Case — 1

Contributed by: Phil Allen, M.D.

Case Identification: FMC 14/S00025
Contributor: Dr Esther Quick, SA Pathology, Flinders Medical Centre, Bedford Park, South Australia.

History: The patient is an aborigine weighing between 160 to 200 kg who had noticed a slowly growing, large subcutaneous mass which had been present for many years in the right groin. Recently the skin over the mass became ulcerated. The underlying fat then became infected and a chronic abscess discharging pus prompted admission to Flinders Medical Centre. The pendulous mass was described clinically as a “pannus.” It did not involve the abdominal musculature. The intense induration around the ulcer raised the possibility of a carcinoma. No organ imaging was performed. The entire mass including the ulcer and abscess was excised. Post operatively, the wound healed well.

The specimen comprised skin and underlying subcutaneous tissue weighing 1901g and measuring 250x220mm by up to 65mm from superficial to deep. An irregular area of indurated skin crusting extended over an area 90x60mm as in the photograph below. The remainder of the skin surface exhibited a rugose, cobblestone, or peau d'orange appearance. Slicing the specimen revealed a large amount of unencapsulated subcutaneous fat in which there was an abscess measuring 50x40x30mm surrounded by haemorrhage and congestion. The subcutaneous fat distant from the abscess was traversed by fibrous septae. The dermis was thickened and oedematous.
Photograph of sliced specimen showing the haemorrhagic abscess cavity, the accentuation of the subcutaneous fibrous septae, the thickened dermis, the rugose skin and the unencapsulated, large, subcutaneous mass of fat.

The circulated sections show the rugose elevations of the thickened epidermis, pigmentation of the basal layer (the patient is an aborigine), gross thickening and oedema of the dermis in which there are numerous dilated vessels, perivascular chronic inflammatory cells, proliferating fibroblasts and newly formed, thin walled blood vessels. The subcutaneous fibrous septae are grossly thickened and oedematous with entrapped, dilated, thin walled vessels, chronic inflammatory cells and reactive fibroblasts. There are numerous, small, thin walled blood vessels in the subcutaneous fat which is infiltrated by foamy macrophages and scattered cells that an imaginative pathologist might call lipoblasts. The abscess wall has not been included in the circulated section.

**Diagnosis:** Massive localised lymphedema in morbid obesity complicated by a non-specific subcutaneous abscess.

**Comment:**

Massive localised lymphedema in morbid obesity was first described by the South Australian pathologist, Gelerah Farshid, and Sharon Weiss in 1998(1) and has been reviewed by Manduch associates in 2009(2). The condition is commonly confused with liposarcoma because of the degenerating fat cells which resemble lipoblasts. As subcutaneous fatty tumors that recur and
metastasise virtually never involve arise in the subcutis, any diagnosis of subcutaneous liposarcoma should always be regarded with scepticism.

Patients are usually middle aged and are morbidly obese. Lesions are most common on the inner thigh but two reported cases involved the upper arm and were associated with axillary lymphadenectomy(1). Three other thigh lesions were associated with previous damage to inguinal lymphatics or veins(1). The lower anterior abdominal wall is not a common location, although I have previously seen one other pendulous, suprapubic lesion that was clinically thought to be a lipoma.

The prognosis is more related to the underlying obesity than to the excised masses. Six of Farshid’s 12 patients with follow-up suffered from recurrence or persistent disease from within 10 months to 10 years after excision and one lesion recurred twice. Shon and associates(3) recently reported five instances of angiosarcoma arising in massive localised lymphedema. All their tumors were histologically “conventional high-grade angiosarcomas”. Although five cases seem to be an extraordinarily large number of such a rare tumor arising in a condition that had not previously not been complicated by angiosarcoma, one of the authors, Andrew Folpe, was a co-author of Manduch’s paper(2) so the tumors were likely to be genuine angiosarcomas, although follow-up of four cases (range 2-32 months) revealed that only one patient died of disease. One died from treatment and two were alive without disease, although the follow-up time for one patient was too short to be significant.

I understand that Saul is working up another series of massive localised lymphedema, a condition that is becoming increasingly common in those countries subject to the promotional wiles of the associates of the most famous of all the Kentucky Colonels.

References:

Case — 2

Contributed by: N. Volkan Adsay, M.D.

Clinical History: This is a 72-year-old male with a pancreatic mass discovered incidentally during workup for an inguinal hernia. MRI showed multifocal cystic dilatation of the ducts ranging from 0.9 to 1.6 cm in addition to a 2.2 cm enhancing pancreatic mass within the neck/proximal pancreatic body. Due to vascular proximity, patient underwent neo-adjuvant chemotherapy, followed by resection that was performed in two parts that mounted up total pancreatectomy due to margin positivity during frozen section. In gross examination, the main pancreatic duct revealed a solid, granular, friable mass spanning to a region of 5.7 cm of the MPD, and dilating the MPD to up to 2.7 cm. Separate small cysts measuring up to 1.9 cm were also identified both around and away from this main lesion.

Diagnosis: Intraductal papillary mucinous neoplasm with extensive high-grade dysplasia (CIS), pancreatobiliary type, (with microinvasion not present in your slides).

I believe this is a fairly nice example of pancreatobiliary type of intraductal papillary mucinous neoplasm (IPMN). As you know predominantly cystic (branch duct) IPMNs are becoming commonplace “incidentalomas” but main duct IPMNs and especially those that are pancreatobiliary (PB type) are relatively rare. I thought I should share this case with the group because the PB type IPMN is probably the rarest variant of this entity. In fact, some Japanese colleagues even question its existence, partly because it overlaps with the high-grade transformed areas of gastric type IPMNs, and thus they think what is called PB type IPMN may merely be a gastric type IPMN with extensive HGD. However, a case like this I think makes the argument that there is a distinct variant of IPMN different than the intestinal (villous intestinal), oncocytic and also gastric variants. As in this case, these PB type IPMNs process typically qualifies as HGD/CIS.

There was focal invasive carcinoma in this case that I unfortunately could not share with you because it was small. PB-type IPMNs often have invasive carcinoma and the invasion is often of the tubular type, which was the case here. Both the invasive and non-invasive components were positive for MUC1 but in a limited fashion.

Another perhaps interesting angle of this case is that it illustrates the overlap with the recently recognized entity of intraductaltubulopapillary neoplasms of the pancreas. ITPNs are very close kindred of IPMNs, but characterized instead by tubular configuration and non-mucinous (or minimally mucinous) cells. There were several foci with very prominent tubular configuration in this case, which, together with the non-mucinous cytology can be indistinguishable from ITPN. In fact, we suspect some of the cases reported as intraductaltubulopapillary neoplasm of the pancreas by some Japanese groups are PB type IPMNs. Many authors in the West prefer the entity of ITPN to be defined as “tubular” rather than “tubulopapillary”. Truth be told, this distinction may essentially be mostly academic anyways.

Regarding the prognosis PB-type IPMNs, both in our experience and in the literature, those with convincing invasive carcinoma behave aggressively but not as bad as ordinary pancreatic ductal adenocarcinomas.

I hope you all agree with me on the diagnosis and enjoy the case. Looking forward to your comments.
References:


Contributed by: Carlos Bacchi, M.D.

Clinical History: This is a 72-year-old white female with a left cervical lymphadenopathy.

Pathological findings: This is a large lymph node with its general architecture totally distorted by the presence of neoplastic follicles, which are arranged in a back-to-back pattern with very little amount of interfollicular tissue. These neoplastic follicles are composed by follicular center cells with virtually absence of mantle zone. In some follicles few tingible body macrophages are present. Most of the follicles have a round to oval contour. There is no polarization of the cells present in these follicles. The cellular composition of the follicles is made mainly by centrocytes with some interspersed large blastic cells (centroblast). Another important histological feature in this lymph node is the expansion of the sinuses (subcapsular and medullar) by anaplastic large cells (see figure 1). These cells have large nuclei, prominent nucleoli and distinct amphophilic cytoplasm. In this cell population mitotic figures are commonly seen. These cells are confined to the sinuses only. Immunohistochemistry study are summarized in the table below. The neoplastic cells of the follicles were positive for CD20, BCL2 and CD10 with no expression of CD30. On the other hand, the large anaplastic cells present in the sinuses showed expression for CD20 and CD30 with negativity for CD10. Both components were negative for ALK, CD3 and EBER EBV.

Diagnosis: Transformation of follicular lymphoma, Grade 2 into CD30-positive large B-cell lymphoma with anaplastic features with exclusive involvement of subcapsular and medullary sinuses.

Comment: This case is a nice example of transformation of follicular lymphoma with a peculiar morphology of the transformed component, i.e., CD30-positive large B-cell lymphoma with anaplastic cytology side by side with the classic follicular component in the same lymph node. Interesting to note that this transformed component is confined to the sinuses of the lymph node only. This unique type of follicular lymphoma transformation was described in 1997 by a member of our group: Larry Weiss! As stated by John Chan, follicular lymphoma is a dynamic and "unstable" neoplasm that can take up different appearances in different sites at different times. The natural history of follicular lymphoma is to eventually accumulate neoplastic large lymphoid cells and become diffuse, which results in progression/transformation to higher-grade lymphoma. This event (progression/transformation) occurs in about 60% of the all cases of follicular lymphomas. The transformation usually takes places into conventional diffuse large cell lymphoma but it can have as in this case an anplastic appearance with sinusoidal distribution and CD30 expression. Several genetic changes can mediate the transformation, such as TP53 gene mutation, somatic mutation in translocated BCL2 gene, RAS mutation, MYC rearrangement and P16 deletion or inactivation. The diffuse/sinusoidal component of these lymphomas is composed of large B lymphoid cells with anaplastic cytological features that expressed the CD30 antigen, indistinguishable morphologically from anaplastic large cell lymphoma, in contrast to the follicular component, which is consistently CD30 negative. Despite the markedly different histologic and phenotypic features, it is believe that both the follicular and diffuse/sinusoidal components of these
lymphomas represent two manifestations of a single neoplastic clone. In Larry's paper, there were described six cases of follicular lymphoma, large cell in five cases and mixed in one case, that transformed into diffuse or sinusoidal CD30-positive large cell lymphoma with anaplastic cytological features, both components of B-cell phenotype, as in our case. The case presented here is very recent and the patient is still being worked out in order to initiate treatment. One differential diagnosis considering the morphology that should be raised in this case is anaplastic large cell lymphoma. As the anaplastic cells in the sinusoidal are of B-cell phenotype, ALCL is automatically excluded. As ALK was negative by immunohistochemistry the diagnosis of ALK-positive ALCL is automatically ruled out. In summary, I decided to present this case due this unusual form of histological transformation of follicular lymphoma, which can show up in our routine case and should be recognized. Another relevant point to consider is that the presence of anaplastic histologic features in a lymphoma does not rule out the possibility of prior follicular lymphoma, particularly when a B cell lineage of those cells is demonstrated.

<table>
<thead>
<tr>
<th>IHC MARKERS</th>
<th>NEOPLASTIC CELLS PRESENT IN THE FOLLICLES</th>
<th>NEOPLASTIC ANAPLASTIC LARGE CELLS PRESENT IN THE SINUSES</th>
</tr>
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<tbody>
<tr>
<td>CD20 (see figure 2)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>BCL2</td>
<td>+</td>
<td>+</td>
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<td>CD10</td>
<td>+</td>
<td>+</td>
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<td>CD30 (see figure 3)</td>
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<td>CD3</td>
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<td>ALK</td>
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<tr>
<td>EBER-EBV</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ki-67</td>
<td>50%</td>
<td>70%</td>
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</tbody>
</table>
Reference

AMR Seminar #66

Case – 4

Contributed by: David Ben-Dor, M.D.

Clinical History: A parotid mass in a 46 yr old woman.

Gross description: A lobe of the parotid was received which on sectioning showed a well circumscribed nodule measuring 1.8 cm. was identified. The tumor was totally submitted in 3 blocks.

Microscopic Description: On the slide you have the nodule is totally encapsulated. The lesion is composed of small basaloid cells, some having rounded and more open nuclei with delicate chromatin, and others having smaller, dark nuclei with condensed chromatin. In my opinion some of the latter appear angulated. The cells are organized in nests and anastomosing trabeculae; in places the cells with the dark nuclei appear to surround the other type and can appear palisaded. Notably there are multiple sharply defined punched out spaces containing delicate basophilic mucinous material. The cells were variably positive for p63 and calponin, including those lining the punched out spaces. There are in addition small ductal spaces lined by non-basaloid cuboidal epithelial cells. OK 7 stains these epithelial cells while the basaloid cells are variably positive. Only a few cells were positive for Ki-67 and there were few to no mitoses.

Diagnostic Considerations: as a perfectly encapsulated lesion this would have to be benign and the above description fits basal cell adenoma. These tumors and especially the currently employed denomination are relatively recent entries into the diagnostic classification and are relatively rare (3% of epithelial salivary tumors in the AFIP files). They are most common in the parotid and begin to appear in the 3rd decade, reaching peak incidence between the 6th-7th. Grossly they are sharply circumscribed and especially in the parotid are encapsulated. Cytologically they are composed of the two types of cells described above with the cells with darker nuclei forming palisades around the ones with the lighter staining rounder nuclei, in addition to cuboidal epithelial cells. While originally thought to be of ductal basal cell origin, according to currently accepted these cells show differentiation into basal, ductal-luminal, and myoepithelial cells, which is reflected in the immunohistochemical positivity for the appropriate antigens. Histologically they are traditionally divided into solid, trabecular, tubular, tubulo-trabecular, or membranous subtypes. The latter notably can be multinodular and is characterized by abundant PAS-positive hyaline material representing excessive basal lamina production by tumor cells. In my opinion this case has characteristics of the solid and trabecular types with in addition cribriform spaces. Formally there is no established cribriform subtype (see below for further discussion) and the presence of this feature may create some discomfort since this can bring to mind adenoid cystic carcinoma but again the latter is a malignant tumor which by necessity needs to be invasive. In the AFIP fascicle the possibility of cribriform pattern in basal cell adenomas is brought up only in passing and is said to be “rare”. Similarly the entry in the most recent WHO blue book (2005) on basal cell adenomas mentions the cribriform pattern briefly as a possible and “rare” finding in one of the four variants as mentioned above.

More recently, the issue of cribriform morphology in basal cell tumors was reviewed by Tian et al in 2012. Historically, they cite Nagao et al who in their 1982 review in Cancer of basal cell adenomas of the parotid reported that 10% had an “adenoid cystic pattern”; these authors do not ascribe any particular biologic or clinical significance to this feature and appear to write it off as a type of cystic change. In any case they did not find it worrisome. Dardick in different later publications designated the cribriform pattern as a “rare” subtype of basal cell adenoma. Further quoting from Dardick, the cribriform morphology in adenoid cystic carcinomas results from pooling of
extracellular material produced by neoplastic basaloïd/myoepithelial cells, so that this can be expected in other tumors composed of these cell types, such as basal cell tumors. Cribriform morphology can also be found in pleomorphic adenoma, polymorphous low grade adenocarcinoma, and cribriform cystadenocarcinoma. In a review of their own material from a hospital in Shanghai, the authors found 18 of 255 basal cell adenomas (or about 7%) to show 10% or more cribriform changes. Interestingly, 14/18 of these adenomas showed invasion into the capsule but not beyond. However none of these tumors behaved malignantly. These authors point out that capsular invasion can also be seen in pleomorphic adenomas and correlates with regional recurrence.

Now I need to digress from the academic discussion and get back to this particular case. In fact the sections from the block I am able to share with the group is not wholly representative of the tumor. In two of the other blocks there was a limited focus of extra-capsular invasion (length of the focus 0.5-1 cm, and depth 1-3 mm.) into the immediately adjacent fat pushing against and eventually reaching the benign salivary acini but not growing between them. I chose this block out of necessity since the blocks with invasion were sent in consultation and were not available at the time I needed to send the material but I am including photos to illustrate this. The tumor beyond the capsule was identical in all respects to that inside it. Additionally, I was later informed by the clinicians that the patient had discovered the tumor herself by palpation and had been aware of its existence 5 years previously.

This added information changes the context of the discussion. By our conceptions the presence of invasion necessitates a diagnosis of malignancy, and while basal cell adenocarcinoma is a prime consideration, due to the cribriform morphology the possibility of adenoid cystic carcinoma cannot be so easily dismissed out of hand. I sent the slides to Bruce Wenig who pointed out that the cytomorphology of this tumor, with the two basaloïd cell types (and excluding those with true epithelial differentiation) as pointed out above, is inconsistent with adenoid cystic carcinoma, which is said to be monomorphic with the cells often having "clear cytoplasm and angular dark nuclei" (personally I think some of the cells in this tumor answer to that description; further, according to the AFIP fascicle (p. 230), the nuclei can also be "smoothly round ...(with a) lightly basophilic ... homogeneous chromatin pattern" which might describe the second cell type"). I would also expect an adenoid cystic carcinoma to show multiple mitoses, a higher Ki-67 proliferation rate, and more widespread invasion with perineural invasion (which was not seen in any portion of the specimen which was totally submitted for histological examination). Basal cell adenocarcinomas can otherwise have cytological and histological features indistinguishable from those of the corresponding adenomas except for the invasion. It's entirely possible that the lesion was originally a basal cell adenoma in which invasion eventually developed over time.

The Tian article also included a number of basal cell adenocarcinomas with cribriform features (3/15 or 20%). From the description given these tumors showed at most an incomplete capsule "with frank invasion focally with small lobules of tumor lying within adjacent adipose tissue", which sounds to me like the limited invasion shown by this case. One case showed "perivascular invasion" while perineural invasion was not documented.

In another more recent article by Jung et al, basal cell adenomas with or without capsular invasion and basal cell adenocarcinomas were compared with one another. Interestingly they mention that similar to this case, "BCACs (basal cell adenocarcinomas) were mostly encapsulated and had invasive areas at the periphery that varied in extent but were mostly minimal". One salient aspect is that while cribriform changes were seen relatively frequently in the carcinomas and adenomas with capsular invasion, they were not found in the adenomas without invasion. The first two groups were relatively similar in size and significantly larger than the last. These authors state (without giving a reference), "considering that it has now been officially accepted that pleomorphic adenoma has infiltrative and metastatic potential, basal cell adenoma may also be considered as an infiltrative neoplasm and the category of BCAC can be questioned". They go on to claim that "BCAC with extensive infiltrative growth, such as into skeletal muscle and skin, is rarely encountered". Further, while cases of basal cell adenocarcinomas with aggressive behavior have been reported, these authors speculate as to whether those cases were in fact basal cell adenocarcinomas and not something else. They conclude, "BCAC is a low grade tumor with little propensity for metastasis or recurrence. This raises doubt regarding the malignant potency of this tumor".
To recapitulate:

- cribriform morphology in salivary gland basal cell tumors has been overlooked and mostly ignored in the canonical literature;
- basal cell salivary gland lesions with cribriform morphology show a spectrum from benign encapsulated lesions without invasion through benign encapsulated lesions with capsular invasion to malignant (variably encapsulated) lesions with extracapsular invasion;
- cribriform morphology in the context of salivary gland basal cell tumors appears to be significantly associated with the tissue correlates of aggressivity, and if seen in a basal cell salivary gland tumor these should be searched for diligently even if not apparent on first observation;
- but on the other hand, tissue appearances in this context may not be good predictors of biological potential and the meaningfulness of benign and malignant needs to be reassessed for these lesions.

**Final diagnosis:** Basal cell adenocarcinoma of parotid, possibly developing over time in a pre-existing basal cell adenoma

**References:**

Ellis GL and Auclair PL, eds., Tumors of the Salivary Glands, AFIP Atlas of Tumor Pathology Fourth Series, Fascicle 9, American Registry of Pathology, Washington D.C., 2008: - basal cell adenoma in "Benign epithelial neoplasms" chapter 4, pp. 71-85


Nagao K et al, "Histopathologic studies of basal cell adenoma of the parotid gland". Cancer 1982, 50: 736-45

Jung et al, "Basal cell adenocarcinoma of the salivary gland: a morphological and immunohistochemical comparison with basal cell adenoma with and without capsular invasion". Diagnostic Pathology 2013, 8: 171
Fig 1- tumor penetrates beyond capsule (blue arrows) into fat and relation to native acini.

Fig 2- extra-capsular tumor in fat on left in relation to native acini at right. Note collagen strands between the two components.
Fig 3: intracapsular tumor on left (capsule denoted by blue arrows), extracapsular tumor in fat in middle, and native acini on right. Note collagen strands (yellow arrows) between extracapsular tumor and the benign acini. Is the tumor being walled off here by a neocapsule? Maybe in time the now extracapsular tumor would merge with the intracapsular tumor and the evidence of invasion would be lost?
Contributed by: Goran Elmberger, M.D.

Clinical History: A 31-year-old man with a few weeks dyspnoea. CT shows features more consistent with a hypersensitivity pneumonitis than a sarcoidosis with extensive bilateral centrilobular nodules with confluence and ground glass opacities localized to the middle and lower lung sections. The patient worked in a recycling facility with known exposure to hard metal (cobalt and wolfram). BAL revealed increased granulocytes and lymphocytes. CD4/CD8 ratio low - 0.4. Many multinucleated histiocytic giant cells were seen. Eosinophilic granulocytes were prominent (11%). A diagnostic VATS lung biopsy procedure was performed with tissue taken from RML and RLL.

Histology: A patchy bronchiocentric inflammatory infiltrate with bronchiolar metaplasia (Lambertosis) and intraalveolar multinucleated giant cells of both histiocytic and pneumocytic derivation is seen. The multinucleated histiocytic giant cells generally resemble Langhans cells but some are more looking like Touton type. Some giant cells show emperipolisis of macrophages (cannibalism= macrophage eating macrophage). In other areas intraalveolar macrophages of foamy type give a DIP-like pattern. A few fibroblast foci are present. In some sections (not included) mild scar-like fibrosis and microscopic honey-combing are seen. A mild deposition of antracotic pigment and iron (special stain) can be seen in pleura and centrilobular areas. Generally the inflammation is mild and composed of lymphocytes. CD3 and CD 5 shows dominating component with small T-lymphocytes in areas with disease activity and CD 20 reveal some lymphoid follicles close to bronchioli. CD4/CD8 ratio is low. CD1a and S100 highlight few diffusely distributed non-aggregated Langerhans cells. No asbestos bodies. The centrilobular distribution is highlighted by p63 and TTF1 stains. SMA stains indicate myofibroblastic activity in areas of microscopic scarring.

Diagnosis: Hard metal/Cobalt pneumoconiosis (giant cell interstitial pneumonia; GIP)

Follow-up and treatment: Prednisone 10 to 5 mg. New CT May partial regress pulmonary infiltrates. Better values in spirometry. Feeling better. Quit old job. Now looking for new! The factory is under investigation and levels of cobalt were found unacceptable. Legal actions taken.

Discussion: Just sent the case in before going to Tokyo seminar where TC presented a nice case. Tom gave an excellent presentation and there is not much to add but for those not being present I will focus on some newer developments. Actually this was my first encounter with interstitial lung diseases after moving to Örebro University Hospital. Hard metal lung disease is a rare form of lung disease caused by sensitization to cobalt. It occurs in patients exposed to hard metal and in diamond polishers. Before the identification of cobalt as central in the pathogenesis of the disease cases had been classified as giant cell interstitial pneumonia according to the morphology based classification of Liebow. The usual pulmonary manifestations of hard metal are interstitial lung disease, IgE-mediated asthma and a syndrome resembling hypersensitivity pneumonitis. Rarely spontaneous bilateral pneumothorax can be presenting findings. Patients with cobalt related ILD may show latency up to 25 years after exposure.

HR CT abnormalities include patchy bilateral lobular ground glass opacities without zonal predominance, consolidation, reticulation, centrilobular nodules and occasionally honeycombing end stage fibrosis. Some patients may present with a HP-like CT.
BAL analysis shows an increase in neutrophils and lymphocytes with low CD4/CD8 ratios and many multinucleated sporadically cannibalistic giant cells. An increase multinucleated giant cell/alveolar macrophage ratio > 4 % seems to be diagnostic. Some authors claim BAL to be equivalent to tissue biopsy for diagnosing GIP.

**Biopsy procedures:** Diagnosis generally is performed on open or VATS guided large biopsies. Occasional cases have been diagnosed on transbronchial biopsies or even BAL fluids. Tom’s case was ample material from lung explant.

**Uncommon histological patterns:** Some patients show “atypical GIP” with fibroblastic foci as in UIP. HMLD can occasionally be diagnosed on transbronchial biopsies but usually a VATS or open biopsy is required. A few patients have presented with upper-lobe dominant pulmonary fibrosis.

**Detection of cobalt and tungsten** containing particles has previously been reported with scanning electron microscopy with energy dispersive spectrometry (SEM/EDS). Newer techniques like electron probe microanalysis can describe the histological distribution of particles.

**Treatment and prognosis:** Many cases respond to exposure termination and steroid treatment. Some need immunosuppressive drugs and a few will succumb without lung transplantation.

**Lung cancer risk in hard-metal workers:** A French study (Moulin et al) showed that hard metal workers had an increased mortality from lung cancer due to simultaneous exposure to cobalt and tungsten carbide. The odds ratio increased with cumulative exposure and duration of exposure.

**References:**

BAL Giemsa (x 40) with multinucleated giant cells, macrophages, lymphocytes and granulocytes of neutrophil and eosinophil types
Contributed by: Franco Fedeli, MD

Clinical History: A 34-year-old man presented with a rapidly expanding left hypochondrial mass. Pain preceded the appearance of the mass. RMN scan reveals a large, sharply defined, heterogeneous mass with 18 x 12 x 10 cm diameter that involves the entire left lobe of the liver and the gastric wall. It appears heterogeneously isointense and hyperintense in unenhanced T1-weighted and T2-weighted fat suppressed images respectively, compared to the normal parenchima, with multiple round areas markedly hyperintense in T2w sequences. On both scans a starshape central area of lower signal is evident. After paramagnetic contrast medium administration (Dotarem 0.2 ml/Kg) the neoplasm, in the arterial phase demonstrates early, peripheral hyperintense globular enhancement which progress centripetally. Thereafter in the portal and equilibrium phase the mass shows peripheral hyperintense areas, but, also after 3 hours from contrast medium administration, the central part of the neoplasm remains hypointense.

Macroscopic Findings: Macroscopically a 19 cm × 15 cm mass occupying the left lobe of the liver was present.

Microscopic Findings: Fetal cells closely resemble the developing foetal liver, and are arranged in irregular 2-cell thick plates. They are smaller and more irregular than normal hepatocytes, with a moderately abundant acidophilic cytoplasm, and a round to oval, slightly irregular and basophilic nucleus. Pale cells, rich in glycogen, alternate in a typical pattern with darker cells.

Immunohistochemical Findings: Neoplastic cells show positivity for CK MNF116, policlonal CEA, Hepatocyte, EGFR and negativity for CK 7, CK20, Chromogranin, CD56, CD34, S-100 and Synaptophysin, MIB-1 Proliferating Rate 30%.

Diagnosis: Adult Hepatoblastoma fetal type.

Follow up: After surgical resection of the left liver and subtotal gastrectomy patient received 2 cycles of sistemic chemotherapy (gentamicina) that soon he couldn’t tollerate and 2 months later a RMN scan showed multiple liver metastases which were treated with TACE (transarterial chemoembolization). Five months later a total body CT scan revealed multiple lung nodules and new liver metasteses. He died after 11 months.

Discussion: Hepatoblastoma is rare in older children and exceedingly so in adults. The age span of adult patients presenting with presumed hepatoblastoma was 17– 78 years. The gross findings in the described adult hepatoblastoma are not different from those described in children. Some tumours are described as encapsulated or surrounded by a pseudocapsule, whereas others may display indistinct margins. The diagnosis of hepatoblastoma is mainly based on histology.

In 1967, Ishak and Glunz proposed two HB subtypes: epithelial with foetal and embryonal cells and mixed epithelial and mesenchymal (1). The common denominator between adult and paediatric cases is the occurrence of embryonal or immature aspect of the tumours. Gonzalez-Crussi et al. (2) described the more aggressive macrotrabecular pattern in HB, stressing the difficulties of classifying such tumours as hepatoblastoma or hepatocellular carcinoma.

Another hepatoblastoma subtype described in children is the small-cell undifferentiated pattern previously called “anaplastic” (3). This pattern is characterised by small, undifferentiated and poorly cohesive cells, with scant cytoplasm and hyperchromatic nuclei, initially described as “resembling neuroblastoma cells” (4).
The presence of mesodermal derivatives is characteristic of mixed, epithelial and mesenchymal hepatoblastoma (1). These mesenchymal elements consist of a proliferation of primitive-appearing mesenchymal spindle-shaped cells, intimately admixed with the epithelial elements in a highly cellular pattern.

Whether the adult cases of hepatoblastoma represent blastemal tumours, stem cell tumours, or unusual differentiation patterns in otherwise more frequent adult liver tumours remains to be established.

The following table (5) summarises the main histological criteria to distinguish hepatoblastoma from hepatocellular carcinoma.

<table>
<thead>
<tr>
<th></th>
<th>Hepatoblastoma</th>
<th>Hepatocellular carcinoma (classical HCC)</th>
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<tbody>
<tr>
<td>Histological clues</td>
<td>“Light and dark” pattern</td>
<td>Underlying cirrhosis</td>
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<tr>
<td></td>
<td>Extramedullary hematopoiesis</td>
<td>Cytoplasmic inclusions, bile production</td>
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<td></td>
<td>Mesenchymally-derived tissue</td>
<td>Bizarre nuclei, giant tumour cells</td>
</tr>
<tr>
<td>Foetal type HB</td>
<td>Cords or thin plates, intervening sinusoids</td>
<td>Trabecular architecture in macrotrabecular HB</td>
</tr>
<tr>
<td>Embryonal type HB</td>
<td>Dense sheets, rosettes</td>
<td>Large 10-20 cell-thick trabeculae in macrotrabecular HB</td>
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<tr>
<td>Tumour cell</td>
<td>Thinner</td>
<td>Larger</td>
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<tr>
<td>Trabeculae</td>
<td></td>
<td>Trabecular architecture in macrotrabecular HB</td>
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<tr>
<td>Tumour cell size</td>
<td>Smaller cell size</td>
<td>Cells larger than normal hepatocytes</td>
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<td></td>
<td>Small cells</td>
<td>Small undifferentiated cells (SCU HB vs. undifferentiated characteristics in HCC)</td>
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<tr>
<td>Cell characteristics</td>
<td>Uniform small cuboidal cells resembling foetal liver</td>
<td>Large polygonal cells (varies with tumour grade)</td>
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<td></td>
<td>Distinct cell membrane</td>
<td>“HCC-like” cells in macrotrabecular HB</td>
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<tr>
<td></td>
<td>Uniform nuclei</td>
<td>Nuclear anisocytosis, hyperchromasia (vary with tumour grade)</td>
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<td></td>
<td>Abundant clear, granular or smooth cytoplasm</td>
<td>Moderate amounts of eosinophilic cytoplasm</td>
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<td></td>
<td>Low N/C ratio</td>
<td>Variable N/C ratio according to tumour grade</td>
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<tr>
<td>Mitoses</td>
<td>Low mitotic rate</td>
<td>Frequent; bizarre mitoses un­common</td>
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<td></td>
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<td>Frequent; bizarre mitoses</td>
</tr>
</tbody>
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References:


Contributed by: Jerónimo Forteza, M.D

Clinical History: 25 year old woman with retroperitoneal tumour 16cm long above and in relation with the left kidney in the adrenal gland.

Microscopy features: Diffuse proliferation of the undifferentiated cells of intermediate size, small lymphocytes in plasma cells scattered throughout. These cells have a round nucleolus in acidophilic cytoplasm.

Electron Microscopy: With high power electron microscopy it is possible to see in the cytoplasm, rough endoplasmic reticulum, mitochondria and isolated electrodense granules. We found electrodense unions between the cells.

Immunohistochemistry: Negative for Factor VIII, CD31, WT1, CK5/6, CK20, Ck7, Ck AE1/AE3, Chromogranin, Synaptophysin, Melan A, Enolase, Calretinin, BCL2, Desmin, EMA, LCA, C-kit, S100, a-Fetoprotein, GFAP, CD15, CEA, Laminin, Caldesmon.


Diagnosis: EWING-PNET retroperitoneal sarcoma.
hemi desmosomes (arrow), electron dense granules (*)
Contributed by: Masaharu Fukunaga, M.D. (S13-2667 B7)

**History:** A 60-year-old, gravida 1, para 1, female presented with abdominal discomfort. CT, MRI and physical examination indicated a left ovarian borderline tumor. Serum levels of SCC were mildly elevated 44U/ML. The patient undertook a bilateral salpingo-oophorectomy, hysterectomy and omentectomy. The patient is alive with no evidence of disease at five months after surgery.
Macroscopic features: An ovarian tumor measuring 10x7x5 cm was mono-cystic with small papillary fronds and it contained 400 ml dirty yellowish liquid. Hemorrhage and hemosiderin deposits were observed.

Diagnosis: Mixed-epithelial papillary cystadenoma of borderline malignancy, Mullerian type MEBMM with squamous overgrowth (SO).

Comments: Histologically, the cyst was predominantly lined by squamous epithelium with mild atypia. Benign looking mucinous epithelium was intermingled with squamous epithelium. Endometrioid type glands with mild atypia were focally observed. There was no evidence of stromal invasion. Intraepithelial infiltration by neutrophilic and eosinophilic infiltrates was prominent. The stroma was fibrous. Endometriosis is noted in other sections. The right tube, left ovary and tube had no significant abnormalities.

The case is a typical example of MEBMM (1) with SO (2), characterized by mixed Mullerian epithelial components (mucinous, endometrioid, squamous, serous) without stromal invasion and predominant squamous components. The differential diagnoses include borderline (proliferating) Brenner tumor, transitional cell carcinoma, squamous cell carcinoma associated with mature cystic teratoma. MEBMM is considered to arise from endometriotic cyst (2). Compared with MEBMM, MEBMM with SO arises in older patients and it is opt to be higher stage. It is assumed that squamous epithelium gradually overgrows in a substantial time (1).

References:

Contributed by: Allen Gown, M.D.

Clinical History: The patient is a 47 year old female who presented with a one week history of lower abdominal discomfort, pain and fever. Ultrasound revealed the presence of large, 15 x 14 x 11 cm and 7 x 6 x 4 cm pedunculated masses in the pelvis. Her endometrial thickness was 9 mm. Ovaries were not seen. She had a TAH-BSO, omentectomy and bilateral pelvic lymphadenectomy.

Pathologic findings: The specimen received by pathology included an enlarged uterus with attached right and left fallopian tubes. The fallopian tubes and fimbriated ends were unremarkable. The attached 132 gram right ovary was distorted by the presence of a 5 cm light tan, focally fibrotic and focally edematous mass. The uterus was unremarkable save for a 1 cm fibroid. A specimen representing the resected left adnexal mass was a red-tan, bosselated, firm 17 x 15 x 11 cm mass with well defined borders. An intraoperative frozen section was interpreted as likely Krukenberg tumor. Histology revealed the tumor to be a high grade adenocarcinoma with both glandular and solid areas.

Immunohistochemistry findings (see accompanying images):

<table>
<thead>
<tr>
<th>Antibodies to:</th>
<th>Results:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX8</td>
<td>Negative</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Uniformly positive</td>
</tr>
<tr>
<td>CDX2</td>
<td>Variably positive</td>
</tr>
<tr>
<td>Villin</td>
<td>Negative</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>Variably positive</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>Variably positive</td>
</tr>
<tr>
<td>WT-1</td>
<td>Negative</td>
</tr>
<tr>
<td>Napsin A</td>
<td>Negative</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>Focally positive</td>
</tr>
<tr>
<td>Mammaglobin A</td>
<td>Focally positive</td>
</tr>
</tbody>
</table>

Diagnosis: Adenocarcinoma, primary or metastatic to ovary.
Discussion: This tumor represents a high grade adenocarcinoma, present in both ovaries, with a very confusing immunophenotype. My initial thoughts were that this was an endometrioid adenocarcinoma, a diagnosis supported by the strong ER expression in the tumor; however, the negative PAX8 studies would be extraordinarily unusual, as virtually 100% of endometrioid, serous, and clear cell (and about 50% of mutinous) are PAX8 positive. And the tumor expresses both GI (CDX2) as well as breast-associated (mammaglobin A, GCDFP-15) markers. Expression of CDX-2 has been described in endometrioid adenocarcinomas as well as the ‘morules’ sometimes present in endometrioid lesions(1,2). Our laboratory has found expression of breast markers such as GCDFP-15 and mammaglobin A in a small subset of ovarian cancers, too, although these are thought to represent strong breast-associated markers. But the present tumor displayed even more unusual findings, i.e. extensive neuroendocrine differentiation, as evidenced by the extensive positivity with antibodies to chromogranin A and synaptophysin, particularly in the solid areas. However, neuroendocrine differentiation has been described in endometrioid adenocarcinoma (3).

Representative immunostains are shown in an accompanying figure.

I vacillated several times in the interpretation of this tumor, initially favoring a primary ovarian endometrioid adenocarcinoma, but eventually favoring a metastatic adenocarcinoma. What is the group's opinion of this tumor? Is it a rare primary PAX8-negative ovarian adenocarcinoma (e.g., endometrioid)? Is it a metastasis from the GI tract? From the breast or other site? The case was subsequently reviewed by Robin Young at the Massachusetts General Hospital, along with Ester Oliva, and both found the immunohistochemistry “very confusing,” but thought that the tumor represented an endometrioid adenocarcinoma. Does the group agree with that assessment? Should we just throw out the confusing immunohistochemistry findings?

REFERENCES:


Contributed by: Thomas Krausz, M.D.

Clinical History: 31-year-old female with recent history of Cushing’s disease, hirsutism and last menstrual period 3 years ago. Investigations revealed markedly increased levels of serum testosterone (both free and total testosterone) and cortisol. CT showed a 10 cm right adnexal mass and normal adrenals, kidneys, pancreas and liver. Exploratory laparotomy located the mass to the right ovary. Frozen section diagnosis was “Leydig cell tumor”. Hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy were performed.

Macroscopic features: The right ovary was entirely replaced by a 12.0 x 9.0 x 7.0 cm mass with a smooth outer surface. The cut surface showed a yellowish brown multinodular mass with areas of necrosis and hemorrhage. No normal residual ovary was grossly identified. Both fallopian tubes and left ovary were grossly normal. Normal sized uterus showed a few small (up to 0.9 cm) subserosal fibroids. The endometrium was thickened, up to 0.6 cm. Frozen section was read as “decidualized endometrium with atrophic glands”. Omentum and pelvic lymph nodes were grossly normal.

Microscopic features: The neoplastic cells are arranged in a nested to diffuse growth pattern and supported by a delicate, richly vascularized stroma. The tumor is mostly composed of medium-sized to large polygonal cells with eosinophilic, slightly granular cytoplasm, however in some areas the cytoplasm is pale and vacuolated. Most of the tumor cells have centrally placed vesicular nuclei with prominent nucleoli, but some groups of smaller neoplastic cells exhibit grooved nuclei. Intranuclear cytoplasmic pseudoinclusions are also seen. There is variable nuclear pleomorphism. Mitotic activity is up to 8 mitoses/10 HPFs. Areas of hemorrhage and necrosis are present. The overall features are those of a steroid cell tumor. Rare cytoplasmic hyaline globules are present but no Reinke crystalloids are identified.

Immunohistochemical analysis:
Positive: cytokeratin (Cam5.2, AE1/AE3), vimentin, SF-1, inhibin, calretinin, Melan-A.
Negative: EMA, cytokeratin 7, WT1, S-100, PAX8, FOXL2, SMA, ACTH

Diagnosis: Ovarian steroid cell tumor, not otherwise specified (malignant).

Follow-up: Multiple peritoneal and retroperitoneal metastases developed 3.5 years later, accompanied by high levels of serum testosterone and cortisol. Patient is currently receiving chemotherapy.

Comments: The pathologist on frozen section service and a different pathologist who signed out the case, both favored the diagnosis of Leydig cell tumor. Subsequent consultation classified this neoplasm correctly as steroid cell tumor, not otherwise specified. In view of the absence of Reinke crystalloids, the large tumor size (12 cm), brisk mitotic activity, nuclear pleomorphism, and necrosis, this tumor is best classified as steroid cell tumor, not otherwise specified. This category of steroid cell tumors, in contrast to Leydig cell tumor and stromal luteoma, has malignant potential, therefore it is important to classify it properly. This particular patient developed metastases 3.5 years later.

Steroid cell neoplasms of the ovary comprise less than 1.0% of all sex cord-stromal tumors. Depending on location in the ovary, size and clinical setting, they have been classified under a variety of names in the past, including hilus cell tumor, stromal Leydig cell tumor, stromal luteoma, pregnancy luteoma and lipid cell tumor. These tumors are
composed exclusively of cells resembling typical steroid hormone-secreting cells (lutein cells, Leydig cells, and adrenal cortical cells). WHO classification includes three groups of steroid-producing tumors: (1) Stromal luteoma; (2) Leydig cell tumors (either hilar or stromal); and (3) steroid cell tumors not otherwise specified.

Stromal luteoma is usually associated with estrogenic symptoms (endometrial hyperplasia, vaginal bleeding) but a minority can be androgenic. It is located in the ovary centrally and surrounded by a preserved ovarian cortex, which usually exhibits features of hyperthecosis. Stromal luteomas are usually unilateral, small (2 – 3 cm) and behave in a benign fashion.

Leydig cell tumors are androgenic (virilism, hirsutism) due to the secretion of testosterone. Leydig cell tumors may occur in the hilus or, rarely, in the ovarian stroma. They are defined by the presence of Reinke crystalloids. However, these structures may not be identified in all the cases. Similarly to stromal luteomas these tumors are usually unilateral and relatively small (< 3cm). Leydig cell tumors may show nuclear atypia in the form of enlarged, bizarre nuclei the presence of which does not indicate malignant potential. They usually behave in a benign fashion.

Steroid cell tumors not otherwise specified represent approximately 60% of steroid cell tumors and cannot be classified as either stromal luteomas or Leydig cell tumors. They can be seen in all ages (mean age 43 years) and cause androgenic (50%) or estrogenic (10%) manifestations. They may also be associated with a variety of other symptoms due to the production of other hormones, including Cushing's syndrome. In the series published by Hayes and Scully (1987) four of the 63 steroid cell tumors, not otherwise specified had hypercortisolemia and Cushing's syndrome. 25% had no evidence of hormonal disturbance. Steroid cell tumors, NOS are usually unilateral (6% bilateral in Hayes and Scully’s series), large, with a mean diameter of 8 cm. In contrast to the benign behavior of stromal luteomas and Leydig cell tumors, steroid cell tumors not otherwise specified have a guarded prognosis. Even though most are confined to the ovary, up to 20% extended beyond the ovary at the time of diagnosis and 34% were clinically malignant in one of the largest series (Hayes and Scully 1987). Interestingly, 17% of the malignant tumors in the same series had association with Cushing's syndrome. The best pathologic correlates of malignant behavior: two or more mitotic figures per 10 high power fields (90% malignant); necrosis (86% malignant); a diameter of 7 cm or greater (78% malignant); hemorrhage (77% malignant); grade 2 or 3 nuclear atypia (64% malignant). Malignant tumors can lead to peritoneal implants. However, the outcome of a given neoplasm cannot be predicted with certainty even if lacking these parameters. Tumors containing Reinke crystalloids are usually benign.

Steroid cell tumors, NOS must be distinguished sex cord-stromal tumors, and from other tumors in the steroid cell category on the basis of location, size, presence or absence of Reinke crystalloids, clinical context and hormonal symptoms. They also can be confused with some malignant germ cell tumors, ovarian clear cell carcinomas (both oxyphilic and clear cell phenotype) and metastatic renal cell carcinomas. Clinical/imaging context and immunohistochemical markers are helpful in this regard. There are useful immunohistochemical markers to help with differential diagnostic dilemmas (Zhao C et al, 2009; Jones MW et al, 2012, Offman SL et al, 2012, Rabban JT et al, 2013).

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Offman SL, Longacre TA. Clear cell carcinoma of the female genital tract (not everything is as clear as it seems). Adv Anat Pathol 2012; 19:296-312


Case – 11

Contributed by: Thomas Mentzel, M.D.

Clinical history: A 73-year-old female patient disclaimed progressive dyspnoea, weakness, loss of weight, and intermittent fever. Clinical examination revealed that the respiratory movement on the right was less than on the left side, percussion showed dullness on the basal right side and a chest radiograph revealed a mass in the basal right thorax. After a biopsy an anterolateral thoracotomy on the right side was performed and there was large solid mass with contact of the diaphragm. The lung was fixed at the mass but not infiltrated. A 15 x 10 x 9 cm neoplasm was excised. Two months later the patient disclaimed again progressive dyspnoea and elevated CRP, and in chest X-ray a relapse of the neoplasm was detected. In addition paracardial and paraesophageal tumour masses and tumour nodules in both adrenals were found. A palliative chemotherapy was recommended, but the patient denied the treatment and died after a short time.

Pathological findings: Histologically, the neoplasm shows in most blocks morphological and immunohistochemical features of classical solitary fibrous tumour. The variable cellular neoplasm is composed of spindled tumour cells that are associated with numerous vessels showing a haemangiopericytoma growth pattern, and are set in a collagenous stroma with focal hyalinisations and areas of ischemic necrosis. Immunohistochemically, neoplastic cells stain positively for CD34 and STAT6 but are negative for EMA, pancytokeratin, actins, and S-100 protein. In some areas an abrupt transition to more cellular areas is present, and in these areas confluent enlarged plump spindled and round tumour cells containing enlarged and atypical nuclei with numerous mitoses are noted. The neoplastic cells in these areas are CD34 negative but show a nuclear staining for STAT6.

Diagnosis: Dedifferentiated solitary fibrous tumour.

Comments: Dedifferentiation represents a form of progression in malignant soft tissues tumours and is seen in neoplasms of different lines of differentiation (i.e. dedifferentiated chondrosarcoma, dedifferentiated liposarcoma, dedifferentiated leiomyosarcoma). Dedifferentiation within solitary fibrous tumour is a rare and recently characterized phenomenon and associated with a poor clinical course. In addition a heterologous differentiation (osteosarcomatous and rhabdomyosarcomatous differentiation) has been reported. It has been shown that expression of CD34 is often lost in dedifferentiated tumour areas that show on the other hand an expression of p16 and p53, and p53 mutations have been reported as well.

References:


Thway K, Hayes A, Ieremia E, Fisher C. Heterologous osteosarcomatous and


Mosquera JM, Fletcher CDM. Expanding the spectrum of malignant progression in solitary fibrous tumors: a study of 8 cases with a discrete anaplastic component--is this dedifferentiated SFT? Am J Surg Pathol. 2009; 33: 1314-1321
Contributed by: Santiago Ramon y Cajal, M.D.

Clinical History: A 18 year old boy with a solid-cystic lesion in right frontal lobe.

Gross: Received in formalin is fixed brain parenchyma fragment comprising two convolutions and a groove, which is 40 x 40 x 25mm. The piece is partially lined by leptomeninges and has a mass of grayish with yellowish areas, elastic consistency.

Histopathological Features: Histological sections show gray and white matter extensively infiltrated by a tumor is characterized by a marked pleomorphism. Consisting of large cells, large eosinophilic cytoplasm and hyperchromatic nuclei and bizarre appearance. It was also observed abundant multinucleated cells and intranuclear pseudo-inclusions. Next to the main glial tumor cellularity habit, another second population is also identified, of moderate size, oval nucleus centered microvacuolado cytoplasm, giving them a foamy habit. Are also common perivascular lymphocytic cuffs, dystrophic calcifications and eosinophil granular bodies. Moreover, vascular endothelial hyperplasia or no necrosis was observed. The mitotic figures are rare (2/10 CGA).

Immunohistochemistry: Immunohistochemical study showed that the primary tumor cellularity (glial) and diffusely expressed intense focal expression for GFAP and Synaptophysin, CD34 and neurofilament. The rate of cell proliferation (Ki67) focally reaches 5%.

Diagnosis: Pleomorphic xanthoastrocytoma, Grade II, WHO 2011.

Comments: Pleomorphic Xanthoastrocytoma is a neoplasm of the brain that occurs often in children and teenagers. First described in 1979 (Cancer 1979;44:1839). Usually cystic with a frequent cyst-mural nodule architecture.

Children affected by Pleomorphic Xanthoastrocytoma can present different symptoms that might include headache, or seizures. They usually arise supratentorial and superficially from the cerebral hemispheres (upper most sections) of the brain and in contact with the leptomeninges, rarely they arise from the spinal cord. Neoplasms are found in the frontal or on top of the parietal lobe, in about 20% of cases more than one lobe was involved. These tumors are usually slow-growing. The neoplasms are associated with the sudden onset of seizures.

Histopathological features are usually seen in superficial compact component of tumor, including pleomorphic cells (mono- or multinucleated with frequent nuclear inclusion and occasional cytoplasmic xanthomatous change), spindle cells arranged in fascicular pattern. Other features include perivascular lymphocytic cuffing, scattered eosinophilic granular bodies, reticulin rich network. Variable hemorrhage and protein granular degeneration (similar to pilocytic astrocytoma). No necrosis and no mitotic activity, except in tumors “with anaplastic features”. GFAP and S100 (Am J Surg Pathol 2002;26:479, Arch Pathol Lab Med 2003;127:1187). Reticulin, class III beta tubulin (73%). Variable expression of neuronal markers including synaptophysin.

Pleomorphic Xanthoastrocytoma is, in general, considered a benign tumor. It will show up as a contrast-enhancing tumor by current imaging investigations (e.g., CT scan, MRI). It is classified as Grade II Astrocytoma. Lesions with
significant mitotic activity (5+ mitoses per 10 HPF) or with areas of necrosis may be designated "pleomorphic xanthoastrocytoma with anaplastic features" and in some series until 15-20% progress to malignancy

Surgery is often the treatment of choice.

**AMR Seminar #66**

**Case – 13**

**Contributed by**: Brian Rubin, M.D.

**Clinical History**: Unfortunately, I don’t have any clinical history other than that the patient was a 50 year old woman with a gastric mass. She had a gastric wedge resection which revealed an ulcerated, exophytic mass in the gastric wall measuring 5 x 3.8 x 3.1cm.

Histologically, the lesion is unencapsulated but circumscribed and does not infiltrate the overlying mucosa. There is however, mucosal ulceration which often happens over gastric mural masses such as GIST and Schwannoma. The lesional cells are arranged around cystic spaces and fibrous tissue with numerous admixed blood vessels of various sizes, many with hyalinized walls. The overall low power appearance is reminiscent of fibrotic lung tissue. The lesional cells are relatively monomorphic, small, ovoid appearing spindle cells with oval shaped nuclei, finely stippled chromatin and a small amount of eosinophilic cytoplasm. Occasionally, a few of the spindle cells appear to join together to form multinucleate cells, but they are not a lot of them. Mitotic activity is low and there are no atypical mitotic figures. Additionally, there are foci or extramedullary hematopoiesis scattered throughout the lesion.

Immunohistochemical studies (see figure) reveal the lesional cells to be uniformly positive for STAT6 (nuclear pattern), focally positive for smooth muscle actin, focally positive for CD34, and negative for KIT and DOG1.
Diagnosis: Extrapleural solitary fibrous tumor, giant cell angiofibroma variant.

Discussion: I submitted this case for two reasons. The first is that it is difficult to diagnose even common soft tissue tumors such as solitary fibrous tumors when they present at unusual sites and with unusual histology. The second is that there is a fantastic new immunohistochemical marker for solitary fibrous tumor known as STAT6.

If extrapleural solitary fibrous tumor isn’t the most common soft tissue tumor, it is one of them. However, there are a variety of histological variants including cellular, myxoid, giant cell-rich and fat-forming (also known as lipomatous hemangiopericytoma) that can be confusing. Giant cell-rich/giant cell angiofibroma variant was originally described by Dei Tos and Fletcher in 1995 as giant cell angiofibroma, a tumor with a predilection for the soft tissue around the eye. Indeed, most of the examples in my files are from around the eye. However, these lesions do occur at other sites less commonly and over time, the existence of hybrid cases with convincing areas of conventional solitary fibrous tumor suggested to soft tissue pathologists that giant cell angiofibroma was a variant of solitary fibrous tumor. In the latest edition of the WHO Classification of Tumours of Soft Tissue and Bone, giant cell angiofibroma has been included in the section on extrapleural solitary fibrous tumor as a histological variant.

Recently, it was discovered that solitary fibrous tumors possess a NAB2-STAT6 fusion. Chimielecki et al. found the fusion in 100% of SFTs, while Robinson et al. identified it in about 55% of cases. However, it is clear that Robinson’s study was suboptimal and they missed a lot of cases. It really looks like NAB2-STAT6 is pathognomic for SFT and seen in a high percentage (at least 90%) of cases. STAT6 is usually a cytoplasmic protein but NAB2-STAT6 fusion results in nuclear localization and strong expression. This has been exploited immunohistochemically. Several
studies have been published showing high sensitivity and specificity for STAT6 IHC as a diagnostic marker for SFT. These studies have also shown that all of the histological variants of SFT, including meningeal HPC are positive for STAT6. STAT is also diffusely and strongly positive in malignant SFTs and CD34 negative SFTs. We recently published our own paper in this area. The only important thing about our paper is that we used an Epitomics rabbit monoclonal antibody, which is really a fantastic antibody. Other publications have used a Santa Cruz rabbit polyclonal which we found to have background staining and to be more difficult to use in general. Finally, the only example of a non-SFT neoplasm that has been identified to be positive for STAT6 is dedifferentiated liposarcoma, which occasionally falls into the differential diagnosis of SFT. STAT6 is sometimes included in the 12q12-15 amplicon which is always amplified in dedifferentiated liposarcoma, explaining while some cases of dedifferentiated liposarcoma are positive for STAT6 IHC. We haven’t really studied it in detail but based on Leona Doyle’s paper and our own experience, dedifferentiated liposarcomas show immunoreactivity for STAT6 about 5-10% of the time. However, SFTs are not amplified for MDM2 so they’ll be negative by MDM2 IHC and non-amplified for MDM2 FISH.

References


Contributed by: Manuel Sobrinho-Simões, MD

Case identification: H13/21564

Contributors: Drs Joanne Lopes, José Manuel Lopes and Fátima Carneiro, Dept of Pathology of the University Hospital of S.João, Porto, Portugal

Clinical history: A 68-year old female was submitted to “right hepatectomy” (1127g) for a large, well demarcated, whitish tumour replacing most of the right lobe of the liver and measuring 13.5x13x8.5cm. The patient had a prior history of invasive ductal carcinoma Grade 2 (Surgery 7 months before the present admission plus radiotherapy and chemotherapy).

Microscopic features: Variably cellular spindle cell neoplasm displaying a patternless architecture and areas of hyaline collagenous stroma. There is, focally, prominent cytologic atypia, the nuclei are moderately pleomorphic and numerous mitotic figures were seen (25-27/10hpf). Foci of necrosis and lympho-vascular invasion were not observed. Immunohistochemically, the tumour cells were diffusely positive for CD34 and negative for pancytokeratins (AE1/AE3 and CAM 5.2), S-100, smooth muscle actin, desmin, c-kit, DOG-1, estrogen receptor and progesterone receptor.

1st Diagnosis: Spindle cell sarcoma, NOS

Comments and 2nd Diagnosis: We thought it was a primary sarcoma of the liver and we did not find evidence to subclassify it as malignant GIST, leiomyosarcoma or MPNST. Some of my colleagues advanced it might be a malignant solitary fibrous tumour (MalSFT) but we had not enough courage to go for it and we just added a note to the diagnosis stating that “we can not rule out a primary MalSFT but it is very rare, namely in the liver”. For the sake of completeness we sent the case in consultation to Dr. Fletcher. His answer came quick and blunt: “The appearance and immunophenotype – positivity for CD34 and STAT6 – fit very well with a Malignant solitary fibrous tumour. Given the large size of the lesion, this would seem likely to be a primary tumour at this site” Touche’. I have no doubts Chris Fletcher is right and we have learned a lot with this case (I must confess I did not even know about STAT6). More recently, the STAT6 group has identified, through gene expression profiling, a novel diagnostic marker for solitary fibrous tumour (GRIA2).

References

Vivero M, Doyle LA, Fletcher CDM, Mertens F, Hornick J.L. GRIA2 is a novel diagnostic marker for solitary fibrous tumour identified through gene expression profiling. Histopathology 65:71-80, 2014
Contributed by: Dominic Spagnolo, M.D., PathWest Laboratory Medicine, Nedlands, Western Australia (Accession Q05B10239E; courtesy of Dr J Ma-Wyatt)

Case history: I was shown this case in 2005. It concerns an unfortunate but brave young female who was diagnosed with common variable immunodeficiency at age 12, managed with intravenous immunoglobulins. Her course was punctuated by repeated respiratory infections including bronchiectasis requiring left lower lobectomy at age 17, and autoimmune haemolytic anaemia (AIHA) requiring early splenectomy and maintenance long-term steroids and cyclosporin. An abdominal CT in March 2005 at age 21 performed to exclude any splenunculi (because of intractable AIHA) revealed 2 mesenteric soft tissue masses. The larger of these was resected (slides circulated from this specimen) but there was residual disease with infiltration behind and into the liver. A second attempt at resection was carried out 7 months later. There were no uterine masses. Chemotherapy was instituted (adriamycin, ifosphamide, dacarbazine). Follow-up CT showed apparent resolution at the site of original disease in the mesentery, but there were multiple smaller mesenteric nodules and several mildly enlarged retroperitoneal nodes noted. She then clinically developed cavernous sinus and pulmonary metastases (not histologically proven), was managed palliatively and deceased 16 months after her original mesenteric resection, aged 22.

Pathologic findings: The slides circulated are from the first mesenteric resection, intraoperatively thought to be a lymph node. It was a circumscribed nodule measuring up to 30 mm in size and had a firm, pale cut surface; unfortunately no gross photos were taken. The slide circulated is representative of the 4 blocks taken from the nodule.

The features are those of a circumscribed though unencapsulated differentiated smooth muscle neoplasm. There is a circumscribed fibrous pseudocapsule merging with peritoneal fat and containing compressed vascular channels, some lined by endothelium resting on a fibrous wall, others containing smooth muscle in their walls. At one edge there is some loose vascularised tissue containing lymphatics with intervening spindly stromal cells, plump histiocytes and lymphocytes (I am not sure of the nature of this, ?distorted nodal tissue, ? inflamed soft tissue, but it does not seem to be part of the lesion based on morphology and immunostaining).

The mass is composed of intersecting fascicles of well differentiated smooth muscle cells. Not seen in all the sections from this block, occasional small foci of more primitive round myoid cells could be found, lacking mitoses. There is no coagulative necrosis, mild random cytologic atypia is present and there is a negligible mitotic rate (fewer than 1 per 200 hpf in my review of the sections). The stroma is richly vascularised and shows small foci of myxoid change and hyalinization including perivascular hyalinisation. Interesting discrete congeries of capillaries may be seen in some sections (see CD34 image). The cells strongly and diffusely express alpha-smooth muscle actin and caldesmon, whilst desmin positivity is more patchy though strong. Striking EBER and EBNA2 positivity is seen in virtually all nuclei (see images) but there is no expression of LMP-1 or CD21 (the C3d/EBV receptor). The MIB-1 proliferation index is <1% and there is barely any PHH3 positivity. There is no expression of ER, PR, CD34, CD117, Melan-A or HMB-45.

Based on the 4 blocks available from this first resection one can argue whether it should have been regarded as a smooth muscle neoplasm of uncertain malignant potential (this was the diagnosis), or a leiomyosarcoma.
The subsequent resection seven months later consisted of another circumscribed nodule (described as “encapsulated”) having a white whorled cut surface. Broadly the histological features were similar, but there were some differences. Large abnormal vessels with thick muscular walls were more prominent and the neoplastic cells often blended with them (see images). There were hypercellular foci showing greater nuclear atypia with increased mitotic activity (up to 4/50hpf) (see images). A diagnosis of leiomyosarcoma would be appropriate here.

**Diagnosis:** EBV-associated smooth muscle neoplasm (EBVSMN) in the setting of congenital immunodeficiency (common variable immunodeficiency).

**Discussion:** The case does not present diagnostic difficulty, but is interesting from the point of view of the association with EBV in a background of congenital immunodeficiency (CVID). These occur most often in the post-transplant setting in both paediatric (typically) and adult groups, and in patients with AIDS or other acquired immunosuppression. Not all HIV-associated smooth muscle neoplasms are EBV-related (about one third). There are very few cases reported in the setting of congenital immunodeficiency. In post-transplant patients, the smooth muscle neoplasms may be of recipient or donor origin. The lesions are often multiple and there is a predilection for visceral and intracranial sites.

Round cell myoid areas (present in this case) and intralesional lymphocytes are said to be characteristic of EBV-associated smooth muscle neoplasms but are not always present. They appear to arise from vessel walls in some cases.

It may be argued whether to have called the first resection a smooth muscle neoplasm of uncertain malignant potential or leiomyosarcoma. There is only mild random atypia and negligible mitotic activity (though definitely present). My preference would have been to call it an EBV-associated smooth muscle neoplasm of uncertain malignant potential though others might call it leiomyosarcoma. In the second resection there was undoubtedly greater atypia and focally increased mitotic activity (up to 4/50hpf) and a diagnosis of leiomyosarcoma seems appropriate. It certainly ultimately behaved as a leiomyosarcoma (at least on clinical/imaging grounds). As multifocality is typical with EBVSMNs, and the separate foci appear to be derived from separate viral clones (reflecting different infection events), distinguishing between multiple neoplasms or metastasis may be impossible.

While most cases behave in a relatively indolent fashion, persistent disease is the norm. Those with intracranial lesions, or unresectable neoplasms have a worse outcome. Some patients respond to antiviral therapy and reduced immunosuppression. Overall they behave more favourably than conventional leiomyosarcoma. In the final analysis, it seems that the nature and severity of the immunodeficiency with its comorbidities, particularly infections, rather than histological features, is the main prognostic determinant in most of these patients. In this case however, metastatic (or multicentric) disease seems to have been a significant prognostic determinant.

**REFERENCES:**


Contributed by: James A. Strauchen, M.D.

Clinical History: 67 year old woman with a past medical history of depression present with a 1.5 cm nodule in the right upper lobe. PET/CT showed 1.4 SUV. Fine needle aspiration was inconclusive. Wedge resection of the superior segment of the right upper lobe was performed.

Pathologic Findings: The specimen consisted of an 8.9 x 1.8 x 1.5 cm wedge of lung. This contained a white tan lobular lesion. Sections show a well circumscribed but unencapsulated lesion composed of small lymphocytes admixed with scattered larger pleomorphic cells in a variably fibrous background. Immunohistochemical stains demonstrated the small lymphocytes were predominantly T-cells with no loss of pan-T cell antigens and scattered B-cells. The large cells stained only for vimentin and Cyclin D1. They were negative for epithelial (Cam5.2, AE1/AE3, EMA), dendritic (S100, CD21/35, D2-40), histiocytic (CD68, CD163), and lymphoid (CD3, CD4, CD8, CD20, CD30, CD45, CD79a). markers. They were negative for desmin, actin, EBER, and ALK-1.

Diagnosis: Inflammatory pseudotumor/inflammatory myofibroblastic tumor.

Comment: Although myofibroblastic markers and/or ALK could not be demonstrated, we favored an unusual inflammatory pseudotumor/inflammatory myofibroblastic tumor. The small lymphocytes appeared to be reactive. A dendritic cell tumor or a peripheral T-cell lymphoma was also considered, however, the large cells were negative for both dendritic cell and T-cell markers. Interestingly they did express Cyclin D1, which has been reported in inflammatory myofibroblastic tumors (see Reference).

QUIZ CASE:

Contributed by: Saul Suster, M.D.

Clinical History: A 60 year old man with a past history of sickle cell disease, atrial fibrillation, hypertension, type II diabetes, obstructive sleep apnea and cholecystectomy was admitted for back pain, lethargia and shortness of breath. He was intubated and found to have serum blood glucose level of 500. His labs showed severe acidosis, severe anemia and trace ketones in urine. Chest X-ray showed consolidation of the right lower lobe of lung. Liver enzymes were elevated. He was admitted to the ICU where he became hypotensive and expired in respiratory distress. The slide is from the lungs at autopsy.
Clinical History: A 60 year old man without any previous significant history was seen for a large retroperitoneal mass. The surgical specimen measured 10 x 10 x 5 cm and consisted of a well-circumscribed but unencapsulated soft tissue mass. On cut section the mass was cystic with a central lumen that measured 6.5 cm. in greatest diameter. The walls of the cyst showed a yellowish brown appearance.

Pathologic findings: histologically the walls of the cyst were lined by sheets of large, polygonal tumor cells with a striking perivascular distribution. The tumor cells appeared cohesive and showed large round to oval nuclei with small nucleoli and with abundant cytoplasm. In some areas there was marked clearing of the cytoplasm and scattered mitoses could be observed.

A “million-dollar workup” showed positivity of the tumor cells for cytokeratin AE1/AE3, CD99, EMA, HBME-1, glypican-3, S-100 protein and CA-IX. Stains for OCT-4, CD10, calretinin, AFP, desmin, Melan-A, PAX8, p63, CD117, MDM2, GFAP, CD1a, CD5, CK5/6, P75 (NGFR) and SOX10 were negative.

Diagnosis: Don’t know. “Low-grade epithelioid neoplasm of undetermined histogenesis”? 

Comment: I don’t know what this tumor is. I recall having seen one similar case at Ohio State University 10 years ago, also in the abdominal cavity, which looked virtually identical to an atypical thymoma (WHO B-3 thymoma), although there was no history or evidence of thymoma in that patient. If this tumor was in the mediastinum I would have had no problem calling it B3 thymoma. As it turns out, not only does this patient have no mediastinal mass or history of thymoma, but the tumor is negative for p63 and PAX-8, which are almost always positive in thymomas.

I am sending this case in the hope that someone can take me out of my misery and tell me what this is. Has anyone seen anything similar before? Am I missing something here? Could this be some rare ectopic pancreatic neoplasm? Other histogenesis? Help!
Contributed by: Paul E. Wakely, Jr., M.D.

History: A 47 y/o woman presented with a 3-month history of dyspnea on exertion, left-sided chest discomfort, and lower extremity edema. Two years prior she had a hysterectomy and left salpingo-oophorectomy for “benign leiomyoma.” Echocardiogram revealed a long linear mass arising from the IVC. CT and MRI demonstrated an intraluminal filling defect within the right common iliac vein extending through the IVC, into the right atrium, right ventricle, main pulmonary artery, and right pulmonary artery. There were filling defects in the right lobar pulmonary arteries. The mass enhanced with gadolinium. The distal end of the mass was removed from the right heart and pulmonary artery through a right atriotomy under cardiopulmonary bypass. There were no attachments to the heart. Pulmonary arteriotomies showed no residual tumor. The tumor was firmly attached to the IVC according to the operative report. The proximal end of the tumor was identified as emanating from a small lateral pelvic wall vein draining into the external iliac vein. The patient was well 9 months post-operatively, and has been subsequently lost to follow-up 9 years later.

Pathology: The specimen was received as several tubular worm-like pieces of dull pink tissue all labeled as ‘atrial mass with vena cava tumor’. Two of the pieces were 12 cm. and 6 cm. in length. The slide you have is from a dilated vein near the fallopian tube. It is identical to tissue removed from the right atrium. It shows a branching ribbon-like proliferation of cytologically bland, monotonous cells emanating from a focus in the smooth-muscled tunica media of this dilated vein. These snake-like ribbons of tissue are covered by CD31-positive endothelial cells. Cellularity varies quite a bit from field to field with markedly cellular foci mimicking a spindle cell sarcoma with extremely high N/C ratios transitioning to less cellular foci with ovoid & spindle shaped nuclei that appear more or less like mature smooth muscle. Foci with small hyaline plaques are also present. From the antibodies we had at the time, there was positive staining with ER, PR, smooth muscle actin (SMA), very scattered and weak staining with CD10, and scattered staining with h-caldesmon. SMA stained all cells diffusely and intensely - even those with minimal cytoplasm. H-caldesmon however only sparingly stained these highly cellular foci.

Diagnosis: Intravascular/Intravenous leiomyomatosis with intracardiac extension.

Comment: This is an old case from our files that belonged to a colleague of mine that I thought members of the club would enjoy seeing. The case was published as a case report by the surgeons and a medical student (of course without having the pathologist who signed the case out as part of the author list). 1

Subsequent recovery of outside slides from that hysterectomy that was performed 2 years earlier showed proliferative endometrium and several myometrial leiomyomas with a focus in one block of an apparent extension of smooth muscle proliferation into a vessel. H-caldesmon staining of that smooth muscle focus was strongly positive. No adenomyosis or evidence of stromal proliferation was seen in that uterus.

Only a small percentage of intravenous leiomyomatosis cases lead to intra-cardiac extension. Du found 298 reported cases of intravenous leiomyomatosis; almost 40% of them associated with uterine leiomyomas and 28% having both leiomyomas and adenomyosis. A variety of histologic changes have been described in these neoplasms along with...
the typical smooth muscle morphology. These include cellular, myxoid, lipoleiomyomatous, symplastic, cellular, and adenomyomatous histology.

The case was actually signed out 9 years ago as a Mixed Low-Grade Intravascular Stromal Sarcoma-Leiomyoma presumably because of focal CD10 staining and the sarcomatous appearance of those hypercellular foci. In reviewing this case I am of the opinion that these are foci of cellular leiomyoma, and not a sarcoma of any kind. On the other hand, some of you may want to consider this as an intravascular stromal sarcoma with leiomyomatous differentiation - even though no endometrial stromal sarcoma was ever found in the hysterectomy specimen. A similar problem was posed by Dr. Forteza Vila back in AMR #59. Your thoughts are appreciated.

**Selected References:**


Case Contributor: Bruce M. Wenig, M.D.

**Clinical History:** 66 year old man with abdominal pain. Workup including imaging showed a large left adrenal mass measuring greater than 13 cm. No contributing history provided. An adrenalectomy was performed.

**Gross:** The resection specimen consisted of a 13.5 x 10.5 x 6.8 cm tan-yellow to brown appearing mass weighing 600 grams. The cut surface showed extensive hemorrhage with yellow to white areas firmer areas.

**Microscopic:** There is a diffusely infiltrative poorly-differentiated malignant neoplasm characterized by solid and trabecular growth composed of enlarged cells with round to oval nuclei, vesicular nuclear chromatin and prominent nucleoli. There is increased mitotic activity including atypical mitoses and readily apparent foci of confluent necrosis. Adrenal cortical cells were identified (not present in your slide) and infiltrated by the malignant neoplasm. Given the clinical presentation of an isolated adrenal mass, the presence of diffuse involvement/effacement of the adrenal gland and overall morphologic features the diagnosis of an adrenal cortical carcinoma was initially entertained. Immunohistochemical staining to confirm this diagnosis was performed.

**Immunohistochemical staining:** Immunohistochemical staining showed focal rare positive calretinin and CK19 and synaptophysin reactivity, patchy reactivity for cytokeratin (AE1/AE3, LMWK), Ber-Ep4 and vimentin, and absence of staining for EMA, Melan-A, Inhibin, HMWK, GATA-3, p63, synaptophysin, CD56, chromogranin, and S100. A proliferation rate of >40% was seen by Ki67 staining.

Due to the less than confirmatory staining in particular the absence of inhibin, calretinin and Melan-A, consideration for the possibility of a metastatic disease to the adrenal gland lead to additional immunohistochemical staining that showed immunoreactivity for prostein, prostatic specific antigen (PSA) and prostatic acid phosphatase (PAP).

Subsequent follow-up with the clinician confirmed the fact that the patient had a history of prostate carcinoma status post radiation therapy and had rising PSA levels. Additional work-up failed to reveal any other sites of metastatic disease.

**Diagnosis:** Metastatic prostatic adenocarcinoma to the adrenal gland.

**Discussion:** In retrospect a diagnosis other than adrenal cortical carcinoma may appear obvious but given the clinical presentation and to some extent the histologic features our initial diagnostic consideration was that of an adrenal cortical carcinoma. This is a good learning case highlighting the fact that infrequently metastatic tumors to the adrenal gland can clinically and pathologically simulate a primary adrenal cortical carcinoma with marked unilateral adrenal enlargement. Further, it is rather uncommon for prostate cancer to metastasize solely to the adrenal gland without additional metastatic sites (e.g., bone). I am unclear why the clinician’s initial approach was to perform an adrenalectomy rather than a CT- or ultrasound guided FNAB especially given the patient’s history unless the surgeon did not fully appreciate that history.

**References**