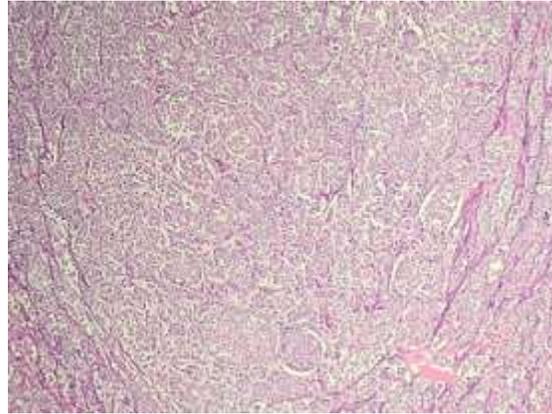
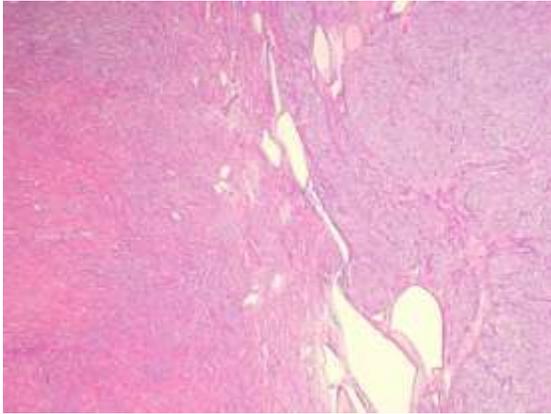
The present tumor show many similarities with Krukenberg tumor but the content of classical signet-ring cells fall below the arbitrarily defined 10% cut-off level for applying that diagnosis. Evenso the differential includes other sources of mucinous-signet-ring cell neoplasms such as tumors in intestines, appendix, stomach, pancreas, biliary system.

1-12

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Falconieri-Case 1

Case history

An 81 year-old Caucasian woman sought medical advice because of lower abdomen pain and anemia. Physical examination revealed an enlarged, fixed, and tender uterus: a biopsy of the endometrium was positive for a malignant, spindle cell neoplasm. A total hysterectomy with bilateral salpingo-oophorectomy was carried out. An exploratory laparotomy revealed several firm nodules scattered within the peritoneal surface. No further therapy was administered. The patient died 6 months following the operation with evidence of diffuse, intraabdominal neoplastic spread.

Pathologic features.

The uterus weighed 200 g and measured 8 x 7 x 4.5 cm. The cut surface was vaguely nodular and fasciculated. The endometrial cavity was filled with hemorrhagic material. The cervix and adnexa were unremarkable. Histologic examination showed a malignant tumor made up of haphazardly arranged cell fascicles diffusely infiltrating the whole thickness of the myometrium. Tumor cells were mitotically active, either epithelioid or spindle, and sometimes displayed optically clear spaces within the cytoplasm. Scattered areas of coagulative necrosis were recognized as well. There was microscopic evidence of neoplastic infiltration of the cervix, fallopian tubes and ovaries. An omental biopsy specimen was positive for malignancy. A cytologic examination of peritoneal lavage fluid was positive for malignant cells. Tumor cells were positive for CD31 (Figure 6A), Fli-1, and factor VIII related antigen. Keratins and muscle markers, including actins, desmin and H-caldesmon, were negative.

Diagnosis: ANGIOSARCOMA OF UTERUS

Discussion

Most angiosarcoma are tumors of the scalp or somatic soft tissues. In visceral locations angiosarcomas are observed sporadically in several organs including the lung, pleura, breast and liver. Uterine angiosarcomas appear to be very rare and only 10 cases investigated by means of immunohistochemistry or electron microscopy have been reported in the medical literature of the past 20 years.

The majority of patients were postmenopausal (age range 49-76 years; mean age 65) and the clinical history was usually rapid with a poor and rapid outcome. Prognostic factors cannot be assessed given the paucity of observation; however, in one of the recent cases reported by Schammel and Tavassoli the patient was alive more than 3 years following the diagnosis of angiosarcoma, apparently the only case of uterine angiosarcoma exhibiting a polypoid/exophytic rather than a diffuse neoplastic infiltration of the myometrium. It is therefore possible, as claimed by the authors, that the endocavitary growth pattern might be viewed as a favorable prognostic indicator.

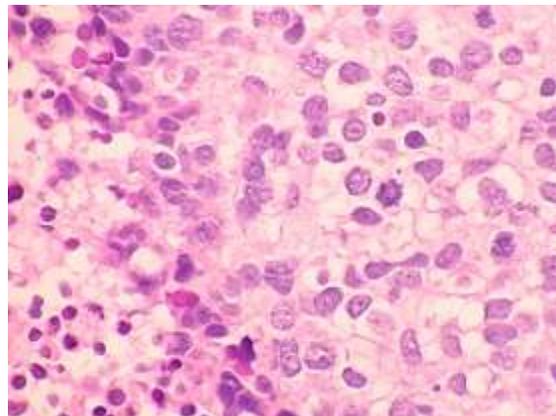
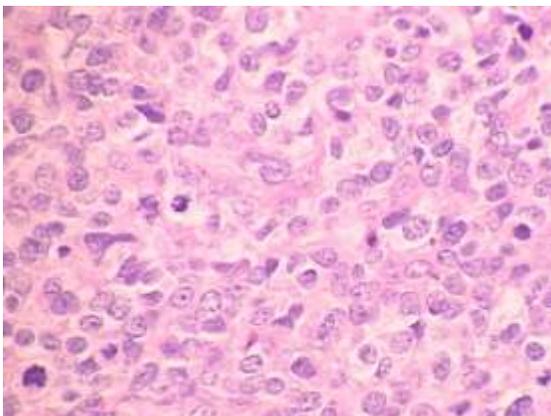
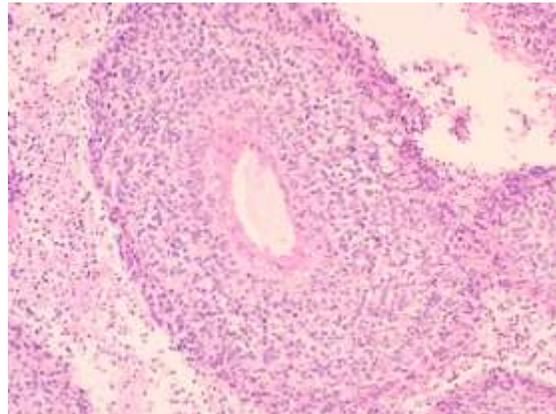
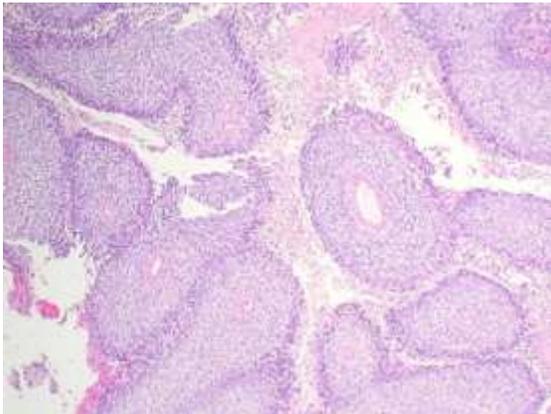
The microscopic recognition of angiosarcoma arising in the uterus may pose diagnostic problems especially when the classic "freely anastomosing vascular channels" customarily described in better differentiated lesions are lacking or when the tumor, like one detailed here, is composed of epithelioid, spindle cells with minimal features of endothelial derivation. In these cases, the tumor can be rubricated under a different heading and the possibility of a leiomyosarcoma entertained because of the fascicular arrangement and spindly quality of cells. However, leiomyosarcoma usually presents with nodular masses rather than a wide infiltration of myometrium. Microscopically, tumor fascicles tend to retain an intersecting pattern at 90°, like their benign counterpart, and the nuclei have blunt ends and are cigar shaped. A careful evaluation of fine cytologic details reveals a fibrillary quality of the leiomyosarcoma cells. Immunohistochemical staining for muscle markers, including desmin, actins, and H-caldesmon is expected in leiomyosarcoma whereas angiosarcoma are most often positive for endothelial cell antigens such as CD31, factor VIII-related antigen, and Fli-1. Investigation by electron microscopy also proves useful if Weibel-Palade bodies can be demonstrated. A keratin-negative sarcomatoid carcinoma is also difficult to rule out on a morphologic basis only. However, strong immunoreaction for endothelial markers and negativity for EMA along with focal, albeit unequivocal, microscopic features of abortive endothelial differentiation, are helpful clues.

The cause of angiosarcoma in this uncommon location remains largely speculative. However, 4 patients had concurrent uterine leiomyomas or leiomyomatosis, and in at least 2 cases, there was an intimate association between the 2 lesions, suggesting that the increased vascular proliferation secondary to a mechanical, pressure effect of adjacent leiomyomata might have induced the endothelial neoplastic transformation. On the

other hand, the role of alternative factors claimed for some visceral angiosarcomas, including radio- or chemotherapy (in the case of breast or liver) or foreign bodies (bone and soft tissue) appears questionable.

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Falconieri-Case 2

Clinical history.

An 83 year-old man was admitted to the hospital complaining of shortness of breath. Instrumental investigations including a MRI uncovered a 8 cm mass of the anterior mediastium. Thoracotomy and mass biopsy were carried out.

Pathologic features. Several fragments of grey-tan tissue were received. Microscopically they were composed of spindle cells haphazardly arranged in fascicles. Areas of coagulative necrosis were present. Tumor cell population was monotonous and enmeshed in a scant ground substance. Mitotic activity was brisk. Immunohistochemistry was positive for bcl2, vimentin, CD56, CD99 and focally for keratins. Desmin, S100 protein, actins, c-kit were negative.

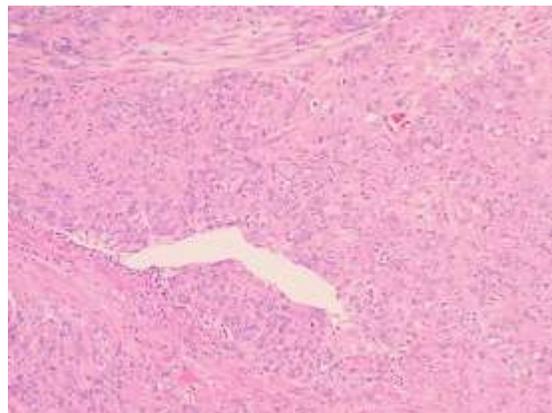
Diagnosis: SPINDLE CELL TUMOR CONSISTENT WITH MONOPHASIC SYNOVIAL SARCOMA

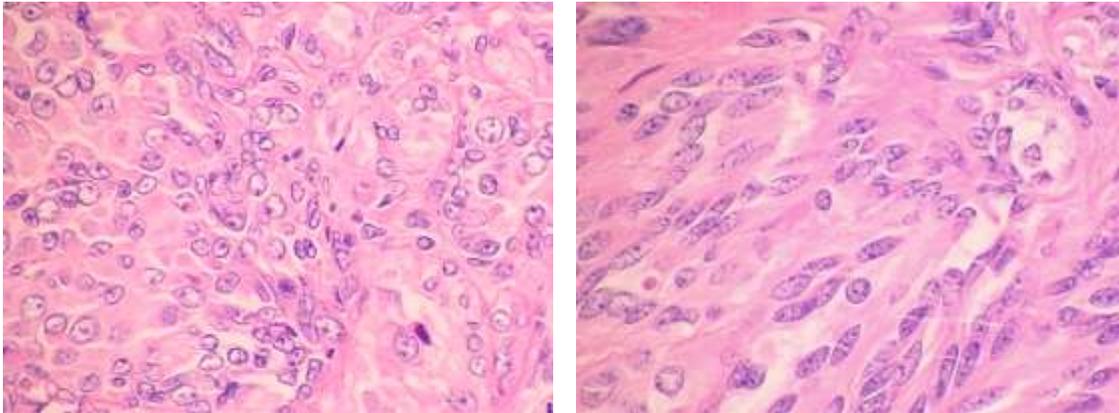
Discussion.

Primary synovial sarcoma of the mediastinum has recently been described in independent series. Although microscopically identical to synovial sarcoma arising in the limb soft tissues, mediastinal lesions may be confused with many, intrathoracic spindle-cell lesions. In addition, mediastinal synovial sarcomas appear to occur in younger patients and to pursue a more aggressive course. MRI often reveals heterogeneous "bright-dark-gray" (or triple sign) masses with a lobulated border. MRI may reveal heterogeneous "bright-dark-gray" (or triple sign) masses with a lobulated border. Infiltration of the adjacent structures is common and makes radical excision of the tumor difficult. Microscopically, synovial sarcoma of the mediastinum may be either biphasic or monophasic. *Biphasic* tumors features gland-like spaces admixed with spindle, fibroblast-like cells; occasionally, the glandular structures may include pseudopapillary structures or intraluminal amorphous material. *Monophasic spindle-cell* tumors are more frequent. They are composed of cellular tumor arranged in whorls or fascicles. The ground substance may be inconspicuous. Tumor cells have tapered-end nuclei and a moderate amount of stainable cytoplasm. Mitotic figures are usually present. Synovial sarcoma is often associated with the t(x:18) translocation product. Immunohistochemistry is often positive for keratins (especially keratins 7 and 19) and EMA; however expression of epithelial markers may be focal or absent, especially in spindle cell lesions. Bcl2 and CD99 are also frequently detected in synovial sarcoma. Because of this morphology and its non-specific immunohistochemical profile, monophasic spindle cell synovial sarcoma may be confused with other malignancies such as sarcomatoid carcinoma, spindle-cell mesothelioma, melanoma, and other spindle-cell sarcomas including malignant PNST. Cytogenetic investigations are of diagnostic help in poorly differentiated cases of synovial sarcoma. Clues to synovial sarcoma are a monotonous population of spindle cells, lack of significant cell pleomorphism, scant ground substance.

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- Hartel, P. H., J. C. Fanburg-Smith, A. A. Frazier, J. R. Galvin, J. H. Lichy, K. Shilo, and T. J. Franks. "Primary Pulmonary and Mediastinal Synovial Sarcoma: A Clinicopathologic Study of 60 Cases and Comparison with Five Prior Series." *Mod Pathol* 20, no. 7 (2007): 760-9.
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Falconieri-Case 2

Clinical history. A 72 year-old man was admitted to the hospital with history of a mass within the scrotum soft tissue stated to be present for “long” time.

Pathologic features.

A 5 cm mass was successfully resected. It was rubbery and glistening on cut surface with no area of necrosis or hemorrhage. Histologically, it featured a loose neoplasm made up of slender, fibroblastoid cells with scant cytoplasm and central tapered nuclei. No significant mitotic activity was noted. Tumor cells were arranged around variably sized vessels characterized by thickened walls, often incrustated with hyaline, pink material. Some lumina were almost totally thrombosed. The intervening stroma also featured scattered inflammatory cells and mast cells. Tumor cells were positive for CD34, CD99 and bcl2 and negative for S100, keratins, desmin, actins. Congo red stain for amyloid was negative.

Diagnosis: SPINDLE CELL RESEMBLING EARLY PLEOMORPHIC HYALINIZING TELEANGECTATIC TUMOR (PHAT-LIKE)

Discussion.

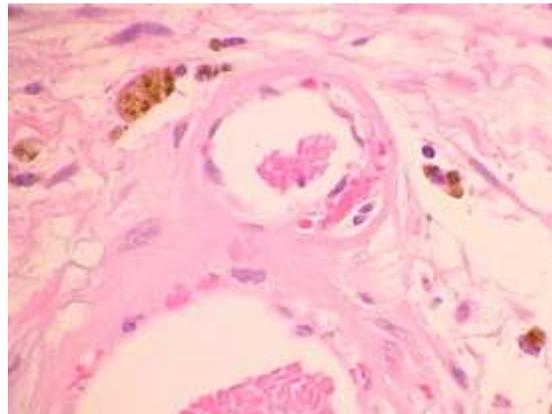
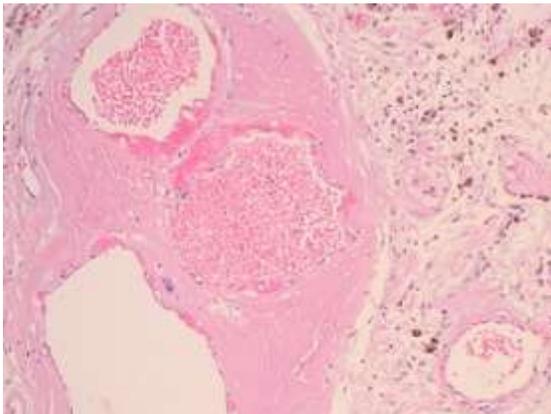
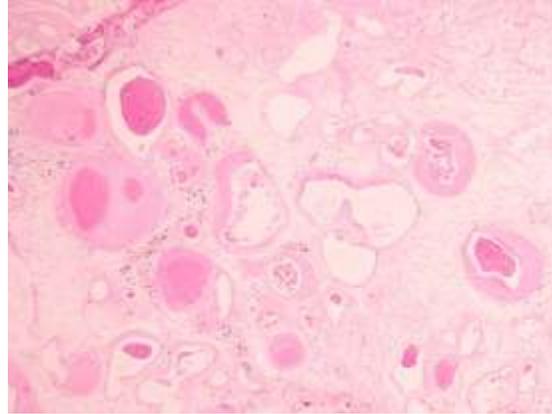
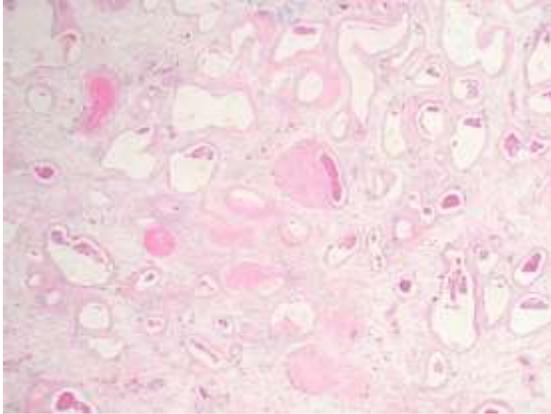
Superficial spindle cell tumors of soft parts include a number of microscopic entities; they are usually benign and can be correctly recognized as such based on available clinical information, gross inspection and evaluation of routinely stained tissue sections. Nevertheless rubrication within a precise tumor category may not be easy since these tumors shares several microscopic as well as immunophenotypic features. In the case at issue spindle cell lipoma-like cytomorphology and prominent vessels with rounded hyaline walls were the key features. The tumor also showed several superimposed degenerative changes such as fibrinoid alterations of the vessel walls, variable edema, and focal degenerative atypia. The differential diagnosis include spindle cell lipoma, schwannoma, with ancientoid changes; myxoid solitary fibrous tumor, dendritic angiomyxolipoma. Because of the extensive teleangiectatic pattern and scattered bizarre nuclear cells another option is early-PHAT, a lesion recently described by Folpe and Weiss. Cellular angiofibroma of the genital area, reported by Iwasa and Fletcher, may be characterized by prominent degenerative changes especially when affecting males an recapitulates several if not all of the microscopic features observed in this case.

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Falconieri-Case 3

Clinical history.

An 83 year-old man was admitted to the hospital complaining of shortness of breath. Instrumental investigations including a MRI uncovered a 8 cm mass of the anterior mediastium. Thoracotomy and mass biopsy were carried out.

Pathologic features. Several fragments of grey-tan tissue were received. Microscopically they were composed of spindle cells haphazardly arranged in fascicles. Areas of coagulative necrosis were present. Tumor cell population was monotonous and enmeshed in a scant ground substance. Mitotic activity was brisk. Immunohistochemistry was positive for bcl2, vimentin, CD56, CD99 and focally for keratins. Desmin, S100 protein, actins, c-kit were negative.

Diagnosis: SPINDLE CELL TUMOR CONSISTENT WITH MONOPHASIC SYNOVIAL SARCOMA

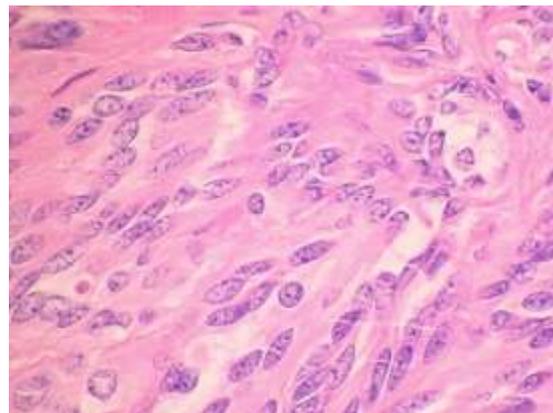
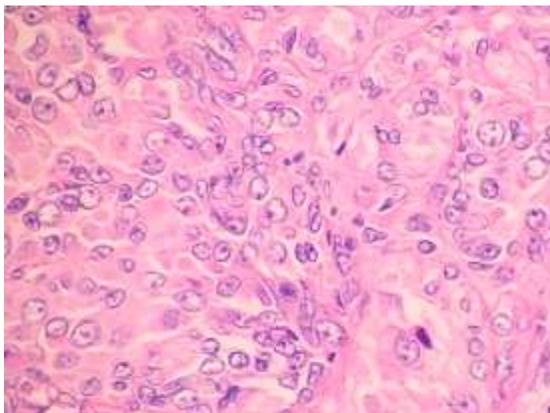
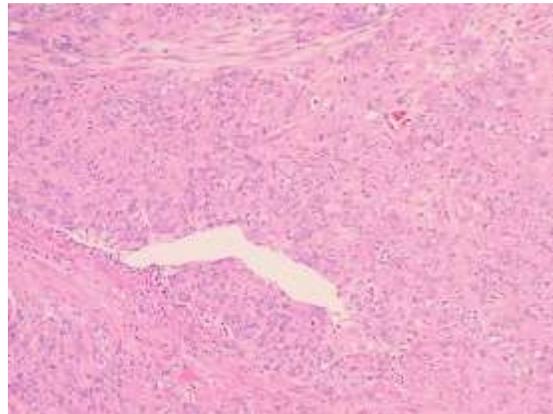
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Fukunaga- Case 1 (S05-2832)

Clinical history :

A37-year-old female (gravida 2, para 2) with a right ovarian tumor the patients presented with lower abdominal pain. Physical examination, CT and EMR indicated a right ovarian tumor. Abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymph node dissection were performed. Serum calcium levels were within normal range. The patient died of the spread disease 4 months after the surgery.

Macroscopic findings : The right ovary revealed a 15x9x8cm, yellowish white, soft solid tumor with prominent hemorrhage and necrosis. The left ovary showed 1cm solid tumor on the surface and there were numerous white nodules in the omentum.

Immunostaining : Some tumor cells arranged in follicles or nests showed CAM5.2, CK7 and EMA immunostaining. The tumor was uniformly negative for inhibin- alpha, calretinin, CD99, and LCA.

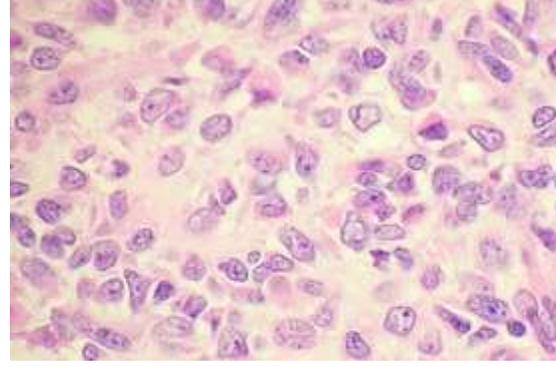
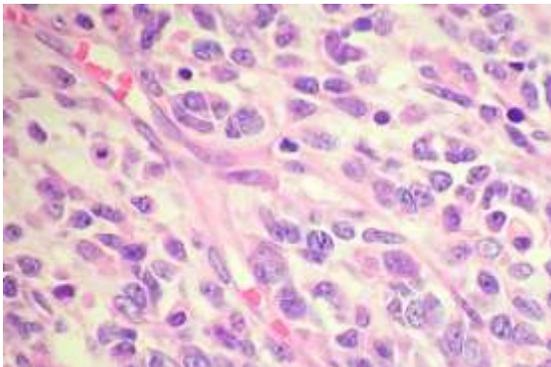
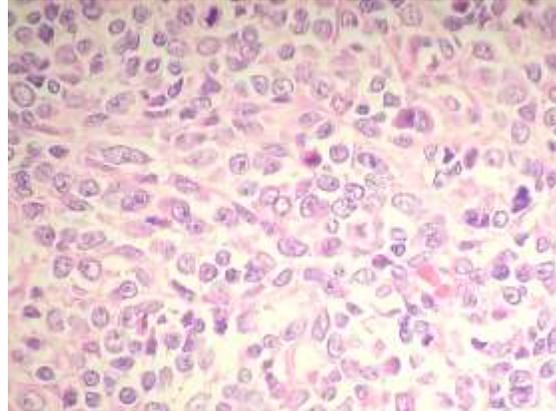
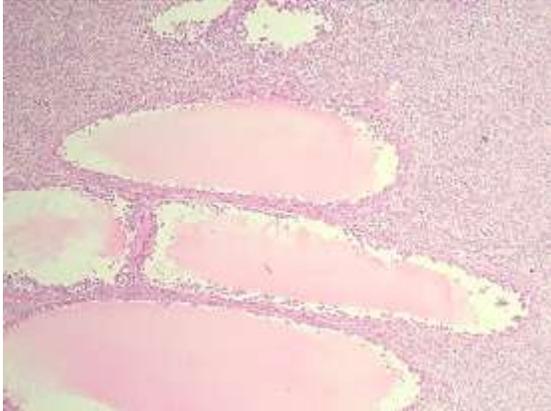
Diagnosis: : SMALL CELL CARCINOMA OF THE OVARY, HYPERCALCEMIC TYPE.

Discussion : The tumor was composed of a proliferation of small to medium-sized round cell in a solid sheet or follicular arrangement. Follicles contained PAS-positive proteinacious material. The tumor cells had hyperchromatic round or oval nuclei and moderate amount of cytoplasm. Atypia was moderate. The stroma was fibrous but inconspicuous. Tumor necrosis and hemorrhage was prominent. The mitotic activity was 20/10 HPF. The small nodules in the left ovary and omentum revealed the same histology of the right ovarian tumor. The immunohistochemical studies confirmed an epithelial nature. Electron microscopical examination failed to reveal specific features to identify the cell type of the tumor. The tumor cells had desmosomes, moderate amounts of mitochondria and dilated rough endoplasmic reticulum. No neurosecretory granules were identified. The patients with small cell carcinoma, hypercalcemic tumor have ranged from 14 months to 43 (mean, 24) years of age (1-6). Most patients present with signs and symptoms related to an abdominal or pelvic mass, but rarely the clinical presentation is related to the hypercalcemia. Approximately 66% of patients presented with hypercalcemia (2). Some studies have documented serologically the presence of parathyroid hormone-related protein (PTHrp). This type of ovarian carcinoma has a dismal prognosis. About 5% of the tumors have spread beyond the ovary at the time of laporatomy. The overall survival rate is approximately 16%. The tumors are almost always unilateral, usually large, solid, soft and white. An important feature that is seen in about 80% of the tumors is follicles that vary from small to large. There is a variant of "large cell type" in which large cells have eccentric nuclei and dense globular cytoplasm (5,6). This tumor is often confused with a granulosa cell tumor, adult type and the juvenile type (7, 8). Adult granulosa cell tumor is rare in the young. Small cell carcinoma has spread beyond the ovary at presentation, which would be unusual for either variant of granulosa cell tumor. In granulosa cell tumors, tumors are usually positive for inhibin-alpha and calretinin, but negative for EMA. These profiles are opposed to those of small cell carcinoma.

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Fukunaga-Case 2 (S03-4339)

History: A 32-year-old, gravida 0, para 0, Japanese woman presented with lower abdominal and left leg pain that had been present for 11 months. MRI revealed a 5-cm subserosal mass in the uterine fundus. Intraoperatively, a rubbery solid uterine mass attached to the left broad ligament was found and locally excised. The patient did not have the tuberous sclerosis complex. Fortunately, she gave a birth at 24 months postoperatively. The patient had no evidence of tumor at 31 months.

Immunohistochemical studies:

Vimentin, h-caldesmon, HMB45, alpha-smooth muscle actin: (+).
Desmin, HHF35, CAM5.2, EMA, S-100 protein, CD34, CD10, Melan A, synaptophysin, chromogranin A, GFAP, CD117: (-).

Diagnosis: PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA) OF THE UTERUS.

Histology and Comments:

Its preoperative diagnosis was a subserosal leiomyoma. A clinician asked me for an intraoperative consultation. He said that the lesion looked like 'a carcinoma' not a leiomyoma and it was soft and hemorrhagic. My frozen section diagnosis was 'epithelioid smooth muscle tumor, borderline, most likely'

Grossly, the mass was fragmented and measured 5.0cm in aggregates. Its sectioned surface was tan-pink, unencapsulated, rubbery, and solid with foci of hemorrhage and necrosis. Microscopically, the tumor was composed of round to polygonal cells with a round nuclei and abundant clear to slightly eosinophilic cytoplasm and the cells were arranged in short fascicles and focally in a perivascular location. No melanosomes or premelanosomes were found in EM studies. Because of the presence of coagulative necrosis, infiltrative growth and the size of the mass 5cm, it is considered that it is a PEComa with an uncertain malignancy potential (1, 2).

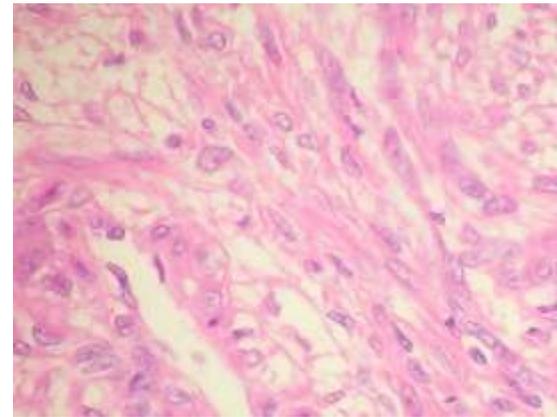
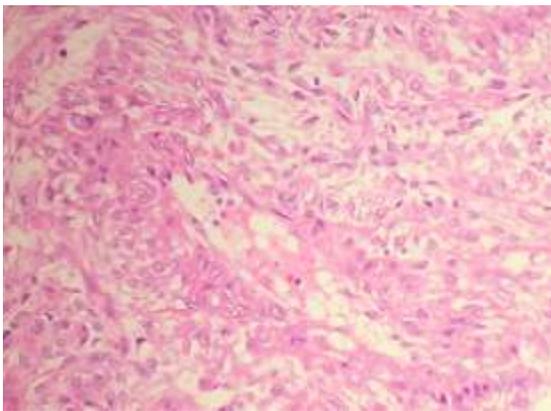
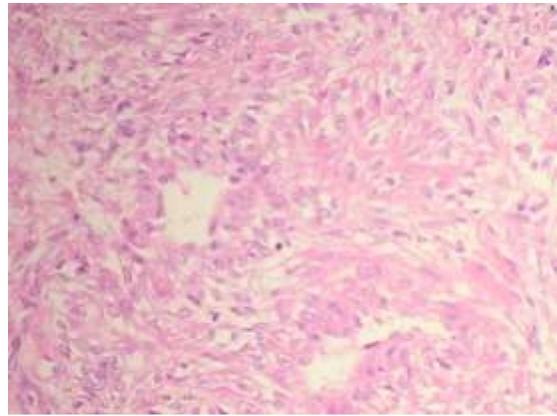
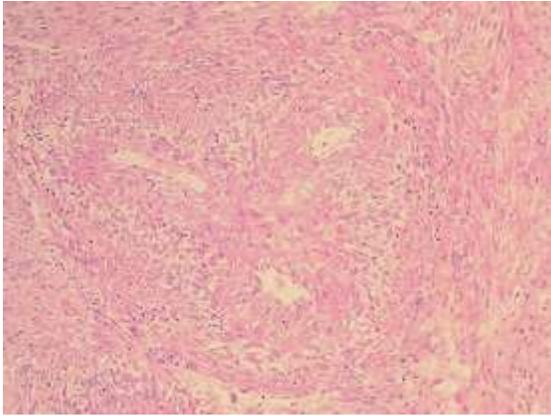
The PEComa family of tumors includes angiomyolipoma, lymphangiomyomatosis, clear cell sugar tumor of the lung, and clear cell myomelanocytic tumor of the falciiform ligament/ligamentum teres. There have been only 26 reported cases of uterine PEComa (1-7). The histogenesis of this family of tumor has been controversial. It has been proposed to be of melanocytic, smooth muscle, pericytic or perivascular epithelioid cell origin. Basic characteristic features of perivascular epithelioid cells are immunoprofiles of HMB45 (+)/ S-100 protein (-) or (+) (rarely) and abundant clear to eosinophilic granular cytoplasm. Other features include expression of the other melanoma-associated antigen Melan A, coexpression of muscle markers without cytokeratin expression, and the presence of melanosomes or premelanosomes.

There is also controversy about relationship between PEComa and epithelioid leiomyosarcoma with clear cells or HMB45 positivity (8). HMB45 immunoreactivity has been noted in uterine tumors, including leiomyomas, epithelioid leiomyosarcomas, stromal tumors, and even in normal myometrium (7). However, generally its expression was focal and weak. Silva et al. (8) asserted that some epithelioid cells in uterine smooth muscle tumors most likely undergo clear cell changes and become positive for HMB45 and argued that the concept of PEComa still needs some refinement. I consider the possible origin of primitive mesenchymal cells that have ability of differentiating to both smooth muscle and HMB45-positive perivascular epithelioid cells. Its degree of differentiation can vary from case to case. Comprehensive studies of uterine PEComas are needed to ascertain whether they represent a distinct entity or an unusual variant of epithelioid smooth muscle tumors exhibiting HMB45 positivity.

Folpe et al. (1) have classified PEComa into "benign", "uncertain malignant potential" and "malignant" categories based on tumor size (> 5cm); infiltrative margins; high grade nuclear atypia and cellularity; mitotic index (>1 MF/50 HPF); necrosis; and vascular invasion. PEComas with nuclear pleomorphism and /or multinucleated giant cells only or size > 5 cm are "of uncertain malignant potential", while PEComas with two or more worrisome features are considered to be "malignant" or at "high risk or aggressive behavior".

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Fukunaga-Case 3 . (BP07-1566)

History:

A 46-year-old, gravida 1, para 1 woman presented with a slow growing painless vulval mass. She noticed the lesion two years ago. The excision was performed under the clinical diagnosis of Bartholin's gland cyst. The patient had no evidence of tumor at 8 months after the surgery.

Macroscopic features:

The lesion was a well-demarcated soft tissue mass measuring 3.0x3.0x2.0cm. The cut surface was nodular brownish and reddish sponge-like tissue. No necrosis was found.

Immunohistochemical studies:

Vimentin (++), desmin (+), progesterone receptor (++). Alpha-smooth muscle actin (-), HHF35 (-), S-100 protein (-), CAM 5.2 (-), EMA (-), CD34 (-), estrogen receptor (-).

Diagnosis: ANGIOMYOFIBROBLASTOMA OF THE VULVA.

Histology and Comments:

Sections revealed a circumscribed mass without capsule. The tumor was composed of a spindle or oval cell proliferation interspersed with numerous small blood vessels within a myxofibrous stroma. Adipose tissue was noted in the periphery of the tumor. The cellularity of the tumor was variable with hypercellular and hypocellular zones. Spindle cells proliferated in a linear or syncytial pattern around vessels. Short fascicles of spindle cells were present focally. The spindle cells were wavy and had bland ovoid to elongated nuclei and scant eosinophilic cytoplasm. Nuclei had fine chromatin and nucleoli were inconspicuous. Some cells are multinucleated. No mitotic figures were noted. A moderate number of mast cells were found throughout the lesion. The vascular component consisted of small to medium-sized blood vessels and collections of capillaries.

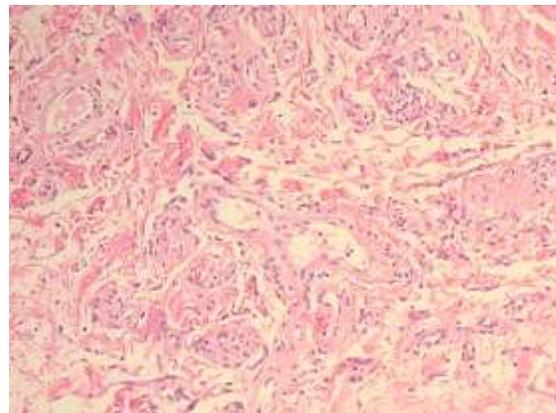
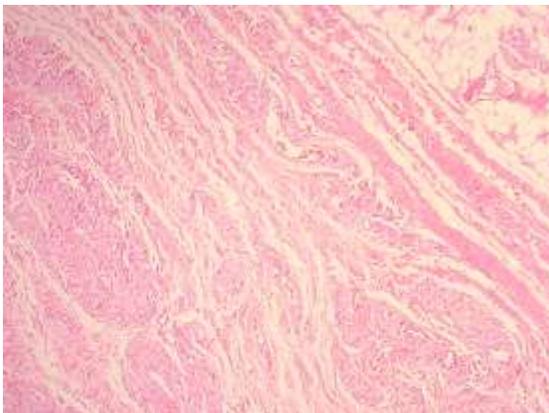
The term "angiomyo-fibroblastoma (AMF)" was first coined in 1992 by Fletcher et al. (1) to describe a distinctive benign soft tissue tumor of predominantly the vulva (1-5), rarely inguinoscrotal region of men (6),

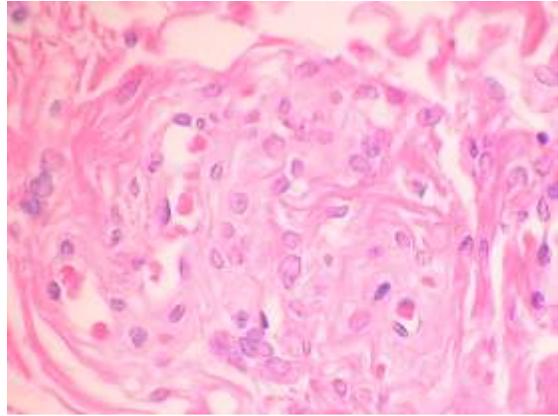
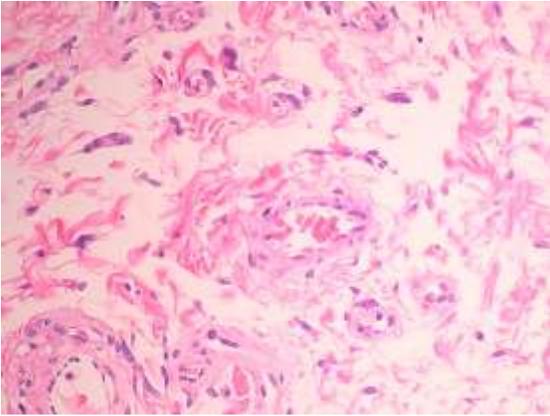
mimicking and often misdiagnosed as a aggressive angiomyxoma. It is a well-circumscribed tumor that clinically is often thought to represent a Bartholin's gland cyst (1-5). AMF usually measures less than 5 cm but can be larger. AMF is a benign non-recurring lesion and local excision with clear margins is adequate treatment. There is one report of AMF with sarcomatous transformation with recurred (7). In this case, areas apparently typical AMF merged imperceptibly with a high grade sarcoma. Histologically AMF is characteristically a well-circumscribed lesion composed of alternating hyper- and hypocellular areas. Plump round to spindle cells cluster or are present in linear array, around numerous delicate capillary-sized vessels within edematous to collagenous matrix.

Differential diagnoses include aggressive angiomyxoma (AA) (8, 9), superficial angiomyxoma (10), cellular angiofibroma (11), neural tumor, myxoid smooth muscle tumors. Distinction between AMF and AA is crucial as surgical treatment of the two lesions is very different with AMF necessitating only local excision, while AA needs wide resection. AA arises most often in the pelvic soft tissues and perineum in relatively young females and rarely occurs in males. In contrast to AMF, AA is an often poorly demarcated infiltrating poorly cellular tumor with less vascularity, more stroma mucin and red cell extravasations

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Krausz- CASE 1

Clinical History: A 21-year-old woman with a history of cough and hemoptysis. Investigations revealed a right lower lobe mass obstructing the bronchus. Right lower lobectomy performed.

Pathology: Pulmonary lobectomy contained an obstructive, polypoid 2.6 cm mass in the lobar bronchus. Histologically this is a typical mucoepidermoid carcinoma composed of mucous cells (polygonal, columnar or more goblet-like) lining cysts or forming glands or solid nests intermixed with squamoid cells and rare intermediate cells. Mitotic activity is low and seen only in intermediate and squamoid cells but not in the mucous cells. There is no tumor necrosis. The tumor is richly vascular with perivascular hyalinization of the stroma. Distal to the tumor there is obstructive pneumonitis.

Diagnosis: PULMONARY MUCOEPIDERMOID CARCINOMA, LOW GRADE

Comments: Salivary gland type of tumors of the lung are relatively rare and include two benign tumors (mucous gland adenoma, pleomorphic adenoma) and three malignant neoplasms (adenoid cystic carcinoma, mucoepidermoid carcinoma and epithelial-myoeplithelial carcinoma). I also presented an unusual pulmonary tumor under the term of pneumocytic adenomyoepithelioma at the last year AMR meeting at the Czech Republic. Mucoepidermoid carcinomas represent less than 1% of all pulmonary tumors. They have an equal sex distribution and form a high percentage of pediatric endobronchial tumors. Most neoplasms occur between the third and fourth decade (age range 3 -78 years). Endobronchial (main, lobar, or segmental bronchi) location is typical.

Mucoepidermoid carcinomas of the lung are histological similar to their counterparts in the salivary glands and they are thought to arise from the precursor cells/stem cells of the tracheobronchial mucous glands.

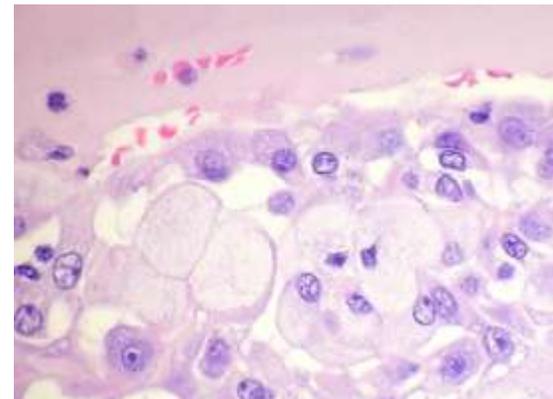
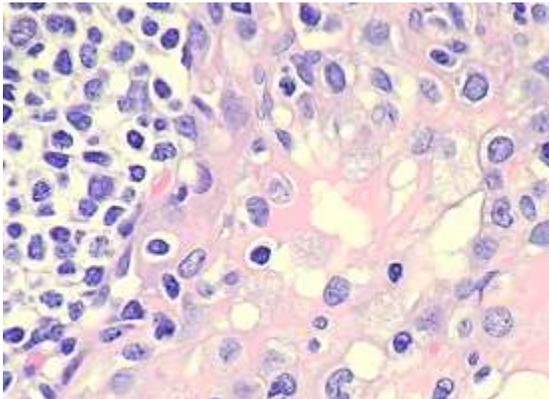
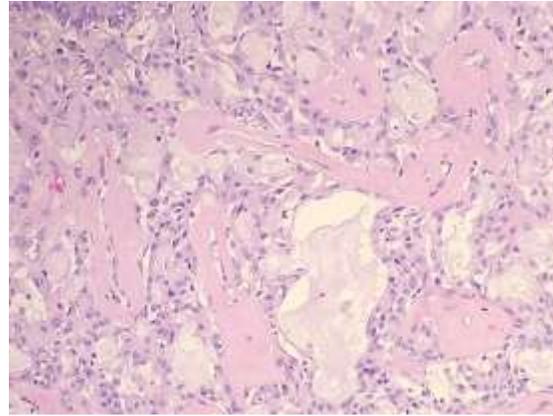
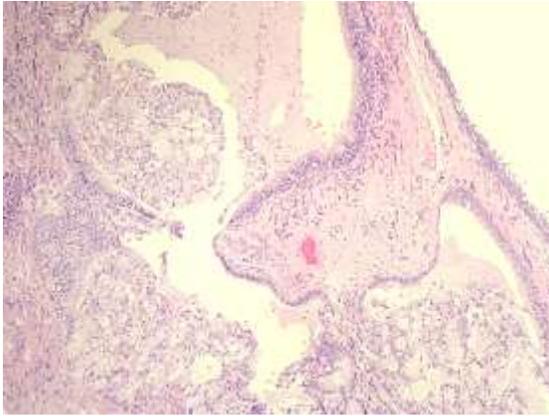
Histologically they are divided into low-grade and high-grade types. The former is circumscribed, predominantly cystic with focal areas of nests and glands composed of cytologically bland mixture of mucous, squamoid and intermediate cells and only rare mitotic figures. The richly vascular stroma is often edematous, focally hyalinized and sometimes calcified. High-grade mucoepidermoid carcinomas are relatively mucin-poor and overlap histologically with adenosquamous carcinomas. They composed mainly of squamoid and intermediate cells with only few mucous cells. Nuclear pleomorphism, nuclear hyperchromasia, high nuclear to cytoplasmic ratio and frequent mitotic figures can be observed. The neoplasm invades the lung parenchyma. The following criteria help to separate it from adenosquamous carcinoma: endobronchial growth, transition to typical low grade mucoepidermoid carcinoma, absence of overlying in situ carcinoma and absence of individual cell keratinization or squamous pearl formation.

Genetic studies have shown various reciprocal translocations: t(1;11)(p22;q13), t(11;19)(q14-21;p12) and t(11;19)(q21;p13). The latter encodes a novel fusion product capable of disrupting the Notch signaling pathway. Chromosome 11 alteration results in upregulation of the cyclin D1 gene and overexpression of cyclin D1. EGFR mutation has been demonstrated in a subset of pulmonary mucoepidermoid carcinomas but not in mucoepidermoid carcinomas of salivary gland origin.

The reported incidence of regional lymph node metastasis in cases of low grade mucoepidermoid carcinomas is less than 5%. In sharp contrast the prognosis of high grade tumors is similar to non-small cell carcinomas.

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Krausz- CASE 2

Clinical History: A 28-year-old woman with growing parascapular 4.5 cm mass of a few weeks duration. Excisional biopsy is performed.

Pathology: This is a deep seated, bland spindle cell, myofibroblastic tumor with short fasciculated growth pattern and extensive areas of hyalinization alternating with myxoid zones. Extravasated red blood cells and scattered chronic inflammatory cells can be observed. There is brisk mitotic activity. Focally intravascular growth of the lesion (not seen on all the sections) is seen. The tumor cells show immunoreactivity for SMA, MSA (focal) and Calponin but are negative for Desmin, Caldesmon and S100. Other melanoma and epithelial markers are also negative.

DIAGNOSIS: NODULAR FASCIITIS (FOCALLY INTRAVASCULAR FASCIITIS). SEE COMMENTS.

Comments: Most examples of nodular fasciitis/intravascular fasciitis are less than 2 cm in size although larger examples are on the record. The presented case is 4.5 cm in maximum diameter and shows focal vascular invasion/intravascular growth (intravascular fasciitis). Nodular fasciitis and intravascular fasciitis are self-limited pseudosarcomatous conditions, characterized by a few weeks of rapid growth followed by slow regression. Even in cases where excision is incomplete, recurrence is very rare (< 2%), so much so that in recurrent cases the review of previous histology is recommended. Metastasis does not occur. Intravascular fasciitis has the same innocent behavior as nodular fasciitis despite its prominent intravascular growth.

In view of the relatively large size of the presented case and the presence of vascular invasion expert consultation was requested. Two experts have confirmed the diagnosis of nodular fasciitis. The presentation will focus on the clinicopathologic aspects of this case.

Nodular fasciitis is a mass-forming myofibroblastic proliferation, which is often misdiagnosed as sarcoma. It occurs in all age groups but more often in young adults. It is usually subcutaneous but may be intramuscular. It may appear infiltrative or circumscribed but not encapsulated. Grossly varies from myxoid to fibrous, sometimes with focal cystic change. Nodular fasciitis is composed of plump but regular spindle-shaped fibroblasts/myofibroblasts. Although mitotic figures are often plentiful (depending on age of the lesion) neither

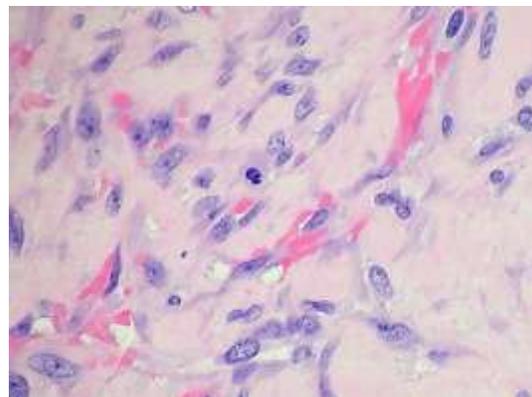
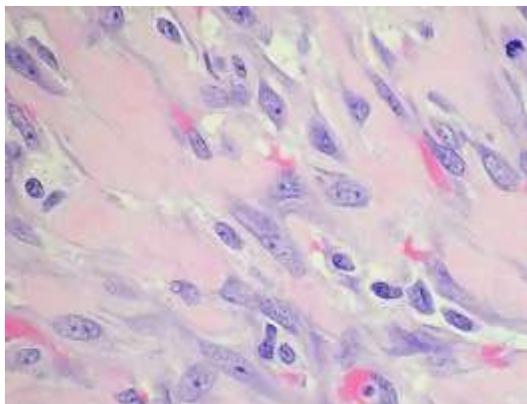
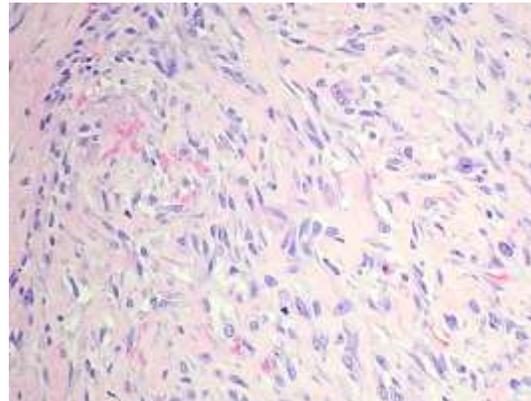
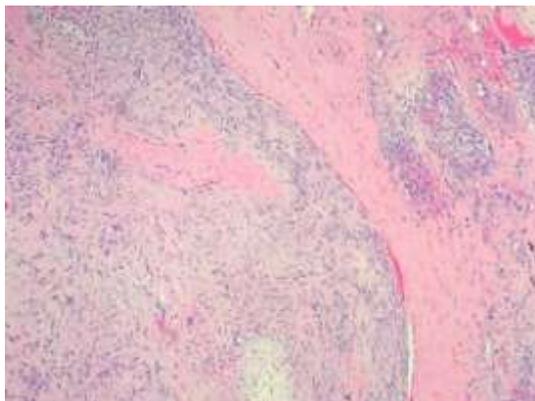
nuclear pleomorphism nor nuclear hyperchromasia is present. It may be highly cellular but focally typically myxoid, loose appearing with a torn or feathery or tissue culture-like appearance. The cellular areas are often arranged in S- or C-shaped fascicles or a storiform pattern. There is usually little collagen in the cellular areas, but focally keloid-like collagen bundles or central extensive stromal hyalinization is present. Extravasated red cells, chronic inflammatory cells are frequently seen and osteoclast-like histiocytic giant cells are present in some cases.

Variants of fasciitis include conventional nodular fasciitis, intravascular fasciitis and cranial fasciitis. Intravascular fasciitis extends into vessel lumens, predominantly veins but occasionally arteries or both. Some examples are predominantly extravascular, with only minor intravascular component while others are predominantly intravascular. Cranial fasciitis occurs predominantly in infants under 2 years of age. It involves the outer table of the skull and contiguous soft tissue of the scalp. It may extend deeper, through the inner table of the skull into the meninges.

Demonstration of clonality in a few cases supports the true neoplastic rather than reactive nature of the process.

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Krausz- CASE 3

Clinical History: A 57-year-old woman with morbid obesity undergoes laparoscopic duodenal switch. Incidental 8.2 cm mass was found in the gastric wall. Partial gastrectomy performed.

Pathology: This is a histologically peculiar myxoid, dyscohesive, epithelioid neoplasm with microcystic and reticulated areas. There is striking anisocytosis and phenotypic heterogeneity including small mononuclear to giant multinucleated tumor cells, from rhabdoid cells to cells with vacuolated cytoplasm (pseudolipoblasts). Despite the pleomorphic histology, mitotic figures are difficult to find. The matrix is richly vascular and of myxoid quality.

The differential diagnosis includes undifferentiated carcinoma, melanoma, epithelioid leiomyosarcoma and epithelioid GIST.

The tumor is immunoreactive for CD34 but not for CD31. Only 5% of the tumor cells express CD117. Epithelial markers (EMA, keratins) and melanoma markers (melan-A, HMB45, MITF-1) are negative. S-100 is seen in <2% of cells. Myogenic markers (SMA, MSA, Desmin, Myogenin) are also negative.

Molecular study: There is PDGFRA Exon 18 mutation. No KIT mutation.

DIAGNOSIS: GASTRIC MYXOID, DYSCOHESIVE, EPITHELIOID GIST WITH RHABDOID CELLS

Comments: It is important for pathologists to be familiar with the rich histologic spectrum of GIST. Miettinen and Lasota (2006) classified epithelioid GISTs as sclerosing, syncytial, dyscohesive, hypercellular and sarcomatous while spindle cell GISTs as sclerosing, palisading and vacuolated, hypercellular and sarcomatous types. Most GISTs contain KIT mutation. However, epithelioid GISTs with or without rhabdoid cells most frequently have PDGFRA mutation and usually occur in the stomach. Some GISTs, especially after treatment, may show heterologous osteocartilagenous or rhabdomyoblastic differentiation.

Although KIT protein (CD117) is present in the vast majority of GISTs, not all cases express it. KIT-negative GISTs are immunoreactive for protein kinase C theta (PKC θ) in the majority of cases. CD34 expression (60-70%) is also useful for diagnostic purposes. SMA can be demonstrated in about 30% of cases (usually reciprocal with CD34), while desmin is present only focally in < 5% of cases. In GISTs, a potential pitfall is the presence of keratin 8 or 18 (5 -10%) and S100 (10%). The presence of keratin should not lead to misdiagnosis of carcinoma or mesothelioma. Care should be taken in the use of CD117 immunohistochemistry as germ cell tumors, melanomas, angiosarcomas and some carcinomas are also positive for KIT. However, these can be excluded on the basis of overall clinicopathologic features and immunoreactivity for other markers.

A KIT gene mutation (exons 9, 11, 13 or 17) is present about 85% of GISTs.

A PDGFRA mutation (exons 12, 14 or 18) can be demonstrated in about 10% of GISTs.

About 5-10% of GISTs are negative for both KIT and PDGFRA mutation.

All GISTs are now regarded as having at least very low risk for aggressive behavior. The most important prognostic factors are: anatomic site, size, and mitotic rate. Risk assessment according to the listed factors helps to determine the biologic behavior. There are separate guidelines for gastric and for non-gastric GISTs.

GISTs metastasize to a limited subset of anatomic sites, predominantly liver and/or peritoneal surfaces. Metastasis to lymph nodes, lung or bone is very rare.

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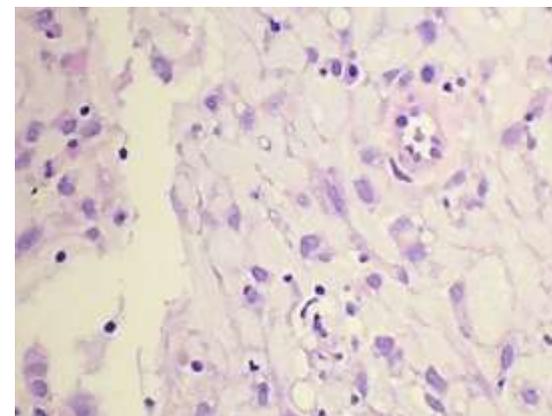
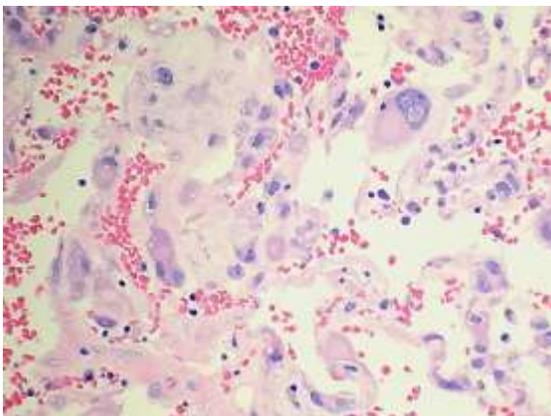
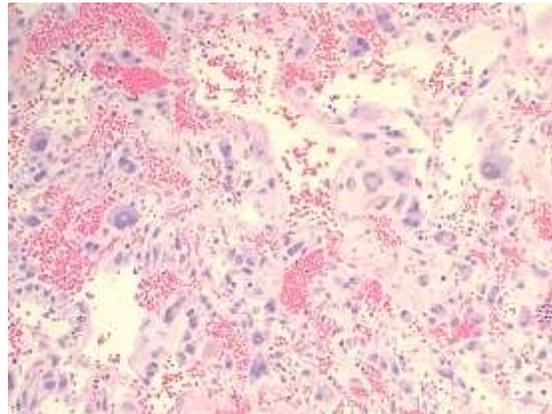
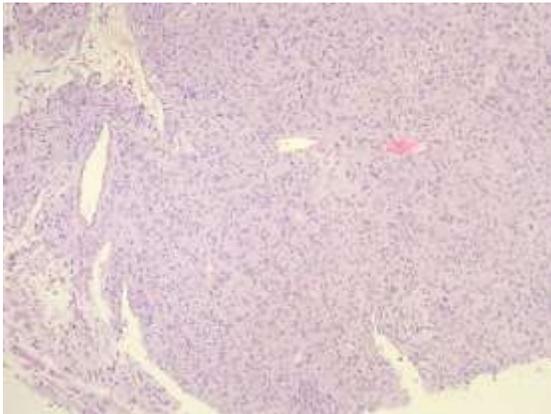
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Lamovec- Case 1 (394 – 01)

.History: A 79-year-old woman presented with pain and swelling of left lower leg of one year duration. Imaging studies showed two osteolytic lesions in the mid-diaphysis of the left tibia with sclerotic margins. She refused either biopsy or operation but was readmitted one year and a half later with worsened symptoms. A drill biopsy was performed, followed by segmental resection of tibia.

Pathologic findings: A resection specimen was represented by a 18 cm long segment of tibia with some surrounding soft tissue and a segment of skin. On cut surface, two mid-portion medullary lesions were seen, measuring 5 x 3, and 2 x 2.5, respectively. They were grey-white in color, focally hemorrhagic or glassy in appearance. Their margins were polycyclic. Tumors eroded corticalis that was focally, in a larger lesion, destructed and overgrown by it.

A drill biopsy specimen showed fragment of relatively sparsely cellular stroma with rare tubular or vascular-like structures lined by slightly pleomorphic epithelioid cells that focally formed short one-cell thick trabeculae. In the resection specimen, the tumor was composed of unevenly cellular stroma and numerous irregular epithelial structures forming tubules, anastomosing vascular-like formations with empty lumina, trabeculae and sheets of loose neoplastic epithelium. Only focally, more compact epithelial squamoid structures were seen. In some areas, epithelial cells showed dissociative pattern of growth.

Mitoses of epithelial cells were very rare. Stroma was composed of spindle cells, in some foci it was almost acellular and hyalinized, elsewhere loose, more cellular, quite vascularized, and focally storiform. In a few foci, trabeculae of a woven bone or osteoid, rimmed by osteoblasts were seen, set in a more cellular stroma.

Immunohistochemically, epithelial tumor cells showed positivity for pankeratin, CK5, CK14 and focally also for CK8. CK18 was negative. MIB-1 showed positive reaction in only an occasional nucleus. Reaction to CD34 and CD31 was negative. Vimentin decorated both stromal and epithelial cells.

DIAGNOSIS: ADAMANTINOMA OF TIBIA.

Follow-up: The patient died 6 years following surgery, at the age of 85, of unrelated cause and with no evidence of disease.

Discussion: Adamantinoma of bone is a rare bone tumor defined as a low grade malignant biphasic tumor characterized by a variety of morphological patterns, most commonly as epithelial cell structures surrounded by relatively bland spindle cell stroma often resembling fibrous or osteofibrous dysplasia - OFD (1, 2). It may appear at any age but most commonly around the age of 30. There is a slight preponderance of the tumors in males. A mid-shaft of the tibia is characteristically affected in around 85% of cases. Synchronous involvement of fibula is present in 10% of cases. Rare cases of tumor in other bones are on record.

Radiologically, a tumor characteristically involves a mid-shaft of tibia, is osteolytic, eccentric, expansile and medullary in location and longitudinally oriented with sclerotic lobulated margins. Multifocality within the same bone is a rule. Intralesional opacities and septations may be observed. Occasionally, the tumor destructs corticalis and spread into the soft tissue.

Histologically, the tumor is typically biphasic, with epithelial and stromal component; the latter may present an OFD appearance.

Epithelial component may show different structures that define several adamantinoma varieties: tubular, basaloid, squamous, spindle cell, and osteofibrous dysplasia – like variety. Two additional, extremely rare varieties were also described: Ewing sarcoma-like (3) and dedifferentiated adamantinoma (4).

Immunohistochemically, epithelial cells express pankeratins, CK5 and CK14 (basal epithelial type keratins) while luminal keratins such as CK8 and 18 are negative. However, this may not be so in every single case of adamantinoma; our case showed some clear focal CK 8 positivity but was negative for CK18. Proliferation marker Ki-67 (MIB-1) show low level of reactivity in predominantly epithelial cells.

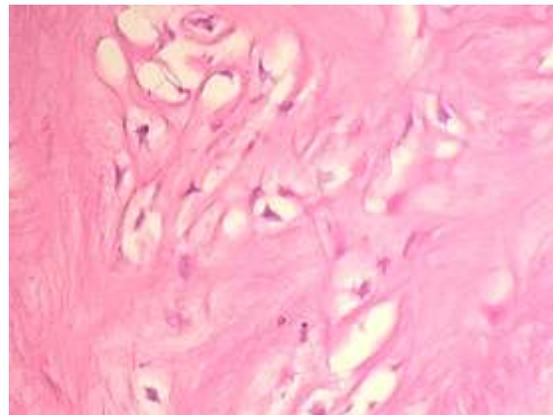
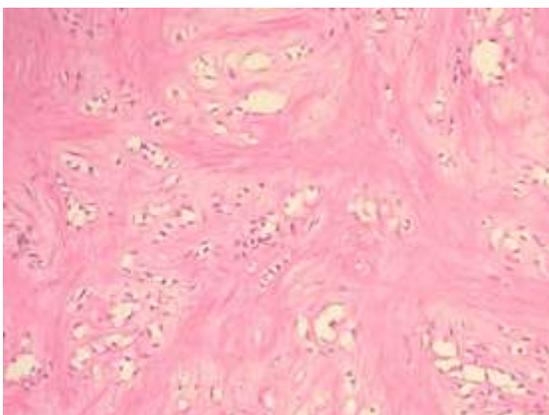
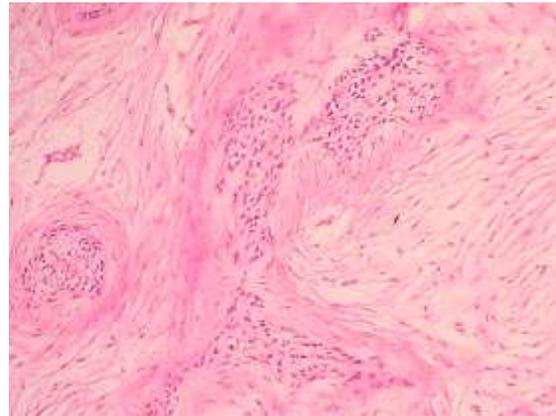
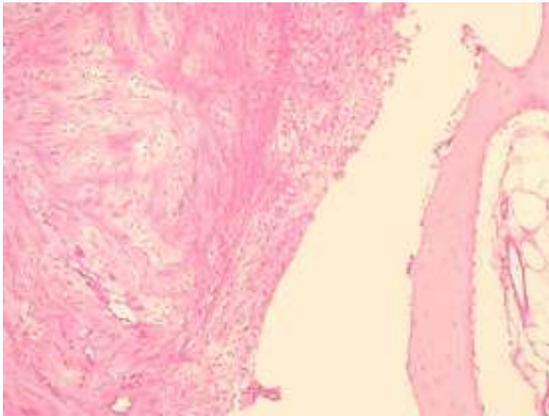
The tumor is histogenetically related to so-called osteofibrous dysplasia, a lesion most frequently found in children and preferentially involving tibia and in some cases also fibula. The lesion is radiologically radiolucent, well marginated with peripheral sclerosis, of “ground glass” appearance. Histologically, it resembles fibrous dysplasia but differs from it by woven bone spicules set in fibrous stroma that are rimmed by uniform plump osteoblasts quite in contrast to fibrous dysplasia in which bone spicules do not exhibit such a rim (5). A relationship of the two lesion is suggested by the presence of scattered isolated keratin positive cells in OFD and on the other hand OFD like stromal foci in adamantinoma. In addition, rare cases of OFD exhibited small nests of epithelial cells (differentiated, juvenile adamantinoma) and some of such cases progressed to classic

adamantinoma. Furthermore, trisomy of 7, 8 and 12 chromosomes were demonstrated cytogenetically in both entities (2).

Adamantinoma have a propensity to locally recur and also may metastasize, predominantly to lungs. Late local recurrences may be observed. A wide local excision is the treatment of choice with similar results as amputation. Radio-chemotherapy has not proven to be effective.

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Lamovec- Case 2 (847-03)

History: A 68-year-old female presented with a lump in the left breast of 6 years duration. After repeated FNAB, the tumor was excised.

Pathologic findings: Fine needle aspiration biopsy was performed on three occasions, on two occasions a reactive process was suspected and on last biopsy, a spindle cell sarcoma was suggested.

Grossly, the excision specimen was represented by 12 x 6 x 5 cm segment of breast tissue with superficial segment of skin. On cut surface, the tumor was well delineated from the surrounding fatty parenchyma, white-grey, of firm consistency, with a peripheral shell of bony tissue. It measured 4 x 4 cm.

Histologically, this was a spindle cell neoplasm with a prominent peripheral rim of bland metaplastic ossification. The cellular population of the tumor was dense and rather uniform and consisted of elongated spindle cells, with minimal or without atypia or pleomorphism; the cytoplasm of cells was eosinophilic, nuclei showed finely punctuated chromatin, mitoses were rare, < 1 per 10 HPF. The distribution of collagen was uneven, focally dense. In rare foci the matrix appeared edematous, no myxomatous change was present. Tumor cells were arranged in fascicles of different length or formed somewhat storiform structures. Peripheral rim of ossification was discontinuous and showed a mature lamellar bone with bland scant osteocytes. The rest of the peripheral tumor border was covered by fibrous capsule. There was some septal extension of bone into the tumor tissue. No infiltration of neoplastic tissue beyond the capsule/bone rim was evident.

Immunohistochemically, the tumor cells showed strong diffuse positivity for vimentin and S-100 protein, focal positivity for bcl-2, and positivity of scattered cells or small foci of cells for CK AE1/AE3, CD56 and calponin. Reactions for EMA, pankeratin, CAM5.2, cytokeratins 1, 5, 7, 14, 18, 20, CK LMW, CKHMW, alpha SMA, desmin, GFAP, HMB-45, CD21, CD34 and CD117 were negative.

DIAGNOSIS: SPINDLE CELL TUMOR OF THE BREAST, PROBABLY BENIGN, SPINDLE CELL MYOEPITHELIOMA VS OSSIFYING FIBROMYXOID TUMOR

Follow-up: The patient had no additional treatment and shows no evidence of disease 5 years following excision of the tumor.

Discussion: The tumor we present is difficult to be categorized with certainty. Morphologically and clinically it appears to be a benign lesion; though it is a cellular tumor, it shows very low mitotic activity, clinically, a long history of a tumor before operation and no evidence of local or distant spread 5 years after surgery are in favor of a benign tumor.

On the other hand, the histological classification of this tumor is not easy and unequivocal. Essentially, three tumors enter the differential diagnosis, in all of them metaplastic bone formation is possible and all of them may be on rare occasions predominantly or exclusively of spindle cell morphology and all of them may be diffusely S-100 protein positive. These tumors are spindle cell myoepithelioma, ossifying fibromyxoid tumor, and schwannoma (cellular schwannoma).

Myoepithelioma of the breast is a rare tumor that may be entirely monophasic and composed of epithelioid, plasmacytoid or spindle cells and their mixture thereof with a different proportion of myxoid or chondroid matrix that is in contrast to adenomyoepitheliomas that show biphasic glandular and myoepithelial component (1, 2). Their counterparts in soft tissues exhibit similar features (3, 4). Metaplastic chondroid, osteoid or osseous metaplasia is a recognized feature in these tumors (3). Pure spindle cell myoepithelial tumor of the breast in a series of 27 myoepithelial tumors of the breast described by Hungermann et al (1) was found in only one case of benign and 1 case of malignant tumor. In the rest of 25 benign, borderline or malignant lesion as defined by the authors, 17 cases showed predominant spindle to more epithelioid monophasic morphology; one malignant and 7 benign cases were morphologically biphasic. Immunohistochemically, all tested tumors showed positivity for CK 5/6, CK 14 (markers of basaloid/myoepithelial cells) and CK 18 (luminal antigen) and also for SMA. Similarly, in two other studies of myoepitheliomas of the soft tissues, the latter were positive for cytokeratins (CAM5.2 and CK AE1/AE3) and S-100 protein (4) and for pankeratin and S-100 protein (3); the reaction to SMA was less consistent. Although the metaplastic bone formation was seen in some of the described cases of myoepithelioma of soft tissues, no peripheral rim of bone in such tumors was explicitly mentioned (3).

Ossifying fibromyxoid tumor, first described in 1989 (5) is an uncommon tumor of soft tissue of uncertain lineage, of mostly benign behavior, usually located in subcutaneous or intramuscular tissue. No such tumor in the breast have been described. Morphologically, it is characterized by lobulated growth of small bland cells arranged in cords or nests within a fibromyxoid stroma. They show a characteristic peripheral rim of bone. Atypical and malignant forms exist. Pure spindle cell forms are highly unusual (5, 6, 7). Immunohistochemically, such tumors most consistently show diffuse or focal positive reaction to S-100 protein and much less often to SMA, desmin and pankeratin and GFAP (6, 7). The positive reaction for CD56 has also been reported.

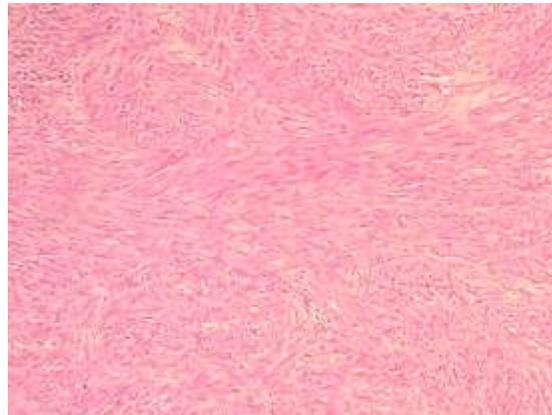
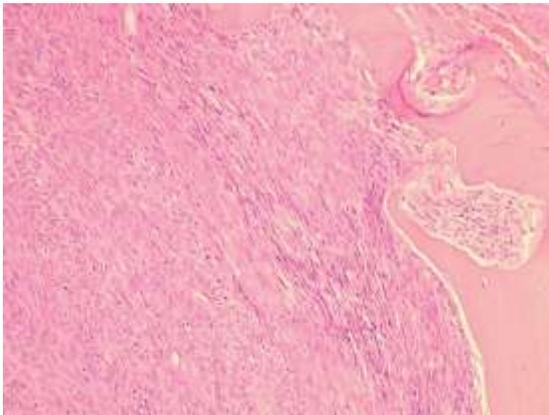
The histogenesis of the tumor is unclear; schwannian and also myoepithelial derivation was suggested. Future cytogenetic studies may clarify this issue.

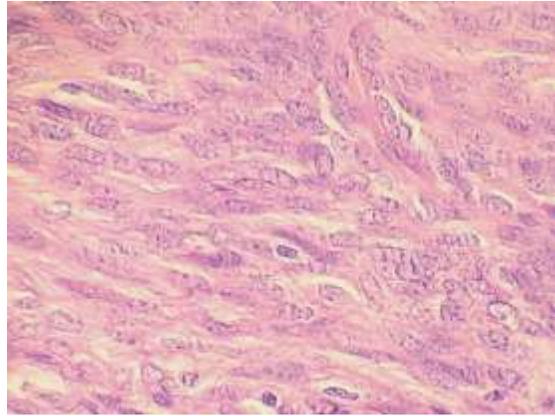
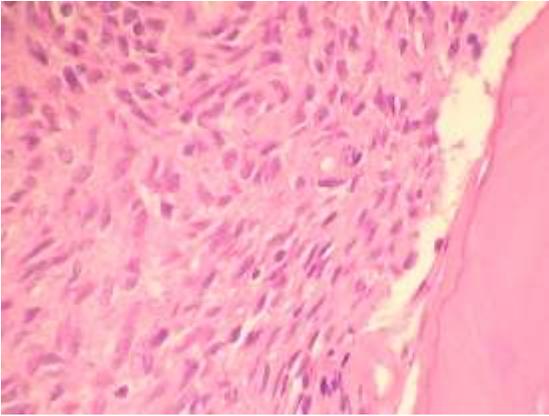
The last tumor that is spindle cell neoplasm that is uniformly S-100 positive and may show metaplastic bone formation is schwannoma, usual or cellular type that would come into consideration in our case. Such tumors show at least some foci of Antoni A or even B pattern, it is commonly hemorrhagic, and often show subcapsular lymphoid infiltrates. None of these features were evident in our case. To the best of my knowledge, no peripheral shell of bone has been described in schwannomas.

In summary, the breast tumor presented here may not be classified with absolute certainty and shows some features more consistent with spindle cell myoepithelioma and other that more closely relates it to ossifying fibromyxoid tumor. However, it almost certainly appears to be a benign spindle cell tumor of the breast.

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Lamovec- Case 3 (3769-04)

History: A 71-year-old woman with a huge tumor of upper quadrants and central part of the right breast. A fine needle aspiration biopsy was performed followed by modified mastectomy with axillary dissection.

Pathologic findings: Grossly, the resected breast was deformed and bulged out in the region of upper quadrants and centrally. On cut surface, the 14 x 12 cm partly multilocular septated cyst filled with red-brownish fluid was found underneath the bulge. The fibrous wall of the cyst was internally covered with a membrane that was partly necrotic and of variegated (brown-yellow-reddish) color. In some foci, a solid grey-white neoplastic tissue was seen infiltrating the capsule and septae of the cyst and in some areas growing intraluminally, as plaques or solid ingrowths.

Histologically, capsule of the cysts and septae among secondary cysts was fibrotic, with abundant hemosiderin deposits, with focal cholesterol clefts. Inner surface of the cysts showed a massive almost exclusively papillary epithelial growth with different types of ramifying papillae: slender ones with fibrovascular core, micropapillae without cores, anastomosing papillae forming focal cribriform structures. They were covered by a single layer or multilayer of relatively uniform columnar epithelial cells with elongated to fusiform nuclei and relatively scant eosinophilic cytoplasm showing some superficial blebs. Mitoses were rare. Epithelial cells lay directly on the stromal core of papillae without an intervening myoepithelial layer. In rare foci, stromal cores were filled with clear polygonal cells that grew beneath superficial layer of columnar cells (pattern of dimorphic papillary carcinoma). In cystic spaces, hemorrhages were seen with abundant fibrin deposition. No clear infiltrative growth into a fibrous capsule or beyond was seen; however, small ducts in the capsule showed the same type of intraluminal growth as the cysts. The rest of the breast parenchyma was unremarkable. In none of the 35 isolated axillary lymph nodes metastases were seen.

Immunohistochemically, no myoepithelial cells could be demonstrated by reaction to CK5, CK14, smooth muscle actin, calponin and p63. Peripheral layer of epithelium toward fibrous capsule of cysts was likewise devoid of myoepithelium, except for a vary rare remnants of it. Tumor cells were strongly positive for estrogen and progesterone receptors. HER-2 was negative immunohistochemically and by FISH method.

DIAGNOSIS: BREAST, INTRACYSTIC (ENCAPSULATED) PAPILLARY CARCINOMA.

Follow-up: Four years following surgery, the patient show no evidence of disease.

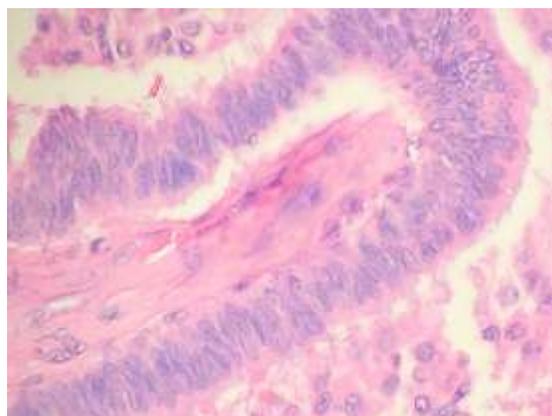
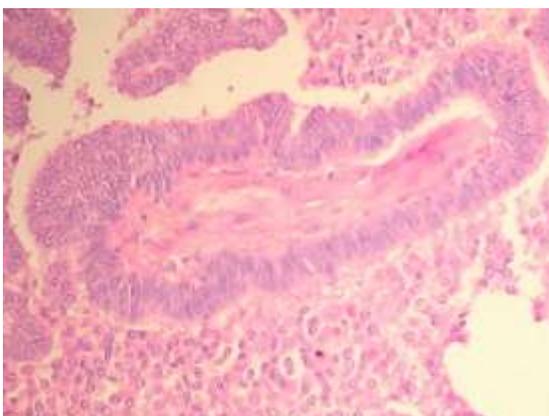
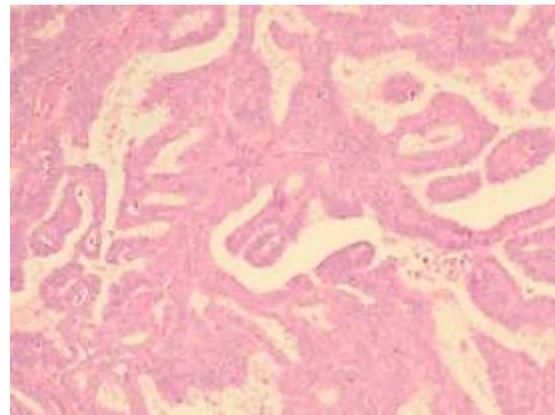
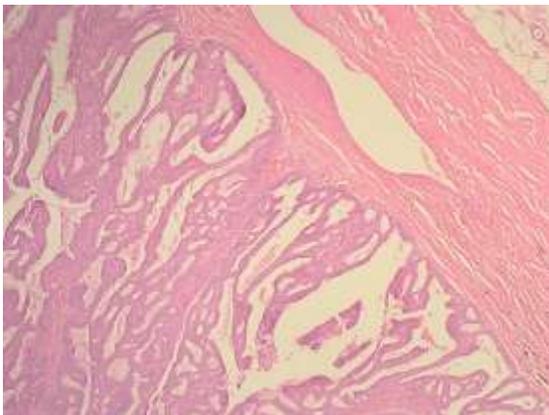
Discussion: The redefinition of intracystic papillary carcinoma is of a relatively recent date (1). The lesion has been traditionally considered to be a variant of intraductal papillary carcinoma without invasion. The use of a panel of antibodies against basal type epithelium and myoepithelium has cast doubts as to its non-invasive character. It has been demonstrated that the peripheral rim of cells toward fibrous capsule lacks a myoepithelial layer that is the supposed to be a prerequisite to prove the lesion's non-invasiveness (1, 2). Therefore, it was hypothesized that this type of tumor is essentially an invasive type of carcinoma exhibiting so-called expansive type of invasion into the stroma. It was argued that the attenuation and disappearance of peripheral myoepithelial layer that might have happened in intraductal type of carcinoma due to compression and distension seems unlikely; in authors' series of in situ papillary carcinomas the peripheral myoepithelial

layer was always preserved (1). It was suggested that in regard to papillary tumors of the breast a whole spectrum of progression exists: from papilloma to intraductal papillary carcinoma to well circumscribed encapsulated well differentiated papillary carcinoma with prominent fibrotic rim; the latter being an expansile invasive variant of the tumor (3). In this regard, it was proposed that “intracystic” adjective should be replaced by “encapsulated”. It was further remarked that a striking similarity of this type of carcinoma and encapsulated papillary carcinoma of the thyroid exists (1).

The most important issue in encapsulated papillary carcinoma is to what extent this type of invasiveness modifies its behaviour in comparison to a true non-invasive tumor. It was shown that the patient with intracystic papillary carcinoma have an excellent outcome with adequate local therapy alone, similar to that in DCIS (4). Therefore, in practical terms it is most prudent to manage these patients as before, i.e. as those with DCIS, intracystic or otherwise.

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Miettinen-Case 1

Case 4022.

Clinical history: 22-year-old male who had been previously healthy had shortness of breath, and bilateral pleural effusion was diagnosed. Multiple pleural nodules were detected and many were excised in thoracotomy.

DIAGNOSIS: DESMOPLASTIC SMALL ROUND CELL TUMOR

Discussion:

Desmoplastic small round cell tumor (DSRCT) was originally reported by Gerald et al in 1989 (1) who subsequently described them in a series of 19 cases in 1991 (2). Apparently similar tumors were described in an abstract form by Sesterhenn et al. in the paratesticular region some years earlier (J Urol 1987:137, 214, abstract). Previously these tumors were variably diagnosed as neuroblastomas, Ewing sarcomas, and rhabdomyosarcoma variants, among others. The first two cases I saw (also included in the paper of Gerald et al) were believed to be disseminated carcinoid tumors in children, both 8-year old boys with peritoneal and small intestinal and mesenteric involvement.

DSRCT is a typically a tumor of children and young adults with a marked male predominance. It is clinically characterized by involvement of serosal cavities, usually the abdomen. Approximately 5% of cases involve pleural cavity (1-4). The tumor is often multinodular and disseminated at the onset, but a dominant mass, "primary tumor", may be present. The tumor is highly malignant, and in addition to dissemination in body cavity, metastases occur, especially in the liver, lungs, and peripheral soft tissue.

Histologically typical is a nested architecture with variably shaped cellular nests set in a desmoplastic stroma. The tumor cells vary from small to medium sized, and in some cases the cell size is larger and even pleomorphism can occur. Carcinoma-like cohesive pattern and luminal differentiation are also possible (3). Mitotic activity is often considerable, and larger tumor deposits usually have necrosis.

Immunohistochemical features include variable keratin cocktail and desmin immunoreactivity. These markers can be expressed in various proportions. More common is dominance of keratin over desmin, but in some cases, the opposite is true.

This case was strongly positive for keratins and showed moderate desmin-positivity with a dot-like pattern, a common finding in this tumor. Nuclear positivity for WT1, a typical finding, was also noted. When examining DSRCT one has to use a WT1 antibody that reacts with the carboxyterminus, as the aminoterminal is eliminated in the gene rearrangement. Focal (but not prominent) CD99 expression may be present, but the tumor is negative for myogenin, chromogranin and synaptophysin, which together with the polyphenotypic pattern helps to differentiate it from Ewing sarcoma, neuroblastoma and rhabdomyosarcoma (2,4,5).

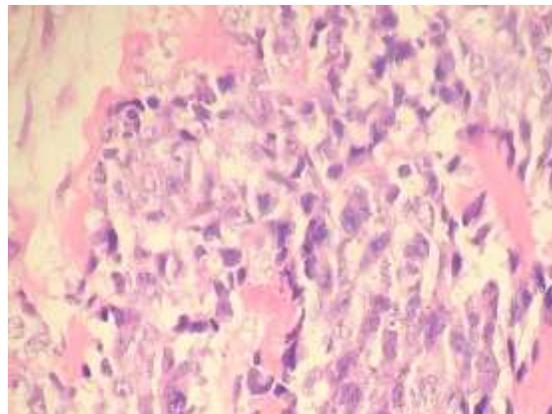
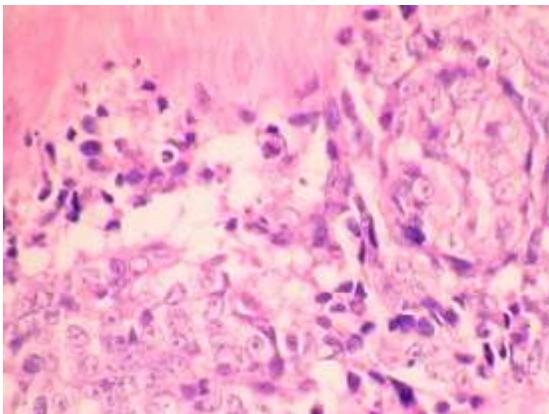
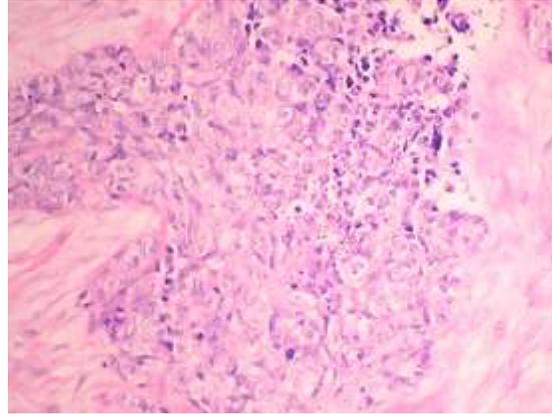
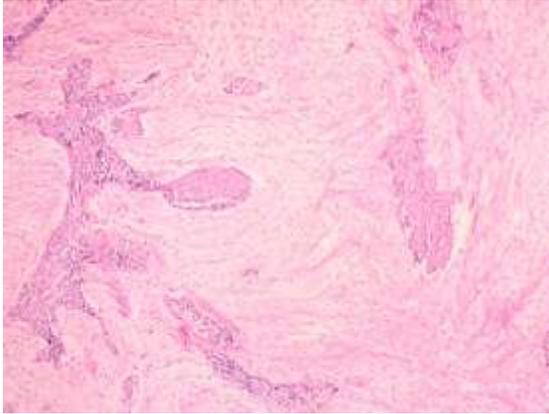
DSRCT has a characteristic EWSR1-WT1 fusion translocation, cytogenetically observed a t(11;22)(p13;q12) translocation (6). RT-PCR fusion transcript assay (starting from RNA extracted from the tumor) and interphase FISH for EWSR1 gene rearrangement using a break-apart probe are practical ways to detect this translocation.

Both tests were positive in this case.

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Miettinen-Case 2

Case 6865

Clinical history: 71 year-old man with 6x4x3 cm partly calcified subcutaneous mass in the right lateral thigh. Tumor was excised, and the patient experience no recurrence during clinical follow-up. He died from multiple myeloma 4 years later.

DIAGNOSIS: OSSIFYING FIBROMYXOID TUMOR OF SOFT PARTS

Discussion:

Ossifying fibromyxoid tumor (OFT) was described by Enzinger et al in 1988 (1). The initial series reported 59 cases of mainly subcutaneous soft tissue with a moderate potential for recurrence but no definite metastatic potential. Subsequent series have reported atypical (2) and malignant (3) variants. However, careful analysis of a large series of tumors coded as possible of definite OFTs concluded that all overtly malignant tumors represented entities other than OFT (4). These malignant variants differed from OFT by their negativity for S100 protein and by lack of conventional OFT components, despite trabecular cellular arrangement and metaplastic bone formation. Many were interpreted as low-grade fibromyxoid sarcoma variants, and some as extraskeletal osteosarcomas. Many of these tumors were deep and intramuscular.

When narrowly defined, OFT is a mesenchymal tumor of low biologic potential. Recurrence rate is approximately 20% (often late recurrences 10 or more years after primary excision), but distant metastases are

not observed. The tumor occurs in adults of all ages with the median age of 51 years in the largest series (4). There is a 1.5:1 male predominance. Most common location is the lower extremity (especially, thigh). The tumor occur with a lower, equal frequency in the trunk wall, upper extremity, and head and neck. Many patients have a long, sometimes > 20 year history of tumor.

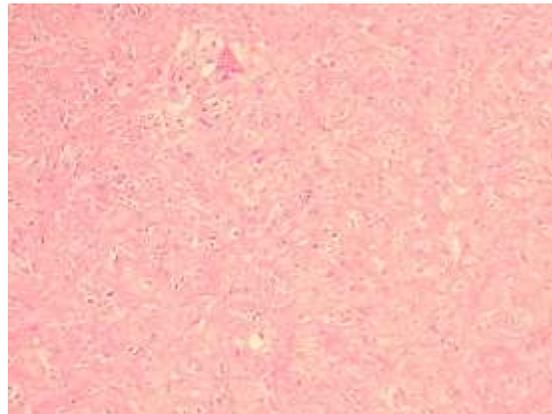
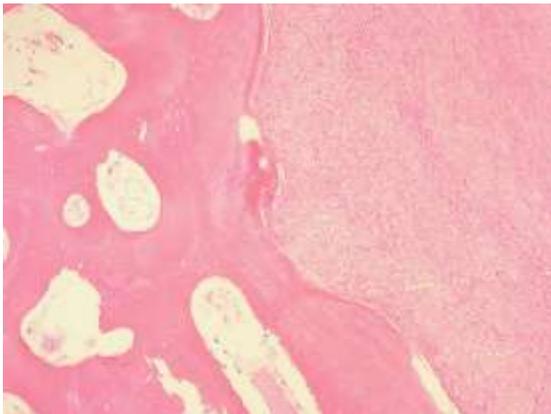
Grossly OFT often contains a partial bony shell in tumor periphery. Histo-logically, there is a discontinuous rim of metaplastic bone in 80% of cases. Some examples have no metaplastic bone. The tumor is composed of relatively small to medium-sized epithelioid cells that are arranged randomly or in trabeculae, sometimes forming a net-like pattern. These cells have moderate size nuclei with delicate nucleoli. There is a moderate amount of variably eosinophilic cytoplasm, and some cells are surrounded by cleavage spaces. Mitotic activity is usually low (< 2/10 HPFs), but some cases have higher mitotic activity and higher cellularity. Higher mitotic activity seems to increase recurrence potential.

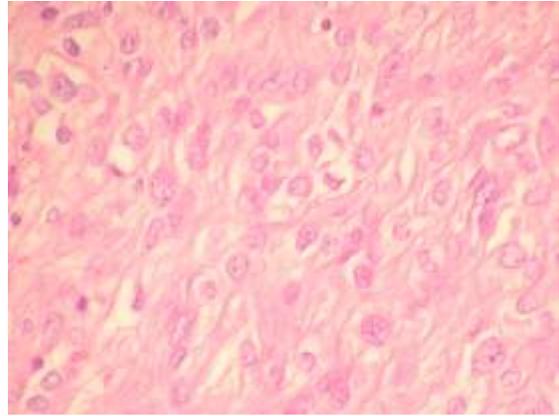
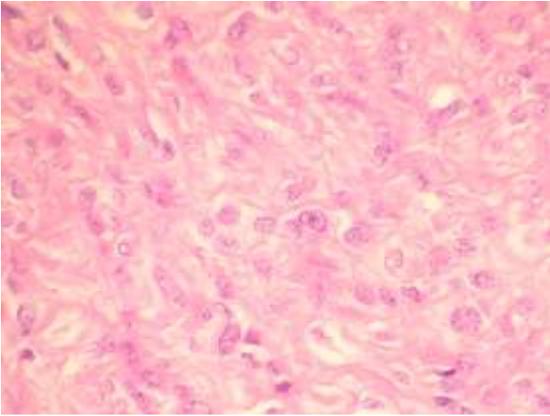
Immunohistochemically typical is positivity for S100 protein and CD10. Rare cases show focal desmin or keratin-cocktail positivity. Genetic information is scant. One case with a t(6;14) translocation has been reported.

Differential diagnosis includes mixed tumor/myoepithelioma, that typically has evidence of epithelial differentiation, either histologically, or immunohistochemically. Sarcomas with focal tumor osteoid (extraskelatal osteosarcoma), or metaplastic bone (mostly low-grade fibromyxoid sarcoma) should not be confused with OFT. They show greater overall atypia, are S100 negative (except for osteocartilaginous components), and are often deep, intramuscular tumors.

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Suster Case No. 1

Clinical history: A 63 year old man was seen for progressive chest pain and dyspnea. A chest X-ray showed widening of the mediastinum. CT scan showed a well defined mass in the anterior mediastinum 10 x 8 x 6 cm. without evidence of infiltration into adjacent structures. A complete surgical excision of the lesion was done.

Pathologic findings: The tumor showed a biphasic appearance, with anastomosing cords and islands of large epithelioid cells surrounded by a spindle cell proliferation. The cords and islands of epithelial cells showed large, round to polygonal cells with abundant cytoplasm and round nuclei with occasional small nucleoli. In some areas, the epithelial cells showed some degree of nuclear atypia with enlarged nuclei and occasional prominent nucleoli. Mitoses were absent or inconspicuous. There was no evidence of tumor necrosis, infiltration of surrounding structures or vascular invasion. The spindle cell stromal component consisted of fibroblast-like spindle cells with elongated nuclei and scant cytoplasm without any evidence of cytologic atypia or mitotic activity. In some areas, the spindle cells were quite dense and adopted a prominent storiform pattern.

Immunohistochemical stains showed strong positivity of the epithelial cells for cytokeratin and negative staining for vimentin. The spindle cells in the stroma were negative for cytokeratin and strongly positive for vimentin. A few of the spindle cells stained faintly positive for EMA. Electron microscopy showed well-developed tonofilaments and intercellular junctions with desmosomes in the epithelioid cell component, and features of fibroblastic cells in the spindle cell stromal component.

Diagnosis: THYMOMA WITH PSEUDOSARCOMATOUS STROMA (“metaplastic thymoma”).

Discussion: this represents a very unusual variant of thymoma that was first introduced in the literature by Suster et al under the designation of “thymoma with pseudosarcomatous stroma”. A couple of years later, Yoneda et al reported 5 additional cases of the same tumor under the designation of “low-grade metaplastic carcinoma of the thymus”. In more recent years, the tumor has been renamed “metaplastic thymoma” by the WHO to acknowledge its indolent biologic behavior.

The tumor is histologically characterized by a biphasic appearance, with interconnected cords and strands of tumor cells separated by highly cellular stroma displaying a dense but cytologically bland spindle cell proliferation. The tumors are always well-circumscribed and encapsulated. All cases reported in the literature have behaved in an indolent fashion and have essentially been cured with simple local excision; although one case presenting in advanced stages showed a local recurrence.

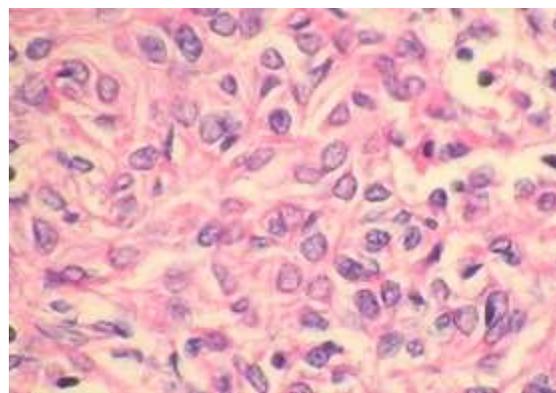
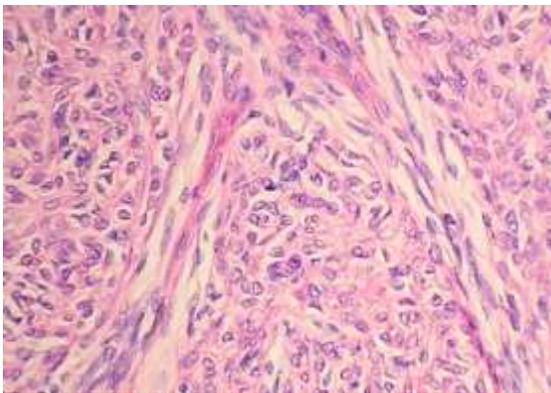
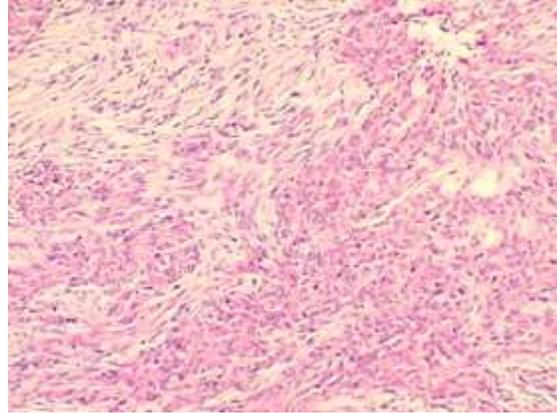
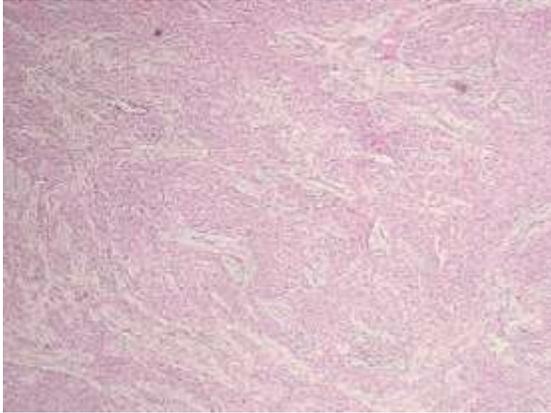
The differential diagnosis for this tumor essentially involves thymic carcinosarcoma. Carcinosarcoma is a rare type of thymic malignancy that is characterized by a biphasic population of cells composed of frankly carcinomatous elements admixed with frankly sarcomatous elements. The majority of cases reported in the literature has shown a combination of carcinoma with rhabdomyosarcoma and have behaved very aggressively with metastases and tumor deaths in most instances.

The present case, although sharing the biphasic morphologic appearance of carcinosarcoma and some degree of cytologic atypia in the epithelial cells, is characterized by displaying a totally benign-appearing spindle cell stromal component that is devoid of cytologic atypia, mitoses or necrosis. The spindle cells can show some faint EMA positivity, a finding that has been interpreted by some authors as indicative of spindle cell “metaplasia” of the epithelial cells. However, all cases studied to date have been consistently negative for cytokeratins and ultrastructural studies have shown only fibroblastic features in the spindle cells.

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Suster- Case No.2

Clinical history: A 56 year old woman was seen for left chest pain. The patient had a history of hypertension and gastroesophageal reflux disease. On physical exam and imaging studies, a well-circumscribed 5 cm. mass was seen in the anterior mediastinum. A thoracotomy with complete excision of the mass was carried out.

Pathologic findings: On scanning magnification the tumor showed multiple, cystically dilated spaces. The walls of the cysts were lined by round to cuboidal cells with round nuclei and scant cytoplasm. Lymphoid aggregates with reactive germinal centers could be seen scattered throughout the lesion. Also present within the walls of the cysts were strands, cords and islands of large epithelioid cells showing prominent vacuolization that adopted a honeycomb or canalicular configuration. Some of the vacuoles displaced the nuclei towards the periphery resulting in a signet-ring cell appearance. There was no evidence of mitotic activity, necrosis or vascular invasion.

Immunohistochemical stains showed strong cytoplasmic positivity of the tumor cells for cytokeratin AE1/AE3, CK5/6 and calretinin, and negative staining for CD31, CEA and MOC31. Electron microscopy showed frequent desmosome-type intercellular junctions and occasional short microvilli.

Diagnosis: CYSTIC ADENOMATOID TUMOR of the mediastinum.

Discussion: Adenomatoid tumor is a term introduced in 1945 by Golden and Ash for a benign mesothelial proliferation that usually arises in the genital tract (ovaries, uterus, fallopian tubes, paraovarian connective tissue, testes, epididymis and tunica vaginalis). Extragenital locations are rare and have only been described in the adrenal gland, pleura, small bowel, heart, pancreas, lymph node and mediastinum.

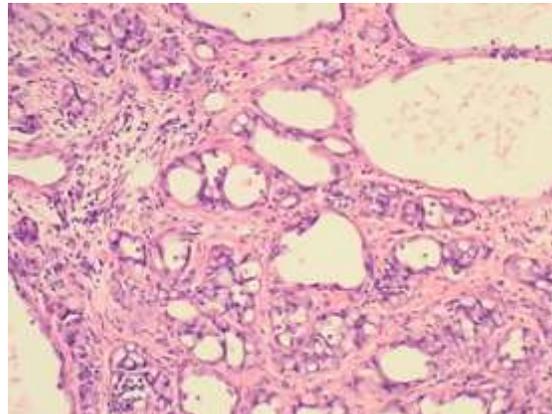
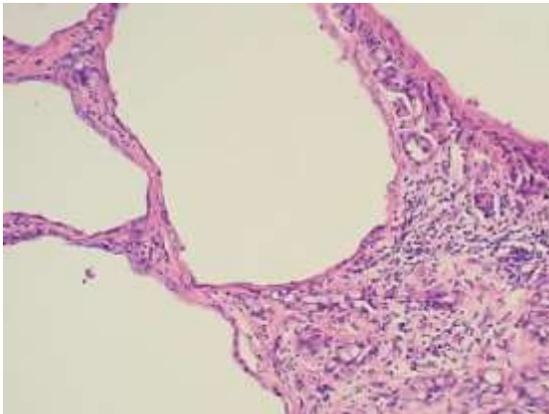
The present case was located in the mediastinum and presented as a cystic mass. Histologically this lesion showed a honeycomb appearance with numerous small-to medium sized cystic spaces lined by flattened to cuboidal epithelial cells. In other areas, the walls of the cyst were thickened by cords and nest of small canalicular structures that were composed of round to polygonal epithelial cells with abundant cytoplasm, some of them showing vacuoles with a signet- ring cell appearance. Mitotic figures and nuclear pleomorphism were absent.

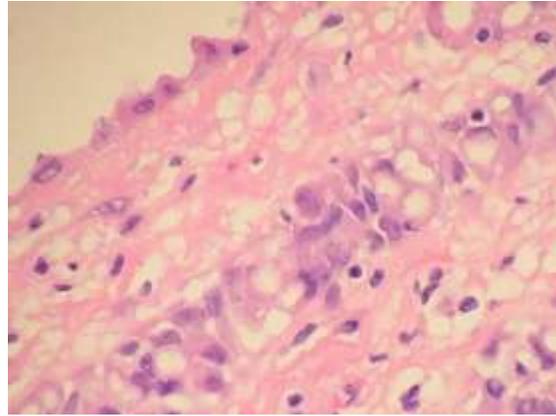
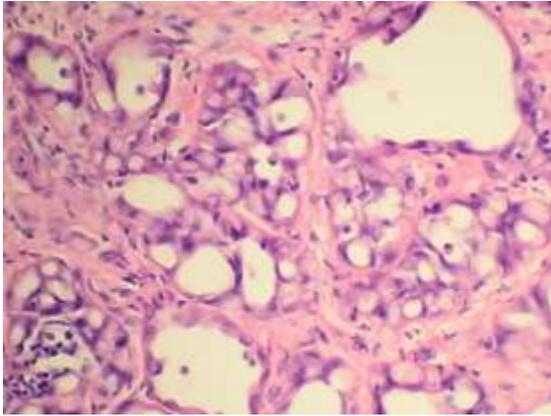
The differential diagnosis for this case includes neoplastic and non neoplastic conditions such as acquired multilocular thymic cyst, Hodgkin disease and thymoma with cystic degeneration, and less commonly cystic seminoma and lymphangioma. Another important differential diagnosis is that of metastatic carcinoma, particularly mucinous adenocarcinoma with signet-ring cell features, adenoid cystic carcinoma or mucoepidermoid carcinoma. The absence of any significant nuclear pleomorphism, stromal desmoplasia, necrosis and mitotic activity should raise the possibility of an alternative diagnosis in mediastinal tumors with prominent signet-ring cell features. Epithelioid hemangioendothelioma can also occur in the mediastinum and display prominent cytoplasmic vacuolization with signet-ring cell features and should also be considered in the differential diagnosis.

The majority of the above conditions can be easily ruled out by the application of a panel of immunohistochemical stains. Adenomatoid tumors are positive for cytokeratin (AE1/AE3 and CK5/6) and also strongly co-express calretinin, which can be very useful in difficult cases, especially in small biopsies. Lymphangiomas and multilocular thymic cysts can also bear a superficial resemblance to these tumors due to the prominent cystic spaces and lymphoid hyperplasia, but will not harbor the distinctive epithelioid cell population in the walls of the cysts observed in our case.

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Suster-Case No. 3

Clinical History: An 80 year old man with no significant past medical history presented with a soft tissue mass in his right foot that measured 8 cm. in diameter. The lesion was well-circumscribed, unencapsulated, and showed a homogeneous gray-white cut surface. The lesion was completely excised.

Pathologic findings: The tumor showed a gray white, homogeneous cut surface. On histologic examination, it was composed of cords and strands of round, epithelioid cells with abundant clear cytoplasm. In some areas the tumor cells formed small nests or clusters; other areas adopted a prominent single-file arrangement. Many of the tumor cells contained small eosinophilic nucleoli and a few scattered mitotic figures could also be seen. A few cells showed multivacuolated cytoplasm. There was no evidence of infiltration into surrounding structures, hemorrhage or necrosis.

Immunohistochemical stains showed strong cytoplasmic positivity of the tumor cells for cytokeratin AE1/AE3, vimentin and EMA. Many of the tumor cells also showed nuclear and cytoplasmic positivity for S-100 protein. Stains for calponin, SMA and desmin were negative.

Diagnosis: Soft tissue PARACHORDOMA.

Discussion: Parachordoma is a rare soft tissue tumor that resembles morphologically axial chordoma, but presents in non-axial locations. This tumor was initially described by Laskowsky in 1955 under the designation of “chordoma perifericum” and later renamed “parachordoma” by Dabska in 1977. Some confusion existed for a while with the introduction of the term “chordoid tumor” by Fred Stewart in the United States in 1948 for similar lesions, and the addition of the term “chordoid sarcoma” coined by Martin et al in 1973. It is now generally agreed that the terms “chordoid tumor” and “chordoid sarcoma” are synonymous with extraskeletal myxoid chondrosarcoma, and that “parachordoma” refers to a totally different and distinct entity.

This tumor has been described in a wide age range (4 to 86 years) without sex predominance. The tumors are usually deeply located beneath the fascia in the limbs, limb girdles or trunk but cases in the liver and stomach have been reported. The tumors are slow-growing with relatively indolent behavior and occasional local recurrence; however some cases with metastasis and death have been reported.

Histologically the tumors are well circumscribed, non-encapsulated and may show a variety of histologic patterns. These include cords and nests of large round to polygonal cells, with moderate amounts of clear or lightly eosinophilic cytoplasm that is sometimes multivacuolated resembling the physalliphorous cells of chordoma. Myxoid change or fibrosis with spindle or whorling of cells can be present.

The tumors cells are characterized by an immunohistochemical profile that coexpresses cytokeratins, vimentin, EMA and S-100 protein. A few cytogenetic studies have demonstrated non-recurring chromosomal translocations in a few single cases studied.

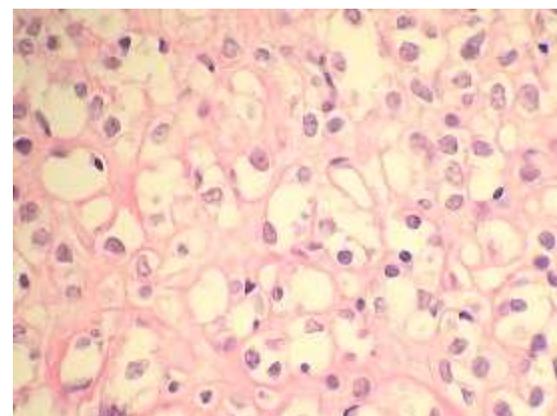
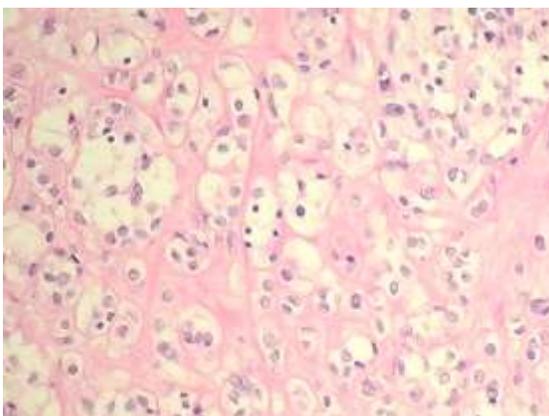
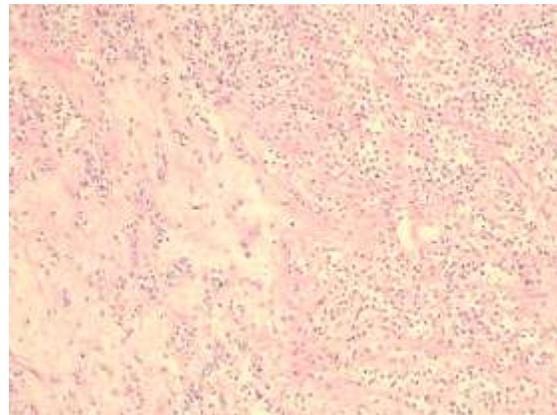
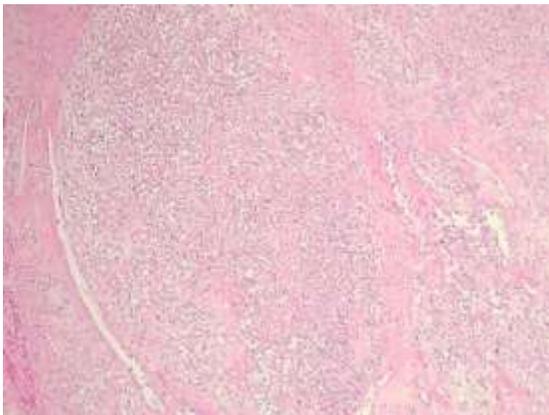
Recently, parachordoma has been regarded by the WHO as part of a heterogeneous group of lesions that include myoepithelioma of soft tissue because of similarities in morphologic and immunohistochemical features; however, many authors are not in agreement with this approach and have suggested that these are two different diseases. The latter is supported by the observation that myoepithelioma of soft tissue is a

biphenotypic neoplasm that should demonstrate, by definition, a dual epithelial/myoid differentiation and marker profile (i.e., coexpression of epithelial and muscle markers). Parachordomas, on the other hand, coexpress epithelial and neural markers (Ker/S100) but are negative for myoid markers. All cases of parachordoma reported in the literature so far have been negative for muscle markers.

The pathogenesis of this tumor is still in dispute, but the morphologic and immunohistochemical features seem to support the theory that they may correspond to extra-axial chordomas that may arise from misplaced notochordal rests. The tumors should be regarded as low-grade neoplasms with potential for local recurrence but little if any metastatic potential. Complete local excision appears to be the treatment of choice.

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WAKELY-Case 1.

History: A 44-year old woman presented with cough and retrosternal discomfort. Chest x-ray showed right sided cardiomegaly and echocardiogram demonstrated a large mass involving the right heart.

Pathologic Findings: The resected specimen consisted of a 12 cm. circumscribed unencapsulated, firm mass. The margin of resection had a 1.0 x 1.0 x 0.2 (thickness) cm portion of myocardium that was grossly normal. Cut section of the mass showed lobulated tan-pink tissue with 30% necrosis.

Microscopy showed an admixture of hypocellular myxoid and hypercellular spindle cells areas in a collagenous stroma with numerous large hyalinized collagen rosettes. An abrupt transition occurred from hypocellular to hypercellular areas in which spindle cells formed an indistinct storiform or whorled pattern. A cuff of tumor cells with rounded nuclei surrounded large rosettes and showed a radial orientation pattern. Spindle cells had bland nuclei, evenly dispersed chromatin & indistinct nucleoli. Mitoses were 1-2 per 50 hpf. The vasculature consisted of open and compressed, sometimes branching arteriole-sized vessels with few arcades of smaller vessels. Areas of necrosis contained foci of dystrophic calcification. The attached portion of myocardium was uninvolved by tumor.

Immunohistology showed diffuse strong staining with vimentin, CD99 (weak), and focal staining with smooth muscle actin. No staining occurred with CD34, EMA, HHF-35 actin, cytokeratin AE1/3, desmin, and S-100. FISH analysis showed that >50% of nuclei displayed a one fusion/one green/one orange signal pattern, confirming a translocation involving the *FUS* gene locus.

Diagnosis:

Heart: LOW-GRADE FIBROMYXOID SARCOMA WITH GIANT COLLAGEN ROSETTES [HYALINIZING SPINDLE CELL TUMOR WITH GIANT ROSETTES].

Discussion: LGFMS, 1st described by Evans as a deceptively bland sarcoma is now known to harbor metastatic potential. Over the last 20 yrs., roughly 150 cases have been documented with local recurrence, metastasis, and death. The histopathology is that of a spindle cell tumor with an admixture of collagenous and myxoid zones, a whorled growth pattern, and arcades of curvilinear blood vessels. In slightly < ½ of cases, foci with large collagen rosettes are found. Recurrent and specific genetic abnormalities involving t(7;16) (q33;p11) results in a fusion of the *FUS* and *CREB3L2* genes appears unique to this neoplasm. The entity initially reported as **Hyalinizing Spindle Cell Tumor with Giant Rosettes (HSCT)** is now synonymous with LGFMS, specifically "LGFMS with giant collagen rosettes" (**LGFMS-GCR**). Combining both morphologies into one entity is based on identical ultrastructural, immunohistochemical, cytogenetic and biologic parameters between both tumors – the only difference being the presence of collagen rosettes in 1 of them.

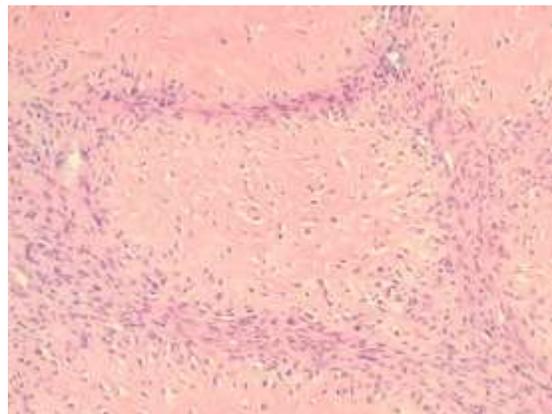
All reported primary intra-thoracic LGFMS occurred in adults (x=38 yrs., range 20-50 yrs.). Two occurred in the anterior mediastinum (left innominate vein and superior vena cava), 1 from the pleura, and 2 from within the lung. None involved the epicardium/heart. LGFMS-GCR morphology occurred in 4/6 cases of intra-thoracic LGFMS. One patient developed local recurrence 9 years after resection; 3 others had follow-up of ≤1 year. A long hiatus (≥10 years) is common prior to the appearance of metastatic disease in LGFMS.

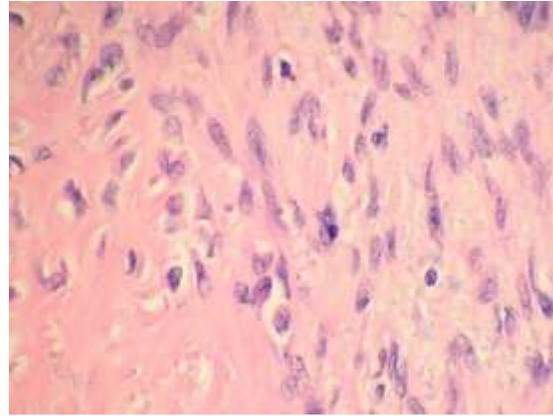
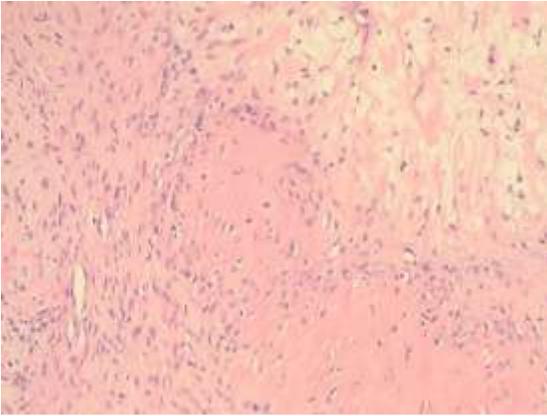
This epicardial-based tumor displayed the features of LGFMS-GCR including a bland spindle cell proliferation, and numerous large collagen-centered rosettes. Other neoplasms reported to contain collagen rosettes include schwannoma, leiomyoma, myxoid leiomyosarcoma, malignant peripheral nerve sheath tumor, and perineurioma. These entities are discernible from LGFMS-GCR based on their other unique microscopic features and immunohistology.

Distinguishing LGFMS *without* collagen rosettes from other spindle cell proliferations arising within the thoracic cavity including solitary fibrous tumor (SFT), inflammatory myofibroblastic tumor, benign nerve sheath tumor, hyalinizing granuloma, and fibromatosis is more difficult. A low power whorled spindle cell pattern and alternating myxomatous/collagenous foci are generally absent in these other neoplasms. Immunohistology shows an absence in LGFMS of diffuse staining with CD34 (SFT), S-100 protein (schwannoma), ALK-1 (inflammatory myofibroblastic tumor) and HHF-35 actin/smooth muscle actin (fibromatosis, myogenic, and myofibroblastic tumors). Moreover, demonstration of a t(7; 16)(q34;p11) translocation by conventional cytogenetics or by FISH analysis is diagnostic being present in >95% of cases. Metastatic LGFMS-GCR may differ from the primary tumor by exhibiting a more undifferentiated sarcomatous appearance with loss of collagen rosettes, increase mitoses, and nuclear atypia.

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WAKELY-Case 2.

History: A 53-year-old HIV+ man presented with fever, as well as pain and swelling of his posterior hard palate. Although born in Mexico, he has been a resident of the United States for > 20 years. At the time of presentation he was found to be hypotensive and tachycardic. A 5-6 cm ulcerated irregular mass was seen involving the hard palate, the buccal mucosa and extending to the gingiva on the upper and lower bridge. The patient had no anterior or posterior cervical lymphadenopathy.

CT revealed a L maxillary sinuses mass that had eroded the medial wall. A chest X-ray revealed mediastinal, axillary, and perihilar lymphadenopathy. Biopsies of the palate and maxilla were obtained. No flow cytometry was performed.

Pathologic Findings: A dense, solid population of medium to large cells was present just below the epithelial surfaces of sinonasal tissue and palatal mucosa. These had rounded nuclei with smooth contours, coarsely clumped chromatin, and variably present enlarged single nucleoli. Most cells had a moderate amount of amphophilic cytoplasm. Many had nuclei in an eccentric position, but mature plasma cells were distinctly rare. A perinuclear clear zone (hof) was absent. Individual cell necrosis was present, but not widespread, and a so-called starry sky pattern was not seen. Mitoses were common. Multinucleated cells were largely absent. Immunohistology results:

● **positive:** CD138, CD38, vimentin, EBV-EBER in-situ hybridization

● **negative:** CD3, CD20, CD56, cytokeratin AE1/3, CD10, bcl-1, bcl-2, CD5, bcl-6, CD23, CD99, actin, desmin, cytokeratin 7, CD30, S-100, HMB-45, CD79a

Diagnosis:

Oral Cavity: PLASMABLASTIC LYMPHOMA OF ORAL CAVITY.

Discussion: Plasmablastic Lymphoma of the Oral Cavity (PLOC) is one of the known AIDS-associated non-Hodgkin lymphomas. The others include: ^{a.)} diffuse large B-cell lymphoma (DLBL), ^{b.)} Burkitt Lymphoma, ^{c.)} Primary Effusion Lymphoma, and ^{d.)} Plasmablastic Lymphoma Associated with Multicentric Castleman's disease. In the most recent WHO classification, plasmablastic lymphoma (PL) is considered a variant of DLBL. The relative risk of B-cell NHL among HIV positive individuals is markedly increased (reported as 80-100 times greater) compared to the non-HIV population.

The initial report of this neoplasm and its association with HIV was recognized by Delecluse et al. 9 years ago when they presented 16 patients with a lymphoma of the oral cavity. Only 2 of 16 had bone marrow involvement, and unlike multiple myeloma none had a serum monoclonal protein. Cells of PLOC are essentially monomorphic with little variation in nuclear or cytoplasmic appearance. Most have immunoblastic morphology with coarse chromatin, a distinct nucleolus, and a plasma cell immunophenotype. Some examples show multinucleation and binucleation. Cells with features of maturing plasma cells are present, but often inconspicuous. Giemsa staining reportedly will allow one to see a paranuclear cytoplasmic hof. Unlike plasma cell myeloma PL is rapidly growing with a high mitotic index with some authors reporting a "starry sky" pattern in most cases, while others report it to be an infrequent finding.

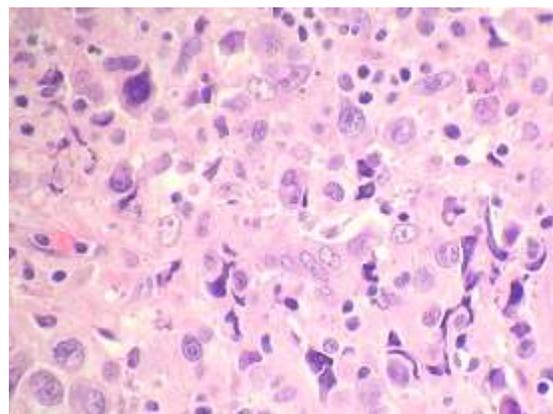
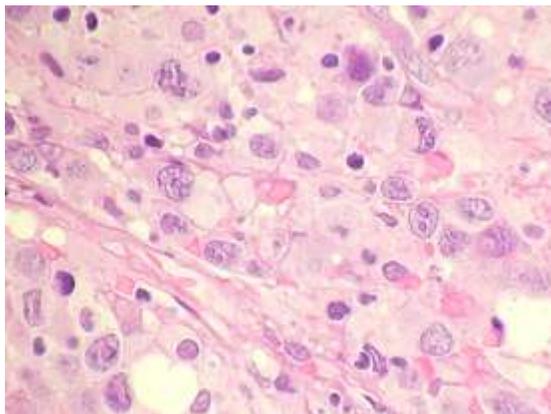
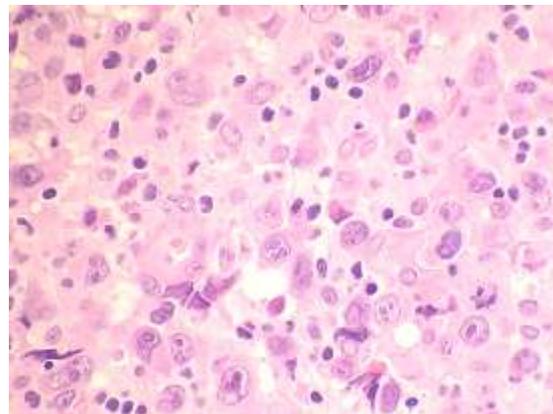
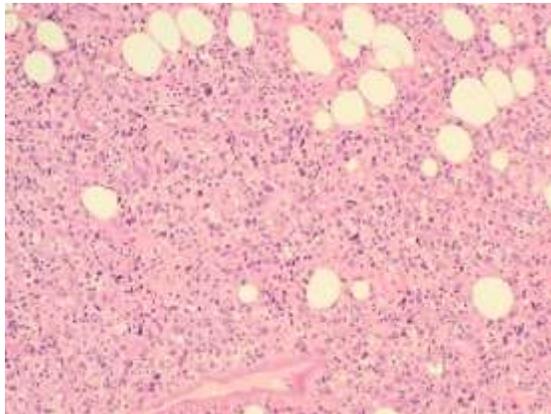
A recent large series by Dong et al. studied 13 patient with a median age of 41 yrs., and a M:F ratio of 5.5:1. All had extramedullary disease, and 85% had extranodal tumor at the time of presentation with the oral cavity being the most common site (46%) followed by bone & soft tissue (31%), and GI tract (23%). All 11 of their patient with follow-up died of disease within 3 years. The initial report of Delecluse showed an even more aggressive behavior with 82% of patients dead in 1 year. The typical immunophenotype of PL is negative

staining for CD3, CD20, and bcl-6, variable positivity for CD45, and EBV, and almost universal expression of plasma cell markers CD138, and vs38c. There is no reliable association with HHV-8.

The differential diagnosis includes undifferentiated carcinoma, diffuse large B-cell lymphoma (DLBL) – immunoblastic type, anaplastic plasmacytoma (plasmablastic myeloma), Burkitt lymphoma with plasmacytoid differentiation, and possibly even melanoma. Undifferentiated carcinoma should be easily separated from PL by positive staining for epithelial markers, and an absence of plasma cell markers. DLBL has less of a plasmacytic appearance than PL, and shows consistent CD20 positivity. Extramedullary large cell transformation of myeloma with plasmablastic morphology usually occurs after a prolonged interval as multiple myeloma. These tumors typically arise in immunocompetent rather immune suppressed individuals. Plasmablastic myeloma (PM) shows only a minor number of plasmablasts with nuclei that are often more pleomorphic than those encountered in PL. Also, PM is consistently negative for EBV. Burkitt lymphoma is typically negative for plasma cell markers, and CD20/bcl-6 positive. Rarely, patients with primary effusion lymphoma (an HHV8 + lymphoma) may develop a tissue mass, or present with a tissue mass and later develop a cavitory lymphomatous effusion. HHV8 staining should exclude these cases from diagnostic consideration.

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WAKELY-Case 3.

History: A 68-year old man presented with a 3-month history of progressive dysphagia. After extensive testing a 3rd chest CT scan showed a pedunculated heterogenous esophageal mass that was removed.

Pathological Findings: The resected polyp consisted of a firm, elongated club-shaped 15.0 x 7.5 x 4.5 cm mass with a 2.3 cm stalk. A smooth to finely granular surface was tan-pink; the distal end had a 2.6 x 1.9 cm ulcer. Cut sections showed a central core consisting of various-sized lobules of adipose tissue and fibrous tissue with small hemorrhagic foci

Non-keratinizing squamous epithelium surfaced the polyp with focal ulceration. The polyp core contained fibroadipose tissue with foci of chronic inflammation. Scattered polygonal or stellate-shaped lipoblasts were characterized by markedly hyperchromatic, multilobular/multinucleated nuclei. Also present were single and loose aggregates of large round and elongated cells with abundant eosinophilic cytoplasm typical of rhabdomyomatous differentiation. Many of these displayed long strap-like shapes with multiple nuclei arranged in tandem analogous to primitive myofibers. IHC showed positive nuclear staining of lipoblasts with MDM2 and CDK4, while rhabdomyomatous cells were strongly positive with myoglobin, myogenin, HNF-35 actin, and vimentin. Spindle cell areas of the polyp were positive with CD34 and vimentin. Mitotic figures were scarce. The proliferation index (Ki-67 stain) was <5%. S-100 was positive only in foci of adipose tissue. No staining occurred with CD117, HMB-45, SMA, or cytokeratin AE1/AE3. FISH analysis using the LSI MDM2 DNA probe demonstrated amplification of the *MDM2* gene locus at 12q14-q15 in 64% of the interphase cells.

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| Diagnosis: RHABDOMYOMATOUS WELL-DIFFERENTIATED LIPOSARCOMA ARISING IN GIANT FIBROVASCULAR POLYP OF ESOPHAGUS. |
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Discussion: Large pedunculated polyps (> 5 cm) of the esophagus are rare. At least 111 cases are reported as of 2006. Over 90% are giant fibrovascular polyps (GFVP) as described by Stout et al. GFVP is typically seen in middle aged men (age range 18 mos. - 88 yrs.). 70% present with progressive dysphagia and weight loss. About 25%, have a more dramatic presentation that involves regurgitation of the polyp into the oral cavity with respiratory compromise or even asphyxiation due to glottic obstruction – an unfortunate event recently recorded by Sargent et al.

Pathogenesis of esophageal GFVP is unknown. Likely, it derives from an outpouching of loose submucosal tissue into the lumen of the cervical esophagus where more than 80% of GFVP originate. Through normal peristaltic action, and eventual tractional forces produced by the polyp's own weight, the submucosal outpouching slowly grows to "giant" proportions (mean length, 13.3 cm; mean width, 3.8 cm) and assumes a club or sausage shape. The upper esophagus is where most benign neoplasms or tumor-like lesions arise including leiomyoma, hemangioma, inflammatory pseudotumor, granular cell tumor, and schwannoma. An exception is the rare occurrence of synovial sarcoma in the upper esophagus. Malignant pedunculated polyps such as liposarcoma, leiomyosarcoma, and spindle cell carcinoma more often arise in the mid-distal esophagus.

The histology of GFVP shows a non-keratinizing unremarkable squamous epithelium with occasional ulceration at the distal end. The polyp core contains variable sized lobules of mature adipose tissue, dense to loose fibrous tissue, thick and thin walled vascular spaces, and occasional myxoid change. An admixture of different tissues explains its heterogeneity using MRI and CT scan. Since any one of these components may predominate, a varied nomenclature is applied to GFVP including lipoma, fibromyxoma, fibroma, hamartoma, fibrolipoma, and fibroepithelial polyp. The WHO recommends the term *fibrovascular polyp* for any lesion with these previously described characteristics.

Despite the reported benign nature of GFVP, Caceres et al found 4 cases (3.6%) with malignant transformation. These were primarily either squamous cell carcinoma or liposarcoma. We initially interpreted the lipoblasts in our case incorrectly as "atypical" stromal cells. Positive immunohistology for MDM2 and CDK4 along with confirmatory FISH analysis demonstrating amplification of the *MDM2* locus confirmed the diagnosis of liposarcoma. In one case of GFVP harboring squamous cell carcinoma, the patient presented with dysphagia, but also metastatic cervical lymphadenopathy. Definitive diagnosis of most GFVP cases is possible only with completely resected specimens.

Despite its large size, initial imaging studies fail to demonstrate the presence of GFVP as an intraluminal mass 20-30% of the time. A number of reasons account for this difficulty including the fact that the covering mucosa of the polyp is the mucosa as normal esophagus, and polyps can span almost its entire length. In addition, GFVP can position itself against the esophageal wall and the small stalk may be overlooked. Barium swallow may be interpreted as normal because contrast is allowed to pass smoothly down the esophagus without getting around the polyp to demonstrate its intraluminal location. It may also show a pseudoachalasia narrowing of the distal esophagus caused by compression of the distal esophagus from the bulbous end of the polyp as in our case. Esophageal manometry often shows a hypertensive lower esophageal sphincter that can erroneously lead to a misdiagnosis of achalasia. Esophagoscopy may be misinterpreted as an intramural mass or extrinsic compression by a thoracic mass, or may even be reported as normal. Reports

from 2 different patients showed a GFVP being missed repeatedly by numerous radiographic modalities over a period of years such that the patients were referred for psychiatric evaluation due their continued symptomatology. Only after a more dramatic presentation such as regurgitation of the polyp was 1 of these patients diagnosed correctly.

Despite these difficulties, pre-operative CT and MRI correctly diagnose the majority of cases. The identification of the stalk of the polyp with large feeding vessels, and the heterogenous appearance of the polyp core are the major features that distinguish GFVP from other mass lesions by CT or MRI. Multiple subsequent studies could be necessary to arrive at a correct diagnosis. Radiographic findings are subject to interpretive error as in this case in which the heterogenous appearance was mistaken for foodstuff occupying a dilated esophagus. A final pitfall in radiographic imaging is its inability to reliably distinguish malignant transformation within a GFVP as demonstrated in our case and others.

Treatment of choice for GFVP is local surgical resection. Rarely if ever, would a patient need an esophagectomy; however, this has been performed. Fujita et al found at least 4 patients that were surgically over treated with esophagectomy because of no presurgical diagnosis.

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