June 21, 2002

9:00 am	Surgical Pathology –Session VII: Breast. Case Presentations (5 cases) *AMR Seminar Club Members*
10:40 am	COFFEE BREAK
11.10 am	Surgical Pathology –Session VIII: GI tract & Peritoneum. Case Presentations (6 cases) *AMR Seminar Club Members*
1:20 pm	LUNCH
2:30 pm	Surgical Pathology –Session IX: Thorax. Case Presentations (6 cases) *AMR Seminar Club Members*
4:40 pm	COFFEE BREAK
5:00 pm	Answers and solutions to "Quiz Cases" *M. Bisceglia & S. Suster*
6:00-6.15 pm	Concluding remarks - Closure & Farewell *S. Suster & M. Bisceglia*

SURGICAL PATHOLOGY -SESSION VII. BREAST

CASE PRESENTATIONS (5 cases)

Case 27. Small cell neuroendocrine carcinoma of the breast

(*G. Falconieri*)

Case 28. Low-grade, B-cell lymphoma of the breast c/w marginal zone lymphoma with plasmacytic differentiation

(*N. Weidner*)

Case 29. Microglandular adenosis of the breast

(*J. Lamovec*)

Case 30. Granulocytic sarcoma of the breast

(*J. Forteza-Vila*)

Case 31. Extensive atypical ductal hyperplasia of the breast vs. borderline low-grade DCIS-clinging monomorphic variant

(*N. Weidner*)

CASE 27. 01-12071

Giovanni Falconieri, M. D., Department of Pathology & Laboratory Medicine, division of Anatomic Pathology, "S. Maria della Misericordia" General Hospital, Udine.

CLINICAL HISTORY

A 65 y/o woman was admitted to the Hospital for the work up of a rapidly growing left breast tumor. Physical examination revealed a firm mammary mass. Clinically, there was evidence of ipsilateral axillary lymph node enlargement A fine needle aspiration biopsy yielded scant, non-diagnostic material, made of nuclear debris and crushed cells. Radical mastectomy was done.

PATHOLOGY

GROSS EXAMINATION

The breast contained a lobulated, gray mass with focal hemorrhagic areas measuring 3,5 cm in largest dimension. The axillary lymph nodes were enlarged and fused in matted nodules. The remainder of the breast showed fibrofatty senile involution.

MICROSCOPIC EXAMINATION

Tumor sections featured cellular sheets having a tentacular outline, composed of small elements with scant cytoplasm and hyperchromatic round to oval nuclei. The native breast parenchyma was diffusely obscured by the neoplastic proliferation. Pyknotic cells as well as centers of coagulative necrosis were seen. There was no evidence of invasive ductal or lobular neoplasia. A few small blood vessels showed incrustation by a bluish, dense fibrillary substance. Tumor cells were positive for keratins (Cam 5.2) and negative for LCA, synaptophysin, chromogranin, EMA, calcitonin, ER, PR, TTF and CD117 (c-kit). CK7 and CK20 were negative as well. The axillary lymph nodes contained metastatic carcinoma.

DIAGNOSIS

Small cell carcinoma of breast.

DISCUSSION

Special types of mammary carcinoma include microscopic forms defined in terms of specific histologic criteria that recognize a clustering of features that may or may not have special clinical correlates relevant to the treatment and patient survival.[1,13] Following the first report by Wade et al[17], several articles have been published addressing SCC of breast, either as individual case reports[5,6,16] or review articles.[11,15] The clinical presentation does not significantly differ from that of ordinary mammary carcinoma. Patients are adult to elderly women.[15] Axillary lymph nodes metastases are often present. Pre-operative cytologic examination by means of needle aspiration usually yields hypercellular smears featuring tumor diathesis, crushing artifacts, hyperchromatic cells with scant cytoplasm.[3,14] Microscopically, SCC is basically comparable with homologues observed in extra-mammary sites. Several cases show associated in situ ductal or lobular carcinoma.[12,15] Invasive ductal carcinoma may be also documented. Local spread with vascular invasion and lymph node metastasis is frequent. Neuroendocrine markers are frequently demonstrated by means of immunohistochemistry or electron microscopy.[1] Conceptually, SCC does not equate to neuroendocrine carcinoma since the latter category encompasses different tumors sharing argyrophilic cytoplasmic granules, neuroendocrine marker immunoreactivity (especially serotonin and chromogranin) or ultrastructural evidence of

electrondense granules. As such, these features may also be seen in non-SCC tumors such as mucinous, tubular or glycogen-rich clear cell carcinoma.[1,2,13] Many SCC have been reported to be ER+.[15] Exceptional cases primary in male breast have been also reported.[9] In regards to survival, available published data are contrasting, ranging from the good survival figures compiled by Shin et al[15] to the overall poor outcome noted in remainder small series as well as in scattered case reports. Aggressive chemotherapy, alone or in combination with radiation therapy, may prove useful at least in the short term. Tamoxifen administration may be beneficial in ER+ tumors.[15] Available cumulative data would suggest that primary SCC is as aggressive as other high grade breast tumors, at best, and must be treated accordingly.

The origin of SCC is largely speculative, linking the neoplastic proliferation to a neuroendocrine precursor of the native breast epithelium. Recent studies showed that the genetic changes in SCC of breast resemble those of ordinary invasive ductal carcinoma. Primary mammary SCC would appear clonally related although phenotypically diverging from an ordinary ductal cell line.[7]

DIFFERENTIAL DIAGNOSIS

Traditionally, the diagnosis of small cell carcinoma is based on the recognition of the classic diffuse pattern made by packed, lymphocyte-like cells with hyperchromatic nuclei often molding one to each other.[6,8,11,14,16] The cytoplasm is scant. Mitotic activity is generally high. In classic cases, the correct recognition is prompted by means of routine hematoxyilin-eosin stain. Tumor cells are immunopositive for keratins and EMA, and may be positive for ER and some neuroendocrine determinants such as chromogranin or synaptophysin. The differential diagnosis with other small cell tumors is relatively easy since SCC has a peculiar cytoarchitectural morphology that prompts recognition on routine stains. Other small cell tumors such as lymphomas or pediatric sarcomas (including rhabdomyosarcoma or Ewing's sarcoma/PPNET) are easily excluded clinically, morphologically and immunochemically. As a matter of facts, the most important differential diagnosis is with a metastatic SCC from another site, especially the lung. Obviously, small cell carcinoma of the breast is phenotypically undistinguishable from analogues in other sites which, with the notable exception of primary in the skin, have an aggressive course and tendency to metastasize. Therefore the distinction of a recognition of SCC to the breast can be very difficult on a microscopic basis only.[10] Useful hints are residual of focal ductal or lobular neoplasia which are often, but not always present in primary mammary SCC. ER+ cells may further suggest a mammary derivation. Yet, before accepting a diagnosis of SCC in the breast, it is mandatory to exclude clinically a primary lesion in the lung. Interestingly, primary lung SCC may metastasize to the male breast in patients who had received estrogen-ablation therapy for prostatic carcinoma.[4]

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QUESTIONS

1. What should be done first when dealing with a suspicious small cell carcinoma of breast ?
   - **A.** Rule out a primary small round blue cell sarcoma
   - **B.** Call the ward physician and recommend a chest X-ray film to the patient
   - **C.** Order special stains for argyrophilic granules
   - **D.** Obtain tissue for electron microscopy
   - **E.** Order immunoperoxidase stains for CK7, C20 and chromogranin
2. Which of the following is TRUE in regards to small cell carcinoma of breast
   - **A.** The overall prognosis is good
   - **B.** The tumor is generally localized at presentation
   - **C.** Needle aspiration is an insensitive pre-operative diagnostic tool
   - **D.** In situ carcinoma can be present
   - **E.** It has gross distinctive features.

***Mark the <u>best</u> answer, not just a good answer!**

1. Cosa faresti in primo luogo se avessi a che fare con un caso di sospetto carcinoma a piccole cellule della mammella?
   - **A.** Escluderei un sarcoma primitivo a piccole cellule rotonde.
   - **B.** Chiamerei il clinico e raccomanderei una radiografia del torace per la paziente.
   - **C.** Ordinerei delle colorazioni speciali per i granuli argirofili.
   - **D.** Riserverei un frammento di tessuto per l'analisi ultrastrutturale.
   - **E.** Ordinerei delle colorazioni immunoistochimiche per CK7, CK20, cromogranina.
2. Quale delle seguenti affermazioni è VERA riguardo il carcinoma a piccole cellule della mammella.
   - **A.** La prognosi complessivamente è buona.
   - **B.** Il tumore in questione all'esordio è in genere localizzato.
   - **C.** L'agoaspirazione è un mezzo diagnostico preoperatorio non attendibile.
   - **D.** Il carcinoma in situ può essere presente.
   - **E.** Il tumore in questione ha un caratteristico aspetto macroscopico.

***Contrassegna la migliore risposta, non già solo una buona risposta.**

CASE 28. 16156-00

Noel Weidner, MD. Department of Pathology, University of California, San Diego Medical Center, San Diego, CA, USA

CLINICAL HISTORY

52 y/o woman presented with bilateral breast masses with no known previous history of breast carcinoma or other malignancies.

PATHOLOGY

Sections of both breast excisions show a multifocal mixed lymphoid infiltrate composed (in part) by sheets of monotonous-appearing plasma cells. There are also numerous follicles with germinal centers. The mixed lymphoid infiltrate is largely lobulocentric; and, in many places, lymphoid cells infiltrate the epithelial elements of the terminal-duct lobular unit forming so-called lymphoepithelial lesions. This phenomenon is especially evident on the cytokeratin immunoperoxidase stain. A broad panel of immunoperoxidase stains are performed on tissue blocks from both breasts and are interpreted as follows. The abnormal lymphoid cells stain positively for a leukocyte common antigen cocktail, lambda light chain (i.e., c/w marked lambda light-chain restriction and a clonal ["malignant"] population of plasmacytoid cells), BCL-2, and CD43 (weak) and negatively for CD20, CD23, CD5, CD10, CD3, and kappa light chain. The pancytokeratin, again, shows numerous lymphoepithelial lesions. A differential diagnosis includes lymphoplasmacytoid lymphoma and involvement of breast by multiple myeloma or plasmacytoma; but, we have no history to suggest either of the first two diagnoses, which should be ruled out. Given the findings, we favor "MALToma"; but, continued correlation with clinical findings is recommended. MALToma in one MALT location may be associated with development MALToma in other locations. Thank you for this interesting consultation.

DIAGNOSIS

Low-grade, B-cell lymphoma c/w marginal zone lymphoma with plasmacytic differentiation.

DISCUSSION

Malignant lymphoma can be primary in the breast or involve the breast as a generalized process. A few cases have been reported associated with lymphocytic lobulitis (SEE BELOW). Grossly, breast lymphoma is soft and grayish white and not accompanied by skin retraction or nipple discharge. Multiple nodules may occur, and bilaterally occurs in ~25% of patients. Primary breast lymphoma is almost always of diffuse non-Hodgkin's type. In adults, diffuse large B-cell type is most common, followed by small lymphocytic and follicular small cleaved-cell types. Tumor cells have a tendency to surround and invade ducts and acini (i.e., so-called lymphoepithelial lesions) like lymphomas arising from so-called mucosa-associated lymphoid tissue (MALT), but immunohistochemical studies are inconclusive, some have shown that most lack marginal or mantle-cell differentiation. The targetoid and/or single-file pattern sometimes seen around the ducts may simulate the appearance of invasive lobular carcinoma; and, stains for leukocyte common antigen and/or keratin should solve the

diagnostic dilemma. Occasionally, the lymphoma cells become spindled mimicking stromal sarcoma. Survival relates to stage and subtype.

Burkitt's lymphoma may involve the breast in children and during pregnancy. Primary Hodgkin's disease of the breast is very rare with most cases involving the breast representing secondary disease. Plasmacytoma can present in the breast, sometimes with a serum monoclonal protein. Lymphoid hyperplasia (pseudolymphoma) is a reactive process, which can cause a solid breast nodule and show a polyclonal, mixed, lymphoid infiltrate containing germinal centers and vascular proliferation. As in other organs, the nature and significance of diffuse masses composed of a monotonous proliferation of mature small lymphocytes may be difficult to determine, even with cell marker studies. For these, the noncommittal diagnosis of "atypical small lymphocytic proliferation" is appropriate, and conservative therapy can be followed, if no systemic evidence for lymphoma is encountered. Acute and chronic myelocytic leukemia can cause a breast mass (a.k.a., granulocytic sarcoma or extramedullary myeloid tumor), which can be confused with lymphoma or carcinoma. A clue to the diagnosis is the presence of eosinophilic myelocytes or metamyelocytes, but they may not be present. Then, the diagnosis can be confirmed by performing the Leder's chloroacetate esterase stain or looking for immunoreactivity for myeloperoxidase. Myeloid metaplasia can form in the breast in patients with idiopathic myelofibrosis.

Sclerosing lymphocytic lobulitis of breast is an inflammatory breast lesion thought to be of autoimmune origin, much like Sjogren's syndrome, Hashimoto's thyroiditis, and pancreatic insulinitis. A very similar, if not identical, lesion was initially reported by Soler et al. as fibrous disease of the breast. Subsequent reports emphasized the association of sclerosing lymphocytic lobulitis with diabetes; but Schwartz et al., and Lammie et al. reported very similar pathologic features in non-diabetic patients, but often with other evidence of autoimmune disease (Hashimoto's thyroiditis or circulating autoantibodies). Diabetic patients with sclerosing lymphocytic lobulitis have early onset, long-standing, insulin-dependent diabetes, which developed premenopausally. Their breasts contain hard, painless, irregularly contorted, moveable masses, which are often bilateral but may be solitary. Mammography reveals dense tissue suggestive of malignancy. FNA biopsy of these hard masses yields insufficient material for diagnosis in about 50% of cases. Histologically, the masses show lymphocytic lobulitis (mature lymphocytes and plasma cells surrounding acini and invading across basement membranes), lymphocytic vasculitis (mature lymphocytes surrounding a small venule), and dense keloid-like fibrosis, which, in 75% of cases, contains peculiar epithelioid cells embedded in the dense fibrous tissue. According to Tomaszewski et al., the lobulitis and vasculitis can be found in nondiabetic patients, but the epithelioid fibroblasts appear to be unique to the diabetic condition. Lammie et al. believe that the lobular lesions progress through stages, starting with initial dense inflammation, followed by increasing lobular sclerosis and acinar atrophy as the inflammation resolves. At first, an occasional neutrophil and/or multinucleated giant cell may be present. Immunologic studies of sclerosing lymphocytic lobulitis show a predominance of B lymphocytes in the vast majority of cases, and expression of HLA-DR antigen in involved lobular epithelium. These immunologic features are very much like those found in benign lymphoepithelial lesions of salivary gland and in Hashimoto's thyroiditis. Five of seven patients studied by Lammie et al. had the HLA-DR 3, 4, or 5 phenotype, which is associated with a higher incidence of autoimmune disease (type 1 diabetes and Hashimoto's thyroiditis). Schwartz et al. speculated about a

possible association of sclerosing lymphocytic lobulitis with an increased incidence of lymphoma development, much like that observed with Sjogren's syndrome and Hashimoto thyroiditis. The resulting lymphomas are thought to be related to mucosa associated lymphoid tissue [MALT]. However, with insufficient follow-up, these authors were unable to reach a conclusion. Aozasa et al., Lamovec et al., Hugh et al., and Mattia et al. all concluded that primary breast lymphomas may show features characteristic of MALT lymphomas (i.e., presence of lymphoepithelial lesions, tendency to remain localized or recur at other MALT sites, low-grade cytology, and indolent behavior) arising from other organs, such as the stomach, salivary glands, and thyroid. Moreover, Aozasa et al. found enough histologic and immunologic evidence to suggest that most mammary lymphomas are B-cell tumors and are associated with coexisting or antecedent lymphocytic mastopathy. In fact, histologic evidence of lymphocytic mastopathy in mammary tissue apart from lymphomas could be evaluated in 11 of 19 patients, and evidence of lymphocytic mastopathy was confirmed in 10 of the 11 patients (>90%). The so-called lymphoepithelial lesion, a characteristic finding for MALT lymphomas, was observed in 42% of their breast lymphomas. Other observers have not been able to document MALT features in breast lymphoma. As mentioned, when primary breast lymphomas develop, they are most commonly of the diffuse, large-cell type with B-cell differentiation, but virtually any of the morphologic types defined by the "Working Formulation" can occur. This author has observed a diffuse small cleaved cell lymphoma of the breast that presented with numerous spindle forms and sclerosis, which closely mimicked a primary sarcoma. The diffuse small-cleaved cell variety is the second most frequent lymphoma type reported in the breast. Also, lymphomas can infiltrate in a single file pattern like infiltrating lobular carcinoma, and the lymphoepithelial lesion-like spread can mimic pagetoid spread of a breast carcinoma. Breast lymphomas can mimic solid variants of infiltrating lobular carcinoma, and likewise metastatic lobular carcinoma in lymph nodes can simulate primary lymphoma. A variety of pseudolymphomas (lymphoid hyperplasias) of the breast have been reported, but they may actually represent either florid cases of sclerosing lymphocytic lobulitis or undetected examples of early, low-grade, B-cell, MALT lymphomas. Indeed, Lin et al. concluded their report of five pseudolymphomas of the breast by stating that "the microscopic picture of pseudolymphoma of the breast greatly resembles that seen in the salivary gland in Sjogren's syndrome." Yet, none of their cases actually had Sjogren's syndrome. Sometimes the epithelioid stromal cells in sclerosing lymphocytic lobulitis can be so prominent and abundant that the possibility of an infiltrating carcinoma or granular-cell tumor can be seriously considered. Ashton et al. reported that the stromal cells have features of myofibroblasts, reacting with anti-actin. These cells were negative for antibodies to keratin (AE1/3), S100, desmin, Mac 287, factor XIIIa, CD20 (L26), and CD45RO(UCHL-1); but, they reacted with anti-CD68 (Kp-1) suggesting some lysosome formation. These immunostains are important, because occasional lymphoepithelioma-like carcinoma of the breast occurs, wherein the lymphoid infiltrate could simulate lymphocytic lobulitis and obscure the underlying carcinoma.

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QUESTIONS

1. Low-grade, B-cell lymphoma or MALT-oma is also known as a form of marginal-zone lymphoma. **True or False.** _____.
2. Sclerosing lymphocytic lobulitis of the breast is typically followed by MALT-oma. **True or False.** _____.

1. Il linfoma di basso grado a cellule –B tipo MALT è noto anche come una forma di linfoma della zona marginale. **Vero o Falso.** _____.
2. La lobulite linfocitica sclerosante della mammella è tipicamente seguita da un MALT–oma. **Vero o Falso.** _____.

Case 29. 1117-98

Janez Lamovec, M.D., Institute of Oncology, Ljubljana, Slovenia.

CLINICAL HISTORY

A 57-year-old patient presented with a lump in the right breast of unknown duration. On physical examination, a 2 x 2 cm firm lump was palpated between outer quadrants, close to areola with some retraction of the skin. Mammography showed somewhat denser tissue in this location compared to contralateral breast. FNAB was reported as suspicious of malignancy. An excisional biopsy was performed.

PATHOLOGY

Grossly, the specimen was represented by a 40 grs, 5 x 5 x 4 cm segment of breast tissue which was composed of fatty tissue, breast parenchyma with numerous small cysts and an area of 1.7 cm of firmer white-gray tissue which was grossly not suspicious for tumor.
Microscopically, the lesion shows numerous rounded or oval gland-like structures of unilayered uniform cuboidal cells with round nuclei, with no pleomorphism, with dusty chromatin and small nucleoli and very rare mitotic figures. The cytoplasm of tumor cells is eosinophilic or lucent, moderate in amount. No myoepithelial cells are seen to surround such glandular structures. Glandular lumina are empty or contain deeply eosinophilic secretion. The glands infiltrate breast parenchyma and adipose tissue in a disorganized and random fashion; no lobular configuration of glandular structures is evident.
Immunohistochemically, the glandular epithelial cells were strongly positive for S-100 protein, and negative for EMA, BRST-2, alpha –lactalbumin, c-erbB 2. Collagen IV and laminin reaction clearly outlined glandular structures, while alpha-smooth muscle actin (SMA) antibody failed to demonstrate myoepithelial cells around the glands. Estrogen and progesterone receptors were negative.

DIAGNOSIS

Microglandular adenosis of the breast.

FOLLOW-UP

Four years after surgery, the patient shows no evidence of recurrent disease.

COMMENT

Microglandular adenosis (MGA) is a benign breast lesion which was first illustrated by Mc Divitt et al in 1968 (1). In 1983, three independent publications appeared delineating and defining this peculiar benign glandular proliferation in the breast (2-4). The lesion is characterized by a florid proliferation of small round or oval glands that exhibit a striking degree of non-organoid infiltration of the stroma so that individual glands lie "naked" in adipose tissue or are surrounded by hyalinized stroma (2).
Clinically, the lesion tends to affect middle aged women, may be palpable although it may also be asymptomatic and found incidentally (2-3). Mammographically, it may appear abnormal or even suspicious, rarely it shows stippled calcifications (3).
One of the most consistent features in this lesion is the lack of myoepithelial layer around the glands, seen on H&E, and confirmed by negative reaction for SMA. This finding militates a traditional view that benign ductal/glandular formations are two-layered: with inner epithelial and outer myoepithelial layer (2).

The main clinical significance of MGA lies in the fact that it should be differentiated from infiltrating tubular carcinoma (TC) which is, at least superficially, somewhat similar to MGA. Tubular carcinoma is also characterized by haphazard proliferation of neoplastic ducts without any lobular distribution. It is, however, in almost two third of the cases accompanied by in situ lesion lacking in MGA (5). The ducts in TC are often angulated, pointed, with well developed apocrine-type luminal cellular or apical "snouts"; the latter are never observed in MGA. They are often bridged by epithelial trabecular bars (2). While epithelial cells in MGA are completely bland, those in TC show at least minimal nuclear pleomorphism, nuclei are slightly larger.

Stroma in two conditions also differs, in MGA it is fibrosed or even hyalinized, often very scarce with the glands almost entirely embedded in fatty tissue, while stroma in TC is characteristically desmoplastic and may be highly cellular, fibroblastic or myofibroblastic. The secretion in TC is pale, basophilic, in MGA deeply eosinophilic.

There are also important immunohistochemical differences between the two lesions. Both show no myoepithelial layer, collagen IV and laminin positive membrane completely surrounds the glands of MGA but not those of TC (6-7). Another discriminative immunohistochemical feature is the absence of EMA positivity in MGA and its positivity in TC (8). The latter feature was not confirmed in another study (9). Some other immunohistochemical reactions, e.g. for S-100 protein have no practical value in separating these two lesions.

Another rare breast carcinoma that should be distinguished from MGA is a recently described acinic cell carcinoma of the breast (10). The cells of the latter tumor that may structurally resemble MGA are characterized by the presence of zymogen granules, seen histologically and ultrastructurally. The granules are immunohistochemically positive for salivary type amylase that is a specific marker for acinar cell differentiation. Cells of MGA may occasionally show some apocrine changes but granules in such cells lacked positive amylase reaction (9).

Of the benign lesions, a recently described tubular adenosis should also be separated from MGA (11). It is featured by haphazard proliferation of elongated tubules that are noncrowded, narrow and sometimes branching. The cells lining the tubules are bland and are surrounded by an intact myoepithelial layer, highlighted by SMA an S-100 protein positive cells. The latter feature clearly distinguish tubular adenosis from MGA.

The association of MGA with carcinoma of the breast has come under scrutiny relatively recently /9, 12-13). The two studies from the same institution (Memorial Sloan Kettering Cancer Center) have documented the fact that there is indeed statistically significant linkage between breast cancer and MGA (12-13). However, the absolute augmentation in the risk that is associated with MGA is currently undetermined.

In this regard, it should be mentioned that 43% of patients developing infiltrating carcinoma in association with MGA had a family history of breast cancer (13).

Morphologically, the spectrum of atypical glandular proliferations was observed in those cases of MGA in which carcinoma developed; such lesions were named atypical MGA, some of them suggested the transition to infiltrating carcinoma (12-13). The importance of atypical MGA in the evolution of invasive carcinoma has been recently emphasized (9).

Treatment for MGA, atypical or otherwise, is that of simple excision. Women with this condition should probably be told that they have a higher-than-average risk of developing a subsequent carcinoma of the breast. For them, hightened clinical and mammographic surveillance is advisable.

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QUESTIONS

1. Microglandular adenosis is histologically characterized by:
   - **A.** Rounded gland-like structures of unilayered uniform cuboidal cells.
   - **B.** Random disorganized growth.
   - **C.** Rack of myoepithelium layer.
   - **D.** All of the above.
   - **E.** None of the above.
2. The patients with microglandular adenosis have a risk for developing subsequent cancer which is:
   - **A.** The same-as-average.
   - **B.** Lower-than-average.
   - **C.** Higher-than-average.

***Mark the appropriate letter.**

1. La adenosi microghiandolare è istologicamente caratterizzata da:
   - **A.** Strutture ghiandoliformi di cellule monomorfe, cuboidali, in unico strato.
   - **B.** Crescita casuale disorganizzata.
   - **C.** Mancanza dello strato mioepiteliale.
   - **D.** Tutte le condizioni precedenti.
   - **E.** Nessuna delle condizioni precedenti.
2. I pazienti con adenosi microghiandolare presentano un rischio di sviluppare successivamente una neoplasia che è:
   - **A.** Lo stesso della media.
   - **B.** Più basso della media.
   - **C.** Più alto della media.

***Contrassegnare la lettera giusta.**

CASE 30. 99-17017

Jerónimo Forteza-Vila, M. D. School of Medicine and University Clinical Hospital in Santiago de Compostela.

B. Vieites, M. Fraga, J. Forteza
School of Medicine and University Clinical Hospital in Santiago de Compostela.

CASE DESCRIPTION

CLINICAL HISTORY

Female, 31 years old, presenting a tumor in the upper-outer quadrant of the right breast.

Anatomic-pathological study

With the clinical suspicion of breast carcinoma, an intraoperating biopsy was performed and it was diagnosed as possibly lymphoblastic lymphoma. The patient underwent a lumpectomy. Macroscopically, it was a white tumor, well delimited, with 4 x 3.5 cm of higher diameters. Histopathologically, a diffuse cell infiltrate of intermediate size with scanty cytoplasm and nuclei of blastic characteristics was observed. In the periphery of the tumor, the neoplastic cells adopted an "Indian file" pattern. The immunophenotype showed positivity for CD45, CD43, lysozyme, myeloperoxidase and CD68 (KP1). CD79a, CD20, CD3 and TdT were negative. The IgH and TCR gene rearrangements were polyclonal.

DIAGNOSIS

Myeloid extramedullary tumor, (granulocytic sarcoma), blastic type.

TREATMENT AND EVOLUTION

A later biopsy of bone marrow showed the absence of any myeloproliferative disorder. The patient received a standard treatment for acute myeloid leukemia and is free from the disease two years after the diagnosis.

DISCUSSION

The extramedullary myeloid tumor, also called granulocytic sarcoma, myeloid sarcoma or chloroma can appear at any age. The location is very changeable: The affection of skin, soft tissue, lymph nodes, orbit, gastrointestinal tract, palate, upper respiratory system, genitourinary system, breast and mediastinum has been described.

This lesion can appear in the context of an acute myeloid leukemia already diagnosed in a patient with a myeloproliferative syndrome or myelodisplasyc syndrome (which may represent the beginning of a blastic transformation) or in a patient who was previously healthy. This last situation is the one causing higher diagnostic difficulty for the pathologist, above all, when the morphology is blastic or poorly differentiated as in this case. The differential diagnosis of this breast lesion comprises infiltrative lobular carcinoma, which is easily ruled out by performing cytokeratines, and the non-Hodgkin lymphoma, in which case it is easiest to make the mistake; in fact, if the extramedullary myeloid tumor is not considered. the positivity for CD45 and CD43 can "confirm" the mistaken diagnosis of non-Hodgkin lymphoma. In these cases the use of antibodies against myeloperoxidase and/or lysozime will lead us to the correct diagnosis.

In such cases, where the unique manifestation of the disease is the extramedullary myeloid tumor, the treatment must be identical to the one for acute myeloid leukemia; otherwise, it is common that the patient ends up developing a leukemic phase in the first year after the initial diagnosis of granulocytic sarcoma.

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QUESTIONS

1. The granulocytic sarcoma is mainly diagnosed by:
   - **A.** Leukemic manifestations in peripheral blood.
   - **B.** Cytogenetics.
   - **C.** PCR.
   - **D.** Clinics.
   - **E.** Microscopic and immunohistochemical features of the tumor.
2. The granulocytic sarcoma is associated with:
   - **A.** Lymphoma.
   - **B.** Monoclonal gammopathy.
   - **C.** Philadelphia Chromosome.
   - **D.** Myeloproliferative syndrome.
   - **E.** Anaemia.

***Mark the appropriate letter.**

1. Il sarcoma granulocitico è diagnosticato principalmente:
   - **A.** Sulla base di manifestazioni leucemiche nel sangue periferico.
   - **B.** Sulla base della citogenetica.
   - **C.** Per mezzodella PCR.
   - **D.** Sulla base dei dati clinici.
   - **E.** Sulla base degli aspetti microscopici e immunoistochimici del tumore.

2. Il sarcoma granulocitico è associato con:
   - **A.** Linfoma.
   - **B.** Gammopatia monoclonale.
   - **C.** Cromosoma Philadelphia
   - **D.** Sindrome mieloproliferativa.
   - **E.** Anemia.

***Contrassegnare la lettera giusta.**

CASE 31. 01-2694 or 00-8399

Noel Weidner, MD. Department of Pathology, University of California, San Diego Medical Center, San Diego, CA, USA

CLINICAL HISTORY

43 y/o female presented with abnormal calcifications, and needle localization biopsy was performed.

PATHOLOGY

Sections showed a flat epithelial atypia characterized by proliferation of a monotonous atypical cell population that replaced the native epithelial cell layer and showed occasional mounding or uniform stratification to up to 3 to 5 cell layers. Atypical cells had hyperchromatic nuclei and increased N/C ratios. The ducts involved were often slightly distended and some contained secretory material and less frequently microcalcifications.

DIAGNOSIS

Atypical ductal hyperplasia vs. borderline low-grade DCIS-clining monomorphic variant.

DISCUSSION

A controversial pattern of low-grade, ductal intraepithelial neoplasia is flat-type or "clinging" ductal carcinoma in situ, which was emphasized by Azzopardi. In pure form, this pattern has been more readily accepted by some European pathologists, whereas some pathologists in the USA prefer to refer to low-grade examples of pure "clinging" or flat patterns as atypical ductal hyperplasia (i.e., if less than 20 duct profiles are involved) and extensive atypical ductal hyperplasia (i.e., if over 20 duct profiles are involved). Moreover, the latter type of extensive atypical ductal hyperplasia is recommended by some experts to be further excised, if it is present at a surgical margin. The flat or "clinging" pattern is often found as one of the mixed patterns of low-grade DCIS, which also contains areas of cribriform and/or micropapillary areas. Moreover, "clinging" patterns are frequently associated with invasive, well-differentiated breast carcinomas, especially tubular carcinoma. Indeed, if one considers recent molecular studies, the flat-type or "clinging" variant of DCIS appears to be a "true" example of DCIS. Moinfar et al. *(Cancer 2000;88:2072-2081)* found the same genetic alterations (i.e., loss of heterozygosity) in "clinging" DCIS as those found in adjacent more classical DCIS and/or infiltrating ductal carcinomas. Yet, the clinical significance of the low-grade variant of "clinging" DCIS needs further investigation, especially when present in pure form and at resection margins of biopsies. Because of these yet unresolved issues, this author uses the diagnostic descriptor severely atypical ductal hyperplasia/borderline, low-grade DCIS, "clinging" variant for the pure form of the low-grade lesion and high-grade DCIS, flat-type for the high-grade variant. I believe the high-grade variant should be treated like other examples of high-grade DCIS. When the low-grade form is present at a surgical margin, I recommend conservative re-excision (if clinically feasible); and, the use of radiation would depend upon the findings in the re-excised specimen and may not be needed in selected cases.

REFERENCES AS WELL AS SOME INTERESTING AND RELEVANT ABSTRACTS:

[Pathological differential diagnosis of early breast cancer]. Gan No Rinsho (Japan), Aug 1988, 34(10) p1397-402. Sakamoto G. Early cancer of the breast includes those categories of the so-called early breast cancer (TNM Stage I), minimal breast cancer, noninvasive breast cancer and T0 breast cancer. In the breast, it seems extremely rare that the lesion is genuine borderline of malignancy. A papillary or lobular lesion is usually worrisome in differential diagnosis, either benign or malignant. Sclerosing adenosis is most likely to be over diagnosed as malignant. **Tubular carcinoma, low papillary carcinoma and clinging carcinoma are most likely to be under diagnosed as benign.** To avoid over diagnosis and/or under diagnosis of malignancy, it is essential to learn exactly every histologic feature of various lesions.

Immunohistochemical study of neu protein overexpression in clinging in situ duct carcinoma of the breast. Virchows Arch A Pathol Anat Histopathol (Germany), 1993, 422(5) p375-80. De Potter CR; Foschini MP; Schelfhout AM; Schroeter CA; Eusebi V. The expression of neu protein in 26 cases of clinging carcinoma (CC) of the breast was investigated. A distinction is made between two types of CC: one with pleomorphic nuclei (PN) and the other with monomorphic nuclei (MN). The PN type of CC overexpresses the neu protein in almost all cases (85.7%), its cells generally exhibit abundant cytoplasm and intraluminal necrosis is frequently observed. The MN type of CC does not overexpress the neu protein, exhibits bland cytological features and shows no necrosis. **It is suggested that CC with PN is related to comedo-type carcinoma, while CC with MN is the forerunner of cribriform carcinoma in situ.**

Genetic abnormalities in mammary ductal intraepithelial neoplasia-flat type ("clinging ductal carcinoma in situ"): a simulator of normal mammary epithelium. Cancer 2000:88:2072-81. Moinfar F; Man YG; Bratthauer GL; Ratschek M; Tavassoli FA. BACKGROUND: Mammary ductal intraepithelial neoplasia (DIN)-flat type ("clinging ductal carcinoma in situ [DCIS]") generally is a subtle epithelial alteration characterized by one or a few layer(s) of atypical cells replacing the native epithelium. The "low power" appearance of DIN-flat type can be misinterpreted easily as "normal" because of the frequent absence of multilayered proliferation and often subtle cytologic atypia. Because it presents as an often unrecognized lesion or in association with tubular carcinoma, to the authors' knowledge the clinical and biologic significance of this lesion has not been well established. METHODS. Using polymerase chain reaction, the authors examined DNA extracts from microdissected areas of **22 cases with extensive "clinging DCIS,"** including 13 cases associated with infiltrating ductal carcinoma as well as 5 cases associated with more conventional types of DCIS. Eight polymorphic DNA markers with a high rate of loss of heterozygosity (LOH) in classic types of DCIS were selected to identify possible genetic alterations on chromosomes 2p, 3p, 11q, 16q, and 17q. Two cases also were used for the assessment of clonality by means of X chromosome inactivation (methylation pattern of the human androgen receptor [HUMARA] gene). RESULTS. LOH was detected in 17 of 22 lesions (77%), and monoclonality was established in the 2 cases analyzed. The most common genetic alterations were at chromosomes 11q21-23.2, 16q23.1-24.2, and 3p14.2 with LOH in 50%, 45%, and 41%, respectively, of informative cases. **The DIN-flat type showed the same genetic alterations (LOH) identified in adjacent in situ and infiltrating ductal carcinoma.** In contrast to the DIN-flat type, the perfectly normal mammary epithelium was associated very infrequently (1 of 16 cases; 6%) with LOH. CONCLUSIONS. **The DIN-flat type represents one of the earliest, morphologically recognizable, neoplastic alterations of the breast. Recognition of the DIN-flat type is important not only for the early detection of intraductal neoplasia but also to prevent misinterpretation and utilization of this lesion as a normal control in studies.** This distinctive lesion could be crucial as an explanation for at least part of the > 20% reported incidence rate of breast carcinoma recurrence observed despite ostensibly "negative" margins of breast biopsies.

Goldstein NS; O'Malley BA. **Cancerization of small ectatic ducts of the breast by ductal carcinoma in situ cells with apocrine snouts: a lesion associated with tubular carcinoma.** Am J Clin Pathol (United States), May 1997, 107(5) p561-6. Small ectatic ducts lined by atypical ductal cells with apocrine snouts occasionally have been observed in association with tubular carcinoma; some pathologists have considered these carcinomas to be a form of ductal carcinoma in situ (DCIS). Thirty-two cases of tubular carcinoma, 41 of invasive grade 1 ductal carcinoma with DCIS, 40 of invasive grade 1 ductal carcinoma without DCIS, 40 of invasive grade 3 ductal carcinoma, 40 of invasive lobular carcinoma, 20 of well-differentiated DCIS, and 80 of fibrocystic changes were examined to determine the relationship between the lesion formed by atypical ductal cells with apocrine snouts and invasive carcinoma, DCIS, and benign breast changes. Seventeen cases contained lesions formed by atypical ductal cells with apocrine snouts: 14 were associated with tubular carcinoma (43.7%), and 3 with invasive grade 1 ductal carcinoma (3.7%). In six invasive carcinomas, the associated DCIS was formed by cells identical to those within the lesion. These lesions were found at the periphery of the invasive carcinoma and adjacent to the DCIS. The lesions were

probably composed of low-grade intraductal malignant epithelial cells, which partially involve small ectatic ducts and are often adjacent structures as a form of cancerization. This cytologic and architectural form of DCIS appears to be related to an invasive carcinoma that is usually of tubular subtype. Attention to this form of cancerization by malignant intraductal cells, especially with regard to specimen surgical margins, is imperative when a tubular carcinoma is encountered. If a pathologist encounters only this lesion in a partially sampled breast biopsy specimen, additional (or all) tissue should be submitted for histologic evaluation to ensure that an invasive carcinoma is not missed. This lesion needs to be distinguished from the frequent, benign, columnar alteration within lobules and small ectatic ducts.

Columnar alteration with prominent apical snouts and secretions (CAPSS): a spectrum of changes frequently present in breast biopsies performed for microcalcifications. Am J Surg Pathol (United States), Dec 1998, 22(12) p1521-7 . Fraser JL; Raza S; Chorny K; Connolly JL; Schnitt SJ. We have noted in breast biopsies performed for microcalcifications a spectrum of lesions in the terminal duct lobular unit (TDLU) characterized by columnar epithelial cells with prominent apical cytoplasmic snouts, intraluminal secretions, and varying degrees of nuclear atypia and architectural complexity. The appearance of some of these lesions is worrisome, but diagnostic difficulties arise because the histologic features do not fulfill established criteria for the diagnosis of atypical ductal hyperplasia or ductal carcinoma in situ (DCIS). We have termed such lesions columnar alteration with prominent apical snouts and secretions (CAPSS). The purpose of this study was to define the pathologic spectrum and mammographic features of these lesions. We reviewed histologic sections and mammograms from 100 consecutive breast biopsies performed for microcalcifications. The prevalence and histologic features of CAPSS and the association with other histologic findings were recorded. CAPSS was identified in 42% of cases. At the lower end of the spectrum were lesions similar to columnar alteration of lobules but in which apical cytoplasmic secretion and nuclear stratification were more pronounced and cells with a hobnail configuration were common. More advanced lesions showed columnar epithelial cell tufts, bridges, and micropapillations with prominent apical cytoplasmic snouts and with greater degrees of nuclear stratification and atypia. **At the upper end of the spectrum were lesions that could arguably be considered DCIS.** Calcifications were present within CAPSS in 74% of cases, were frequently psammomatous, and were typically non-branching and often round on mammography. Columnar alteration of lobules was more common in biopsies with than without CAPSS (74 versus 36%, $p < 0.001$). Ductal carcinoma in situ was seen with similar frequency in biopsies with and without CAPSS (38 versus 41%). However, DCIS in cases with CAPSS was more often of the low-grade micropapillary-cribriform type than in cases without CAPSS (56 versus 17%, $p < 0.01$), and **CAPSS and DCIS commonly coexisted in the same or adjacent TDLUs.** In conclusion, 1) **CAPSS encompasses a spectrum of lesions bounded at the lower end by columnar alteration of lobules and at the upper end by low-grade DCIS.** Lesions recently described by Page as "hypersecretory hyperplasia with atypia" fall within this spectrum. 2) Some CAPSS lesions present architectural or cytologic features that create diagnostic difficulties and raise the possibility of atypical ductal hyperplasia or DCIS; however, the level of **cancer risk associated with CAPSS lesions that do not fulfill established criteria for atypical ductal hyperplasia or DCIS is unknown and requires evaluation in follow-up studies.**

[Pathological characterization of atypical ductal hyperplasia of the breast] Gan To Kagaku Ryoho (Japan), Apr 1995, 22 Suppl 1 p36-41. Hoshi K; Tokunaga M; Mochizuki M; Ohtake T; Katagata N; Wakasa H; Suzuki T. To clarify the pathological features of atypical ductal hyperplasia (ADH) defined by Page's criteria, histological patterns and the extent of 17 lesions of ADH including clinging carcinoma were examined. The nuclear measurements (mean nuclear area and irregularity of nuclear shape) and the MIB-1 labeling index of ADH were compared with those of non-comedo DCIS with lower grade nuclei, and usual ductal hyperplasia (DH). All ADH were classified into cribriform or micropapillary/clinging types. **The extent of ADH was always less than 2.5 mm in the cribriform type (1.4 mm in average), against 5 mm or greater in 6 of 8 lesions of the micropapillary/clinging type (7.1 mm in average).** Nuclei of ADH tended to be smaller (< or = 8 microns) than DH and DCIS ($p < 0.05$), and less irregular in shape than DH ($p < 0.01$), although indistinguishable from lower grade nuclei of DCIS using these parameters. The MIB-1 labeling index of ADH was very low (0-2.3%) and was the best parameter to distinguish from DCIS ($p < 0.01$). **It was also suggested that the lower level of proliferative activity is one of the most distinctive features of ADH.**

Cytogenetic findings in invasive breast carcinomas with prognostically favourable histology: a less complex karyotypic pattern? Int J Cancer (United States), Aug 21 1998, 79(4) p361-4 Adeyinka A; Mertens F; Idvall I; Bondeson L; Ingvar C; Heim S; Mitelman F; Pandis N. Seventeen invasive primary breast carcinomas of histological types usually considered to be prognostically favourable (2 medullary, 3 papillary, 3 tubular, and 9

mucinous carcinomas) were analysed as part of an ongoing study of the cytogenetics of breast cancer. Thirteen of the tumours (7 mucinous, 2 medullary, 2 papillary, and 2 tubular carcinomas) showed clonal chromosome aberrations. Trisomy 7 and i(1q) were present as sole and recurrent aberrations in the mucinous tumours. The 2 tubular carcinomas and I papillary carcinoma had simple numerical changes only, whereas the second papillary tumour had a balanced translocation as the sole anomaly. Both medullary carcinomas had chromosome numbers in the triploid range, with clones displaying structural and numerical changes. Our data, especially when collated with information on previously published cases of mucinous, papillary, tubular, and medullary breast carcinomas, show that the former 3 histological types, in keeping with their recognised prognostic advantage, appear to exhibit relatively simple karyotypic changes, i.e., numerical aberrations, balanced translocations, and near-diploid chromosome numbers. Medullary carcinomas on the other hand, appear to have more complex karyotypes, similar to those described for the more common ductal and lobular subtypes of breast carcinoma.

Cytogenetics of benign breast lesions. Breast Cancer Res Treat (Netherlands), Sep 1998, 51(1) p1-15. Lundin C; Mertens F. This review summarizes the cytogenetic information on benign breast lesions of various histologies, i.e., fibrocystic lesions from women with and without a known hereditary predisposition to breast cancer, fibroadenomas, phyllodes tumors, and papillomas, and relate the chromosomal features with those in breast carcinoma. **In general, the frequency of chromosome abnormalities is lower in benign lesions than in breast cancer, and seems to correlate with the histologic features of the tissue, and the corresponding risk of developing invasive mammary carcinoma**; aberrations are more common in proliferative than in non-proliferative lesions. In benign lesions, the karyotypes are generally less complex than those detected in invasive carcinoma, and more often involve balanced rearrangements. **No lesion-specific aberration has so far been detected; on the contrary, changes repeatedly encountered in breast cancer samples can be found in benign lesions as well**, e.g., gain of 1q, interstitial deletion of 3p, and trisomies 7, 18, and 20. Especially intriguing is the prevalence of rearrangements of the short arm of chromosome 3, with the minimally deleted bands 3p13-14, in proliferative lesions from prophylactic mastectomies in breast cancer families. The potential tumor suppressor gene(s) in this region remains, however, need to be identified.

Long-term follow-up of in situ carcinoma of the breast. Semin Diagn Pathol (United States), Aug 1994, 11(3) p223-35. Eusebi V; Feudale E; Foschini MP; Micheli A; Conti A; Riva C; Di Palma S; Rilke F. Eighty cases of duct carcinoma in situ (DCIS) of the breast have been investigated by a cohort-retrospective study. These consisted of 8.5 per 1,000 of 9,446 breast biopsies originally diagnosed as benign, between 1964 and 1976, with a mean follow-up of 17.5 years. There were forty-one cases (51%) of DCIS of clinging type (CC); 30 cases (37.%) of CC associated with other types of DCIS; nine cases of DCIS other than CC two of which were DCIS of comedo-type. Invasive duct carcinoma (IDC) subsequently developed in 11 patients (14%), whereas DCIS recurred in 5 (6%). The recurrence was ipsilateral in 12 of these 16 patients. IDC appeared more frequently, with high statistical significance, when the lesion present in the original biopsy showed pleomorphic (P) nuclei (ie, poorly differentiated cyto-nuclear morphology). The Standardized Morbidity Ratio (SMR) was 8.0 (95% CI; 2.9-17.5) with the general population as reference. IDC that developed following a lesion displaying P nuclei also showed a statistically significantly more aggressive behavior. It is suggested that when cases of DCIS are followed-up for a considerable length of time, a two-wave pattern of aggressiveness becomes apparent. IDC that develops after a poorly differentiated DCIS leads to death more precociously than that appearing after other types of DCIS, especially those showing more bland nuclear cytology.

Ductal carcinoma in situ: a proposal for a new classification. Semin Diagn Pathol (United States), Aug 1994, 11(3) p167-80. Holland R; Peterse JL; Millis RR; Eusebi V; Faverly D; van de Vijver MJ; Zafrani B. Details of a proposed new classification for ductal carcinoma in situ (DCIS) are presented. This is based, primarily, on cytonuclear differentiation and, secondarily, on architectural differentiation (cellular polarisation). Three categories are defined. First is poorly differentiated DCIS composed of cells with very pleomorphic, irregularly spaced nuclei, with coarse, clumped chromatin, prominent nucleoli, and frequent mitoses. Architectural differentiation is absent or minimal. The growth pattern is solid or pseudo-cribriform and -micropapillary (without cellular polarisation). Necrosis is usually present. Calcification, when present, is amorphous. Second, at the other end of the spectrum is well-differentiated DCIS, composed of cells with monomorphic, regularly spaced nuclei containing fine chromatin, inconspicuous nucleoli, and few mitoses. The cells show pronounced polarisation with orientation of their apical border towards intercellular spaces usually resulting in cribriform, micropapillary and clinging patterns, although a solid pattern of well-differentiated DCIS also occurs. Necrosis is uncommon. Calcifications, when present, are usually psammomatous. The third category, intermediately differentiated DCIS, is composed of cells showing some

pleomorphism but not so marked as in the poorly differentiated group. There is, however, always evidence of polarization around intercellular spaces, although this is not so pronounced as in the well-differentiated group. **These two criteria, cytonuclear differentiation and architectural differentiation, have been found to be more consistent throughout a DCIS lesion than previously employed criteria of architectural pattern or the presence or absence of necrosis.**

Eusebi V; Foschini MP; Cook MG; Berrino F; Azzopardi JG. **Long-term follow-up of in situ carcinoma of the breast with special emphasis on clinging carcinoma.** Semin Diagn Pathol (United States), May 1989, 6(2) p165-73 ABSTRACT: Forty-two cases of in situ duct (28 cases) and lobular (14 cases) carcinoma were identified after a review of 4,397 "benign" breast biopsies obtained from the files of departments of pathology of a small area of Northern Italy, between 1965 and 1971. None of the patients with in situ lobular carcinoma developed an invasive carcinoma. On the other hand, three patients with in situ duct carcinoma (one comedo and two clinging type) developed subsequent invasive carcinoma. Therefore, **it appears that clinging carcinoma has the same biological behavior as other types of small in situ ductal carcinoma; the likelihood of our patients developing invasive breast carcinoma is four times greater than that of the general population.**

[Intraductal carcinomas in situ. Retrospective study of 21 cases and review of the literature]. J Gynecol Obstet Biol Reprod (Paris, France), 1991, 20(2) p149-62 Leveque J; Poulain P; Berger D; Broux PL; Grall JY; Giraud JR; Kerisit J. In situ canalicular carcinomas are defined as malignant, galactophoric epithelial cells, that do not invade the basal membrane. The author saw 21 cases of in situ canalicular carcinomas that were treated surgically at the University Hospital of Rennes. It is possible from these cases to include certain themes: there is a pathology of an early carcinoma of the breast that will go on growing. It concerns patients in the menopausal age who (1 in 3) have a family history of neoplasia. Medical examination is important, because in 1 out of 2 cases, it leads to complimentary examinations, which help to make the diagnosis. Mammography is essential, because it leads to the diagnosis of a finding of suspicious microcalcifications as well as arranges an outline. The histology will indicate what the therapy should be. Comedocarcinomas (cellular proliferation with central necrosis) has to be considered as separate from other better differentiated types (solid, cribriform, papillary and clinging carcinomas). In fact comedocarcinomas often have a poor prognosis and the factors are: the size, the mitotic activity, the poor cellular differentiation, peri-galactoriphic reaction, and stromal and multicentre micro-invasion. Treatment has to be adapted to features of this pathology. Mastectomy which used to be routine in these cases because of the high incidence of multiple centres, are to be reserved for cases with a poor prognosis. At present conservative treatment is being evaluated, but it seems logical to recommend it in non-invasive cancers with a good prognosis when a large lumpectomy followed up by radiotherapy to the whole breast can be used, particularly because this form of treatment is now given to invasive tumours. It is very important to follow-up these patients regularly and for a long time, clinically and with mammography if conservative treatment is carried out, in any case when the opposite breast is at risk. Conclusion. Now that treatments have become varied the improvement in prognosis will depend on early diagnosis. This means that mammography screening will proceed to an increasing number of non-invasive cancers of the breast that are discovered, and to a need to work out acceptable and effective treatment for these cancers.

An immunohistochemical study of the breast using antibodies to basal and luminal keratins, alpha-smooth muscle actin, vimentin, collagen IV and laminin. Part II: Epitheliosis and ductal carcinoma in situ. Virchows Arch A Pathol Anat Histopathol (Germany), 1992, 421(4) p323-30. Bocker W; Bier B; Freytag G; Brommelkamp B; Jarasch ED; Edel G; Dockhorn-Dworniczak B; Schmid KW. A detailed immunohistochemical study has been carried out on 63 breast lesions with epitheliosis, ductal carcinoma in situ and clinging carcinoma (lobular cancerization), using antibodies directed against keratins 5/14 and 14, 15, 16, 18, 19, vimentin, smooth muscle actin, collagen IV and laminin. The results have shown that **epitheliosis on the one hand and ductal in situ and clinging carcinoma on the other are immunohistochemically different epithelial lesions**. Epitheliosis appears to be epithelial hyperplasia with keratin 5/14 and keratin 14, 15, 16, 18, 19-positive cells. Compared to epitheliotic cells, tumor cells of clinging carcinoma, lobular cancerization, and ductal carcinoma in situ expressed only luminal keratins 14, 15, 16, 18, 19 in 85% of the cases studied; whereas in 15% there was a basal keratin expression. From our results we conclude that the **clinging carcinoma (lobular cancerization) represents the initial morphological step in the development of ductal carcinoma in situ and thus may be interpreted as a minimal ductal neoplasia.** With the immunohistochemical demonstration of basal and luminal keratins it may be possible in individual cases to differentiate between benign and malignant in situ lesions of the breast.

QUESTIONS

1. Clinging duct carcinoma in situ of the breast is a well-defined lesion universally accepted around the world. **True or False.** _____.
2. Clinging duct carcinoma in situ of the breast is often found in associated with invasive tubular carcinoma of the breast. **True or False.** _____.

1. Il carcinoma duttale in situ della mammella tipo "clinging" è una lesione ben definita e universalmente accettata in tutto il mondo. **Vero o Falso.** _____.
2. Il carcinoma duttale in situ della mammella tipo "clinging" si riscontra spesso associato al carcinoma tubulare invasivo della mammella stessa.
   Vero o Falso. _____.

SURGICAL PATHOLOGY -SESSION VIII. GI / PERITONEUM

CASE PRESENTATIONS (6 cases)

Case 32-I. CMV vasculitis of the colon with ischaemic ulceration.

Case 32-II. Herpes proctitis superimposed on chronic ulcerative colitis

(*K. Cooper*)

Case 33. Extrapulmonary inflammatory myofibroblastic tumor -Inflammatory pseudotumor of the liver

(*S. Ramon y Cajal*)

Case 34. (Extrapancreatic) papillary solid/cystic tumor of the omentum

(*M. Fukunaga*)

Case 35. Lymphohistiocytoid mesothelioma of peritoneum

(*K. Cooper*)

Case 36. Primary melanoma of the cardia

(*S. Suster*)

Case 37. Glomus tumor of the stomach

(*S. Suster*)

Cases 32-I/32-II.

Kumarasen Cooper, M.D., University of Vermont, Burlington, Vermont USA

CASE 32-I. (VVV)28 or (VVV29)

CLINICAL HISTORY

This colectomy specimen was received from a 59-year-old man with a past history of renal transplantation and immunosuppressive therapy.

PATHOLOGICAL FINDINGS

GROSS EXAMINATION

The colon revealed edema and ulceration of the mucosal folds involving the proximal four-fifths of the specimen. The exudate overlying the areas of ulceration gave a gross appearance resembling pseudomembranous colitis.

MICROSCOPIC EXAMINATION

The colon demonstrated a diffuse patchy ischaemic necrosis of the mucosa with overlying fibrinopurulent exudate. The small blood vessels showed vasculopathic changes comprising inflammatory changes in the wall and organizing thrombi within the lumen.

The striking feature in the endothelial cells of small and medium sized blood vessels along the entire length of the colon was the presence of cytomegalovirus endotheliitis. This was evident by the characteristic cytopathic changes of CMV with "owl's eye" intranuclear Cowdry A inclusions and eosinophilic cytoplasmic inclusions on hematoxylin-eosin-stained sections.

The single nuclear inclusion is round to oval with a smooth contoured border. There is a clear zone or halo around the inclusions with margination/condensation of the chromatin on the inner aspect of the nuclear membrane. Intracytoplasmic inclusions are multiple, comprising small, basophilic, irregular granular structures in the perinuclear area; and are usually periodic acid-Schiff (PAS) positive.

In focal blood vessels, the entire lumen was occluded with a "plug" of CMV-infected endothelial cells. This demonstrates the specific tropism of CMV infection for vascular endothelium, leading to a local vasculitis and ischaemic necrosis and ulceration of the mucosa of the colon. The presence of vasculitis in association with CMV-infected endothelial cells suggests that CMV infection was the initiating event and not a secondary opportunistic infection of previously damaged tissues.

DIAGNOSIS

CMV vasculitis of the colon with ischaemic ulceration.

DISCUSSION

CMV-associated vasculitis most commonly affects the gastrointestinal tract, central nervous system and skin. Although the disease is usually confined to one organ, disseminated disease involving multiple sites may occur simultaneously. The common pathologic finding is the presence of CMV infection of the vascular endothelium, inflammatory infiltrate of the vessel, luminal compromise and distal tissue destruction. It is essential to note that the presence of CMV inclusions alone with vascular endothelial cells is not proof of the presence of vasculitis.

The integrity of the vessel wall, inflammation and luminal patency have to be taken into account to make a diagnosis of CMV vasculitis.
CMV infection may involve any segment of the GI tract resulting in oral erosions, esophagitis, gastritis, duodenitis and colonic ulceration (as in the submitted case). In general, CMV involvement of the GI tract usually occurs in patients with an underlying immune compromise from AIDS, immunosuppression, pregnancy, malnutrition and malignancy. The present patient was on immunosuppressive therapy following renal transplantation.

The pathophysiology of CMV disease involving the GI tract is complex and incompletely understood, but may include direct cytopathic effect, immune-mediated damage, soluble mediators of inflammation and virally induced vasculitis. In the colon, acute ulceration is the most common lesion, followed by hemorrhage, mucosal erosion, pseudomembranous colitis and perforation. The likely mechanism for the CMV vasculitis causing intestinal perforation is viral infection of endothelial cells leading to anoxia, local edema, infiltration of inflammatory cells and compromise of the lumen with secondary thrombosis, subsequent ischaemia and perforation.

CMV vasculitis involving the GI tract may have protean manifestations, but most commonly causes diarrhea, weight loss, GI bleeding, abdominal pain and occasionally perforation.

Although the morphological detection of CMV is quite typical, confirmatory immunohistochemical or in-situ hybridization may be useful, especially in the presence of atypical inclusions which have been described in the setting of AIDS. Whilst both in-situ hybridization and immunohistochemistry are both rapid, sensitive and specific, the latter is more suitable as it detects a higher percentage of CMV-infected cells than in-situ hybridization. Another role for special investigation may be in the finding of aggregates of macrophages in both CMV oesophagitis and Herpes oesophagitis. The presence of macrophages in biopsy specimens of the oesophagus without the diagnostic viral inclusions warrants further immunohistochemical study to identify CMV or HSV. Lastly, toxicity induced by chemotherapy may mimic CMV gastritis and immunohistochemistry may be essential to rule out the latter.

COMPARISON OF TYPICAL CYTOPATHIC EFFECTS OF THREE HERPES-TYPE VIRUSES

Virus	Intranuclear Inclusion (IN)	Intracytoplasmic Inclusion (IC)	Other Cytopathic Effects
Cytomegalovirus	+	+	Cytomegaly, IN Cowdry A inclusion. Multiple smaller basophilic PAS-positive IC inclusions.
Herpes simplex	+	-	Early IN "ground glass" appearance. Late Cowdry A inclusion; multinucleated giant cells and "molding".
Adenovirus	+	-	Deeply basophilic with nucleocytoplasmic blurring – "smudge cells".

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CASE 32-II. 99-9313

CLINICAL HISTORY

This is a 33-year-old woman who underwent total colectomy for ulcerative colitis refractory to steroids.

PATHOLOGICAL FINDINGS

The entire colonic mucosa appeared abnormal with evidence of ulceration and pseudopolyp formation.

Microscopically, the majority of areas showed the typical features of chronic ulcerative colitis with acute activity. In the recto-sigmoid region, discrete "punched out" ulcers were seen, the largest measuring less than 1 cm. The submitted slide is representative of such an area. The surface of the ulcer bed comprises fibrinopurulent exudate with an underlying band-like infiltrate of large mononuclear cells with abundant pale cytoplasm and round/ovoid/elongated/irregular nuclei. Closer examination of these nuclei reveal a "ground-glass" appearance with chromatin not being clearly discernible. A further underlying band of chronic inflammation is also present beneath the peculiar clear cells.

IMMUNOHISTOCHEMISTRY

The large clear cells proved to be histiocytic (CD68 positive) with a background of small T-cells (CD3 positive). These cells were also negative with CD20 (B-cell), Leder stain (myeloid), Toluidine blue (mast cells), keratin (AE1/AE3) and CD30. This panel of antibodies were useful to rule out mast cell disorders, myeloid leukaemia and lymphoma. Stains for fungi, acid-fast bacilli and CMV (DDG9/CCH2) were negative. However, the large pale cells showed immunopositivity for HSV I & II (largely intranuclear and focal intracytoplasmic).

ELECTRON MICROSCOPY

Confirmed the presence of viral particles with marginated chromatin and clearing of central portion of the nuclei. Several nuclei showed extrusion (blebbing) of nuclear membrane associated with nuclear membrane duplication. Viral capsids including viral cores were identified within the cytoplasm of one of the cells.

DIAGNOSIS

Herpes proctitis superimposed on chronic ulcerative colitis.

DISCUSSION

The unusual features include the atypical histiocytic infiltrate (with its wide differential diagnosis) and herpes proctitis associated with ulcerative colitis. Herpes infection may involve histiocytes in lymph nodes, but it is an unusual finding within histiocytes in a mucosal site.

Further inquiry revealed that the patient had a history of genital herpes. The hypothesis is that she was immunosuppressed from both systemic and local steroid therapy with manifestation of the Herpes proctitis (spread being either contiguous or neural) as an opportunistic/secondary infection.

Polyclonal antibodies to HSV I and II have been raised against detergent-solubilized HSV I and II infected whole rabbit cornea cells. Both antibodies react with antigens common for HSV I and II: all major glycoproteins present in the viral envelope and at least one core protein. There is no demonstrable cross reactivity with varicella zoster virus, cytomegalovirus or Epstein-Barr virus.

Typically these antibodies demonstrate herpes viral particles in squamous epithelia, e.g. skin and brain. A diffuse intranuclear signal is produced, often coinciding with the ground-glass intranuclear inclusions of HSV.
Similar intranuclear inclusions associated with biotin accumulation have been observed in glandular epithelia of gestational endometrium. Hence, for the unwary any attempt to demonstrate HSV in these biotin inclusions may produce a false-positive immunoreaction, especially when the avidin-biotin immunodetection system is utilized. The recommended use of prewashing with 0.05% free avidin and 0.05% free biotin does not eliminate the cross immunoreactivity. It is therefore recommended that the Envision, PAP or APAAP immunodetection systems be used for any HSV immunohistochemical investigation of tissue suspected of having a high biotin content, e.g. gestational endometria, kidney, thyroid and liver.

Genital lesions with typical multinucleated giant cells with "ground-glass" intranuclear inclusions should be used as positive control tissue.

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QUESTIONS

Case 32-I.

1. What is the cause of the ischemia in this colon?
   Name the cause: .....
2. Where in the cell are the viral inclusions of CMV found?
   Name the intracellular site: .....

1. Quale è la causa della ischemia in questo colon?
   Citare la causa: .....
2. Nella cellula dove si trovano le inclusioni virali?
   Citare la sede intracellulare: .....

Case 32-II.

1. What is the morphological appearance of the Herpes intra-nuclear viral inclusions?
   The descriptive term is .....
2. Which cells are infected with Herpes in this case study?
   Name the cells: .....

1. Quale è l'aspetto morfologico delle inclusioni virali herpetiche intranucleari?
   Il termine descrittivo è .....
2. Quali cellule sono infettate dall'Herpes in questo caso?
   Citare il tipo di cellule: .....

CASE 33. 967533

Santiago Ramon y Cajal, M.D., Department of Pathology, Clinica Puerta de Hierro, Madrid, Spain

CLINICAL HISTORY

A 56-year-old male with progressive obstructive jaundice. A radiological diagnosis of cholangiocarcinoma in the hepatic hilum was reported after a cholangiography (RECP). A liver transplantation was performed after studying the tumoral spreading. A liver sample from the hepatectomy was submitted.

PATHOLOGIC FINDINGS

GROSSLY

A circumscribed, solid white mass was found close to the bifurcation of the two branches of the hepatic duct, affecting the parenchyma of the liver, the left hepatic duct and its branches. Thickening and an unspecific inflammatory reaction of the biliary tree walls and cholelitiasis were also found.

MICROSCOPIC EXAMINATION

Showed myofibroblastic proliferation accompanied by inflammation. A lot of plasma cells were seen.

IMMUNOHISTOCHEMICALLY

miofibroblastic cells expressed positivity for smooth muscle actin, muscle-specific actin and vimentine; and were negative for CD21, EBV (LMP-1), CD35 and CD68. CD20 was positive in plasma cells and Ki67 was focally positive in inflammatory cells. PCR for detecting EBV and mycobacteria were also performed and were negative.

DIAGNOSIS

Extrapulmonary inflammatory myofibroblastic tumor (Inflammatory pseudotumor).

DISCUSSION

Inflammatory myofibroblastic tumors are spindle cell proliferations with a characteristic fibroinflammatory appearance. Different histologic patterns can be observed, including myxoid, hyaline and more cellular areas. These tumors have been detected in virtually all major organs. The inflammatory hypothesis about pathogenesis has been proposed for these tumors. Nevertheless, in some cases, because of its potential for local recurrence and local infiltrative growth, they can be considered as neoplastic processes. In fact, a clonal Epstein-Barr virus has been detected in some tumors.

Although inflammatory myofibroblastic pseudotumor can occur in virtually nay age, the majority of cases occur in childhood and early adulthood. Moreover, lesions like this have been reportedly located in the liver in adults and frequently associated with chronic cholangitis (1 and 2). A differential diagnosis to sclerosing cholangitis has to be made. Sclerosing cholangitis is a diffuse process and inflammatory myofibroblastic tumor is a localized pseudotumoral lesion.

Inflammatory myofibroblastic tumor can mimic fibrous histiocytoma, fibromatosis, and other spindle cell proliferations. Differential diagnosis can be made when the histologic

features described above can be found, and immunohistochemical stains also help in returning a correct diagnosis. Inflammatory malignant fibrous histiocytoma can be ruled out due to the absence of a neutrophils sea. Lymphoma can be excluded by performing immunohistochemical studies if necessary. Myofibromatosis usually shows areas of small cells with basophilic nuclei which are associated with a pericytic vascular pattern, and plasma cell-lymphoid infiltrate is absent.

Follicular Dendritic Cell Tumor of the liver also has to be ruled out. This entity usually shows a well developed storiform or nodular growth pattern as well as concentric whorls resembling those seen in meningioma, and a syncytial pattern. As a characteristic feature it also displays an intimate admixture of tumor cells and small lymphocytes with the presence of perivascular cuffs of mature lymphocytes. Immunohistochemically, it is usually positive for CD21, CD35, Ki-M4p, Ki-FDRC1p and vimentin, and shows occasional positivity for S-100, muscle-specific actin and epithelial membrane antigen (3). A possible aetiologic relation with clonal EBV has been described in tumors with follicular dendritic cell differentiation (4). In contrast, inflammatory pseudotumors usually do not have well formed fascicles, concentric whorls or cellular atypia. The characteristic syncytial quality of FDC tumors is also missing and plasma cells are more abundant in inflammatory pseudotumors. Immunohistochemically, inflammatory pseudotumors are negative for CD21 and CD35.

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QUESTIONS

1. All the liver inflammatory pseudotumors are formed by myofibroblasts.
   True or False. _____.
2. Inflammatory pseudotumors display a cellular pattern with:
   - **A.** spindle cells.
   - **B.** myxoid areas.
   - **C.** inflammatory cells.
   - **D.** hyaline areas.
   - **E.** all the patterns can be observed.

   ***For question 2 mark the appropriate letter.**

1. Tutti gli pseudotumori infiammatori del fegato sono composti di miofibroblasti.
   Vero o Falso. _____.

2. Gli pseudotumori infiammatori presentano un "pattern" cellulare con:
   A. Cellule fusate.
   B. Aree mixoidi.
   C. Cellule infiammatorie.
   D. Aree ialine.
   E. Tutti i "pattern" possono essere osservati.
   ***Per la domanda 2 contrassegnare la lettera giusta.**

CASE 34. (S)00-3742

Masaharu Fukunaga, M.D., Department of Pathology, Jikei University School of Medicine, The Daisan Hospital, 4-11-1 Izumi-honcho, Komaeshi, Japan

CASE HISTORY:

A 46-year-old Japanese woman was incidentally pointed out to have an abdominal mass by an echogram in an annual examination. Laporatomy revealed a well-circumscribed, rubbery mass measuring 5.2 X 4.0 X 4.0 cm, which was located in the omentum and attached to the serosa of the gastric antrum and the second portion of the duodenum. The mass, which was not associated with the pancreas, was excised and the pancreas showed no abnormality. Extensive systemic examination failed to find any other primary sites. The patient was well without recurrence for the three months of follow-up.

PATHOLOGY

GROSS SPECIMEN

The excised abdominal lesion measuring 5.2 X 4.0 X 4.0 cm was a well-circumscribed, encapsulated, rubbery mass. On cut-surface it showed a yellowish to tan-brawn, solid tumor with a central uniloculated cyst measuring 3.0 cm in greatest diameter and containing bloody serous fluid (Scotch egg-like appearance).

HISTOLOGY

The tumor had a fibrous capsule. It showed a combination of solid, microcystic and pseudopapillay growth patterns. The tumor cells were characterized by a round to oval nuclei with fine chromatin and inconspicuous nucleoli and abundant, pale to eosinophilic cytoplasm. The cytoplasm was negative for periodic acid-Shiff, Alcian blue and Grimelius stains. Nuclear atypia was mild and mitotic figures were rarely observed. The stroma was fibrous with hyalinization and vascular-rich. Clusters of foamy histiocytes were scattered. The tumor cells were weakly and diffusely positive for vimentin. Twenty to 30% of tumor cells were positive for EMA and alpha-1-antichymotrypsin. A few cells expressed cytokeratin (CAM5.2) and chromogranin A. The tumor was uniformly negative for desmin, alpha-smooth muscle actin, HHF35, CD117, S-100 protein, synaptophysin, alpha-1-antitrypsin, KP1, estrogen and progesterone receptors. Ultrastructurally, the tumor cells had round nuclei with a narrow rim of marginated heterochromatin. The cytoplasm contained moderate amounts of mitochondria and rough endoplasmic reticulum, variably sized zymogen-like granules and thin filaments. Poorly developed cell junctions were rarely observed.

DIAGNOSIS

Extrapancreatic solid-cystic tumor (SCT).

DISCUSSION

The tumor was macroscopically and microscopically very similar to the SCTs of the pancreas. It showed a solid and pseudopapillay growth patters and the tumor cells were characterized by a round to oval nuclei and abundant, pale to eosinophilic cytoplasm. The immunohistochemical profiles were somewhat different from those of the reported cases; some tumor cells in the current case were positive for EMA and alpha-1-antichymotrypsin. In

electron microscopy, most conspicuous were tumor cells containing large, osmiophilic, zymogen-like granules of variable sizes (500 to 3000 nm). The differential diagnosis includes GIST, paraganglioma and newly described clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres. Eight extrapancreatic SCTs have been reported, a few cases in the retroperitoneum and one each in liver and mesocolon. Some of them were considered to arise from ectopic pancreas. There was no frank evidence that the present tumor originated from ectopic pancreas. Kosmahl et al. mentioned that the occurrence of a few SCTs in the retroperitoneal space outside the pancreas can be related to the localization of the genital ridge during embryogenesis and speculated that SCTs might originate from genital ridge-related cells that were incorporated in to the pancreas during organogenesis.

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QUESTIONS

1. Where does pseudopapillary solid-cystic tumor usually arise?
   Indicate the site: .....
2. What are the differential diagnoses of pseudopapillary solid-cystic tumor?
   List the main ones: .....
   .....

1. Quale è la sede di elezione di insorgenza del tumore solido-cistico (pseudo-)papillare? **Indicare la sede:** .....
2. Quali sono le diagnosi differenziali del tumore solido-cistico (pseudo-)papillare?
   Elencare le principali: .....
   .....

CASE 35. 99-9008.

Kumarasen Cooper, M.D., University of Vermont, Burlington, Vermont USA

CLINICAL HISTORY

This patient is a 61-year-old woman who presented with left lower quadrant pain in her abdomen. A pelvic mass was palpated and removed at surgery. Tumor also involved the left ovary, sigmoid colon and rectum.

PATHOLOGICAL FINDINGS

GROSS FEATURES

The specimen comprised a large irregular mass of tan-white tumor weighing 750 grams and measuring 21.0 x 18.5 x 8.0 cm. Involvement of the surface of the left ovary, sigmoid colon and rectum was observed. The omentum was free of tumor.

MICROSCOPICAL FEATURES

The tumor is characterized by sheets of large histiocyte-like tumor cells with a diffuse heavy lymphocytic background. Focal collections of eosinophils are also noted in the peripheral margins of the tumor. The tumor cells have abundant pale eosinophilic cytoplasm with large nuclei; the latter ranging from ovoid and pleomorphic to bizarre and bi/multinucleated forms. Chromatin in most areas is coarse and vesicular with prominent nucleoli. Mitoses (1-2/10 HPF) including atypical forms were observed. The pattern of the tumor ranges from being cohesive sheets, loosely arranged aggregates or with a myxoid background. Focal microcyst formation was observed. No evidence of tubulopapillary differentiation was present, but a sarcomatoid spindle cell pattern was observed in some areas.

ELECTRON MICROSCOPY.

The ultrastructural examination showed sporadic cells with sinuous villiform processes and intermediate filaments which tend to aggregate into tonofilament bundles.

IMMUNOHISTOCHEMISTRY AND DIFFERENTIAL DIAGNOSIS

- Tumor cells showed the following immunoprofile:

  Cytokeratins: AE1/AE3 ++
  CAM 5.2 ++
  CK7 +
  CK20 -

  Calretinin ++

  The diffuse calretinin positivity (nuclear and cytoplasmic immunoreactivity) favor a diagnosis of mesothelioma.

- Pertinent **negative** markers include:
  CEA, CD15 (Leu-M1), B72.3 (excluding adenocarcinoma)
  CD34, CD117 (C-KIT) (excluding a gastrointestinal stromal tumor)
  MSA (HHF-35), SMA, desmin (excluding leiomyosarcoma and inflammatory myofibroblastic tumor/fibrosarcoma)
  S-100, HMB-45, melan A/MART-1 (excluding metastatic melanoma)

- A histiocytic-rich background was demonstrated with CD68; whilst tumor cells were negative for CD30 (excluding a large cell anaplastic lymphoma).

DIAGNOSIS

Diffuse malignant mesothelioma, lymphohistiocytoid variant.

DISCUSSION

This is a rare unusual variant of mesotheliomas. These tumors comprised less than 0.8 percent of 394 definite cases of diffuse malignant mesotheliomas in the Australian Mesothelioma Surveillance Program. In biopsy material, the lymphocytic infiltrate may sometimes obscure the mesothelial proliferation, resulting in false negativity. These is no evidence that the lymphohistiocytoid character of these tumors confers any prognostic advantage. Lymphohistiocytoid mesothelioma appears to represent one extreme of a spectrum of reactive lymphoplasmacytic infiltrates in predominantly sarcomatoid mesotheliomas.

The advent of immunohistochemistry has had an immense impact on distinguishing between malignant mesothelioma (especially the epithelial subtype) and metastatic adenocarcinoma to serosal membranes. Until recently, the diagnostic contribution from immunohistochemistry for the identification of mesothelial cells has been largely exclusionary of epithelial cells.
Calretinin is a calcium binding protein of 29KD that serves as an excellent positive marker for mesothelial differentiation. Calretinin, like S-100 protein, belongs to the EF-hand family of calcium binding proteins. The EF-hand proteins are characterized structurally by a helix-loop-helix motif which acts as the calcium binding site. Calretinin contains six such EF-hand stretches. The calretinin gene exhibits a 60% homology with Calbindin, and it is expressed in central and peripheral neural tissues. The function of calretinin is unknown, although a possible role as a calcium buffer has been postulated.
Using an antiserum (7696, Swant, Switzerland) raised against the human recombinant protein, Doglioni et al demonstrated almost 100% immunopositivity in 44 mesothelial neoplasm (36 epithelial, 5 biphasic, 3 sarcomatoid). It is important to note that both nuclear as well as cytoplasmic immunoreactivity is demonstrable with calretinin.

About 10% of adenocarcinomas with known metastatic potential to serous membranes may demonstrate focal immunopositivity. Calretinin is also applicable to immunocytochemical analysis of cytologic specimens from serous effusions; with positive immunoreaction in all cases of mesothelioma. It should be emphasized that calretinin decorates both normal and reactive mesothelial cells; hence not playing a role in the differentiation between benign and malignant mesothelial cells.
Other positive markers for mesothelial differentiation include HBME1, which stains the majority of mesotheliomas and approximately 50% of pulmonary adenocarcinomas. A membranous pattern (corresponding to the villous surface) has been demonstrated in mesotheliomas; whilst a cytoplasmic immunopositivity corresponds to adenocarcinomas. However, overlapping patterns have been noted and hence HBME1 serves little value in discriminating between mesothelioma and adenocarcinoma. Thrombomodulin, a regulator of intravascular coagulation, has also been recommended for inclusion in the immunohistochemical panel for the diagnosis of malignant mesothelioma, but also stains a proportion of metastatic adenocarcinomas. N-Cadherin has a high level of expression in malignant mesothelioma, whilst E-Cadherin stains lung adenocarcinomas, providing a useful combination for the immunohistochemical panel; however only E-cadherin is commercially available for use in formalin-fixed paraffin-embedded tissue. Cytokeratin 5/6 has a high sensitivity for mesotheliomas with up to 100% of tumors being positive and negative results in

81% pulmonary adenocarcinomas. The remaining adenocarcinomas were either weak, equivocal or focally positive.
Calretinin is also useful in delineating brain tumors with neuronal differentiation (e.g. central neurocytoma) from gliomas (e.g. oligodendroglioma) being positive in the former.

Immunoreactivity with calretinin has also been observed in steroid producing cells of the testis and ovary. Consistent expression of calretinin has also been demonstrated in cutaneous mastocytomas.

Calretinin immunopositivity has also been demonstrated in cutaneous granular cell tumors, cardiac myxomas and ameloblastoma. In the latter setting, calretinin is useful to distinguish cystic ameloblastomas from non-neoplastic cysts of the jaw. Calretinin immunopositivity in cardiac myxoma cells suggests an origin from endocardial sensory nerve tissue.

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QUESTIONS

1. What is currently regarded as the best positive mesothelioma marker?
   Name the marker: .....
2. Does the heavy lympho-histiocytic inflammatory infiltrate alter the prognosis of this tumor? **Yes or No. ____.**

1. Quale è attualmente considerato il miglior markers positivo nella diagnosi di mesotelioma? **Indicare il nome:** .....
2. L'intenso infiltrato flogistico infiammatorio modifica la prognosi di questo tumore? **Si o No. ____.**

CASE 36. 32074-1

Saul Suster, M.D., Director of Pathology, The Ohio State University, Columbus, Ohio, USA.

CLINICAL HISTORY

A 69-year-old man was admitted for complaints of abdominal distress and melena. The patient had a past history of hypertension but had never undergone surgery or been diagnosed previously with malignancy. A thorough physical examination revealed an adult male in no acute distress, without any external abnormalities, and without any organomegaly or palpable masses. An echoscan of the stomach and esophagus revealed an area of mural thickening at the level of the cardia. On endoscopic examination, an exophytic polypoid tumor mass was identified in the region of the cardia of the stomach. An endoscopic biopsy revealed highly malignant cells consistent with a poorly differentiated, malignant neoplasm and an esophagogastrectomy was performed. The resection specimen showed a large, fungating, ulcerated tan red mass in the region of the cardia and distal esophagus that measured 6 cm in greatest diameter and infiltrated the wall of the stomach into the muscularis propria. Careful physical examination following surgery and pathologic examination of the resected specimen failed to identify any tumor elsewhere.

PATHOLOGIC FINDINGS

Histological examination revealed a monotonous population of atypical tumor cells with a somewhat lobulated appearance on scanning magnification. On higher magnification, the tumor grew as sheets or forming discrete nests of tumor cells. Areas of hemorrhage and necrosis were evident throughout all sections of the tumor examined. The tumor cells were relatively uniform and contained round to oval, large nuclei with scattered chromatin pattern and prominent nucleoli. Mitotic figures were numerous (>50 per 10 HPF). The cells were surrounded by a rim of lightly eosinophilic cytoplasm with poorly-defined cell borders. In some areas, the cytoplasm adopted an optically clear appearance. In one area, a small focus of junctional melanocytic activity was found in the basal layer of the squamous mucosa at the level of the gastroesophageal junction. All perigastric and esophageal lymph nodes (0/15) examined were free of tumor.

SPECIAL STUDIES

Histochemical reaction for PAS/PAS-D and mucicarmine were negative in the tumor cells. Immunohistochemical studies showed strong positivity of the tumor cells for vimentin, S-100 protein, HMB45, and Melan-A. Stains for cytokeratin AE1/AE3, CEA, MOC31, actin, desmin, EMA, CD10, CD20, CD45, CD99, CD117 and AFP were negative. Electron microscopic examination was performed on tissue retrieved from the paraffin block; despite poor preservation, some of the cells displayed a prominent Golgi apparatus with electron lucent vesicles as well as occasional electron dense granules consistent with atypical premelanosomes.

DIAGNOSIS

Primary malignant melanoma of the esophagus.

DISCUSSION

Primary malignant melanoma originating from internal organs is extremely rare but has been well documented in the literature. Primary melanoma originating in the

gastrointestinal tract is particularly rare, with the majority of cases reported involving the oral cavity, esophagus, gallbladder and anorectum.[1-3] Malignant melanoma originating as a primary tumor in the esophagus has been the source mainly of case reports. In a review of the literature presented up to 1989, a total of only 139 cases could be identified in the world literature.[4]

The origin of primary malignant melanoma in the esophagus is controversial; however, most investigators believe that such tumors originate from foci of basal melanocytes present in the squamous epithelium.[5] Melanoma has been estimated to represent less than 0.1% of all esophageal malignancies.[6] The largest reported series from a single institution in the United States, the Memorial Sloan-Kettering Cancer Center in New York, contained only 8 cases reviewed from their files.[7]

The clinical features of primary melanoma of the esophagus are similar to those of carcinoma of the esophagus. Most patients are in their sixth and seventh decades (mean age: 60), with a slight male predilection. Dysphagia, substernal pain, heartburn, and weight loss are the most common symptoms.[4,8] Grossly the tumors are most often polypoid and ulcerated, and can vary in size from small lesions to large, bulky masses. Satellite nodules, sometimes several centimeters away from the main tumor, may be also seen. The mucosa at the edges of the lesion can be pigmented, a phenomenon referred to as "melanosis" of the esophagus. The majority of the tumors are grossly pigmented; however, very rarely completely amelanotic lesions can occur.[9]

Histologically, the tumors usually display the characteristic features of malignant melanoma; i.e., sheets of atypical epithelioid or spindle cells displaying a prominent nesting pattern, with marked cytologic atypia, prominent nucleoli, binucleated cells, and atypical mitotic figures. Pleomorphism with bizarre giant cells is often seen and the cells commonly display fine, dusty cytoplasmic pigmentation. Small cell, balloon cell and signet ring-cell variants have all been described in the esophagus.[10] The most important histological feature suggestive of primary melanoma of the esophagus, however, is the identification of junctional activity by atypical melanocytes within the basal layer of the squamous epithelium. The atypical melanocytes in these areas are often large, with abundant clear or lightly eosinophilic cytoplasm and large, vesicular and hyperchromatic nuclei with prominent nucleoli. Pagetoid spread of melanocytes is not very commonly seen, and large clusters of atypical melanocytes can be seen higher up in the squamous mucosa than in the basal epithelium.[11]

The main differential diagnosis of primary malignant melanoma of the esophagus is with a metastasis to this organ from another site.[12] Because primary melanoma of the esophagus is so rare and regressed or clinically unapparent lesions can give rise to metastases to internal organs, strict criteria have to be applied before a primary diagnosis is rendered. Histologically, the most useful feature is junctional melanocytic activity. However, large tumors are often ulcerated and may no longer display viable overlying epithelium, or metastatic tumors can secondarily infiltrate the overlying mucosa and closely resemble a Pagetoid pattern of growth. The most reliable criterion for diagnosis is to rule out clinically and on thorough physical examination the existence of a primary lesion elsewhere. Another helpful feature is the virtual absence on clinical follow-up of evidence of tumor elsewhere. Metastatic melanoma is usually multiple and eventually will present with lesions in other organs. The majority of metastatic melanomas to the esophagus occur in the context of advanced or very late stages of the disease. A solitary metastasis to the

esophagus from an occult primary, although possible, would be very unlikely. Tumors that recur locally before they metastasize are also another indication that we are most likely dealing with a primary lesion at that site rather than repeated metastases to the same location from an occult primary (the "Toker" law).

In the present case, a thorough physical examination following the diagnosis did not reveal evidence of any cutaneous lesion suspicious for melanoma, or of tumor anywhere else in the body. Clinical follow-up in our patient has demonstrated a recurrent lesion at the site of anastomosis 10 months after surgery, without evidence of any tumor elsewhere. The combination of the absence of a tumor in any other location on thorough clinical examination, absence of development of other lesions in other organs after 10 months of follow-up, local recurrence at the site of surgery, and focal Pagetoid involvement in the squamous mucosa from the resected specimen all support a diagnosis of primary melanoma of the esophagus in our patient.

DIFFERENTIAL DIAGNOSIS

The histologic differential diagnosis for this tumor, particularly the amelanotic variant is quite broad. Melanomas composed primarily of epithelioid cells can closely mimic carcinomas; this can be particularly problematic when the tumor contains signet-ring cells. Melanomas can also be composed of a monotonous and solid proliferation of small cells that can closely resemble a malignant lymphoma. The latter differential diagnosis can be particularly challenging in small endoscopic specimens if melanoma is not included in the differential diagnosis. Melanomas predominantly composed of spindle cells can be easily mistaken for gastrointestinal stromal tumors (GIST) or other malignant mesenchymal neoplasms such as leiomyosarcoma or malignant peripheral nerve sheath tumor. Application of a panel of immunohistochemical stains should be able to clearly define the melanocytic nature of the tumor cells.

Another diagnostic difficulty posed by our case was the confusion generated by the distal location of the tumor in the esophagus, with extensive infiltration and spread into the cardia of the stomach. On both endoscopic and radiographic examination, the tumor was initially though to correspond to a gastric malignancy. Since primary gastric malignant melanoma has not been described in the literature, this possibility was less likely to be entertained at the time of evaluation of the endoscopic biopsy, which was labeled as "biopsy of gastric mass". Secondary extension and infiltration of the stomach by a tumor arising at the gastroesophageal junction should always be entertained in a lesion that displays morphologic features that are unusual for that location.

CLINICAL BEHAVIOR AND TREATMENT

The clinical behavior of primary melanoma of the esophagus is quite aggressive. Some authors have suggested that primary malignant melanoma of the esophagus may be more aggressive that their cutaneous counterparts, but this may be due to their larger size and depth of invasion at the time of diagnosis. The average survival time following esophagectomy for primary melanoma is less than 1 year, with a 5 year survival of about 2%.[4,13] Complete surgical excision is the standard treatment, followed by adjuvant radiation and chemotherapy. Common sites of metastases include regional lymph nodes, liver, mediastinum, lung and brain. Local endoscopic laser treatment may play a role in palliation in locally advances tumors that are unresectable.

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QUESTIONS

1. The most reliable histological feature favoring a diagnosis of primary melanoma of the esophagus is:
   - **A.** Prominent nesting pattern.
   - **B.** Sheets of epithelioid or spindle cells with atypia.
   - **C.** Necrosis.
   - **D.** Junctional melanocytic activity in overlying squamous mucosa.
   - **E.** Intranuclear inclusions.
2. The most helpful information to distinguish primary from metastatic melanoma to the esophagus is:
   - **A.** A history of repeated local recurrence prior to distant dissemination.
   - **B.** A large polypoid mass protruding into the lumen.
   - **C.** Negative total body scan.
   - **D.** Lack of pigmentation of the tumor.
   - **E.** Female gender.

***Mark the appropriate letter.**

1. Il più affidabile reperto istologico che favorisce la diagnosi di melanoma primitivo dell'esofago è:
   - **A.** Prominente "pattern" architetturale a nidi.
   - **B.** Lembi di cellule epitelioidi o fusate dotate di atipie.
   - **C.** Necrosi.
   - **D.** Attività giuzionale melanocitaria nella soprastante mucosa squamosa.
   - **E.** Inclusioni intranucleari.

2. La più utile informazione per distinguere il melanoma primitivo dell'esofago da una metastasi allo stesso è:
   - **A.** Una storia di ripetute recidive locali, prima di una disseminazione metastatica.
   - **B.** Una grossa massa polipoide protrudente nel lume dell'esofago.
   - **C.** Negatività di uno scan total body.
   - **D.** Mancanza di pigmentazione del tumore.
   - **E.** Sesso femminile.

***Contrassegnare la lettera giusta.**

Case 37. 30438-1

Saul Suster, M.D Director of Pathology, The Ohio State University, Columbus, Ohio, USA.

CLINICAL HISTORY

A 62-year-old man was seen for an episode of melena. The patient had a history of arteriosclerotic heart disease, and had undergone a coronary artery bypass operation two years previously. Endoscopic examination revealed a well-circumscribed, polypoid mass in the antrum of the stomach displaying a smooth surface with a small focus of ulceration. Because of the configuration of the lesion, the clinical endoscopic impression was that of a submucosal lipoma. Endoscopic biopsies were insufficient for diagnosis and the patient was scheduled for a gastrectomy. The resection specimen showed an intramural, hemorrhagic tumor that appeared to be very well circumscribed and confined to the muscularis propria of the organ. The tumor measured 4 cm. in greatest dimension and showed a spongy, hemorrhagic cut surface. Eight perigastric lymph nodes were found to be free of tumor. A portion of the greater omentum was also removed and was also free of tumor.

PATHOLOGIC FINDINGS

On scanning magnification, the lesion was very well circumscribed, with smooth, pushing borders and displayed solid, cellular areas admixed with cavernous-like vascular spaces filled with blood lakes. The solid areas were composed of a monotonous proliferation of round to oval cells containing round nuclei with dispersed chromatin and absent or inconspicuous nucleoli. An ample rim of optically clear cytoplasm showing sharply delineated cell membranes surrounded the nuclei. In some areas, the tumor cells were surrounded by strands of hyalinized fibrous tissue and grouped into small nests or islands creating a vaguely "organoid" pattern. Abundant, dilated blood vessels were present throughout the lesion, many of which contained entrapped small islands of tumor cells within their walls. Small islands of tumor cells could also be seen infiltrating into the muscle in the periphery of the lesion, simulating invasion. There was no evidence of necrosis, cytologic atypia, pleomorphism, or mitotic activity encountered in any of the sections examined.

Special Studies:

Immunohistochemical studies were performed for confirmation of the diagnosis. The tumor cells showed strong positivity for vimentin, smooth muscle actin and smooth muscle myosin, and h-caldesmon. Stains for cytokeratin AE1/AE3, CEA, AFP, CD34, bcl-2, c-kit (CD117), chromogranin, CD31 and Factor VIII-RA were negative in the tumor cells. Tissue was not available for electron microscopic examination.

DIAGNOSIS

Glomus tumor of the stomach.

DISCUSSION

Glomus tumor of the stomach is an extremely rare condition that was first recognized by Saul Kay et al in 1951.[1] Since then, several case reports have appeared in the literature. The largest series was described from the Armed Forces Institutes of Pathology in Washington, D.C., by Appelman and Helwig,[2] who reported 12 cases.

Glomus tumors most often occur in the gastric antrum of adults, without any sex predilection. The signs and symptoms can be variable; the most frequent clinical manifestations are pain, nausea and vomiting. Bleeding due to surface ulceration is also a common finding in these lesions; the bleeding can be quite profuse due to the extensively vascularized nature of the lesion, and can lead in some instances to anemia. The majority of the lesions are solitary, although multiple gastric glomus tumors have been described.[3]

Grossly the lesions characteristically present as well-circumscribed intramural nodules confined to the muscularis propria of the stomach. The edges of the tumor often show the formation of a pseudocapsule caused by compression and collagenization of the surrounding tissues. The majority of glomus tumors in the stomach are small, averaging 2.5 cm. in greatest diameter, although a few studies have reported much larger and even massive tumors.[4] It is not clear, however, whether the latter may not correspond to an epithelioid variant of gastrointestinal stromal tumor (GIST).

Histologically, glomus tumors show a very distinctive morphology. The tumor cell population is characterized by a monotonous proliferation of epithelioid cells with central nuclei containing coarsely dispersed chromatin. The cytoplasm can vary from clear to pale, lightly eosinophilic or amphophilic. A distinctive feature of glomus tumors is the very sharply defined and outlined cell borders. Unlike other tumors displaying similar morphology, spindle or multinucleated cells are never present in glomus tumors. Another prominent feature is the presence of prominent vascularity within the lesion. The relationship of the tumor cells to the vascular channels is one of the most distinguishing features of this lesion. The glomocytes do not surround the vessels forming a discrete perivascular cuff, but rather congregate around the vessels in multiple small nests or as single cells. Often, a band of hyaline material separates the glomus cells from the endothelium.

Although these tumors have been traditionally classified in the family of vascular endothelial neoplasms, the proliferating neoplastic cells actually do not exhibit features of vascular endothelium. Ultrastructural studies of glomus cells have shown that they exhibit features of smooth muscle cells rather than of pericytes.[5] At the immunohistochemical level, the tumor cells show characteristically strong positivity for muscle-related antigens, such as smooth muscle actin, smooth muscle myosin and h-caldesmon, and are negative for vascular endothelium-associated markers such as Factor VIII-related antigen, CD31 and CD34.[6,7] Glomus tumors are thought to originate from the neuromyoarterial glomus, a normal arteriovenous shunt abundantly supplied with nerve fibers that acts as a regulator of temperature in sever locations throughout the body.[8] The immunohistochemical and fine structural phenotype of the tumor cells therefore is more in-keeping with this tumor belonging in the family of myoid lesions.

DIFFERENTIAL DIAGNOSIS:

Because the morphologic appearance of these lesions in its more common sites (such as the skin) is quite distinctive, the differential diagnosis is usually very straightforward. However, when found in certain unusual locations, it can pose difficulties for diagnosis. The most important differential diagnostic consideration when presenting in the stomach is with gastrointestinal stromal tumors (GIST). Because of the location of the lesion within the muscle wall, its good circumscription, and prominent epithelioid cell appearance, the tumor can sometimes display more than a passing resemblance with GIST. Moreover, one of the characteristic appearances of GIST is precisely the epithelioid cell morphology,

whereby the tumor cells can grow as sheets or packets of round, monotonous tumor cells with centrally placed round nuclei surrounded by a rim of optically-clear or lightly eosinophilic cytoplasm closely reminiscent of glomus cells.[9] At the morphologic level, features that distinguish GIST from glomus tumor include the absence of a relationship between the tumor cells and the vessel walls, such as is typically seen in glomus tumors, and the absence of any evidence of atypia, mitotic activity, spindling of tumor cells or nuclear pleomorphism in the glomus tumor.

At the immunohistochemical level, it is very easy to distinguish glomus tumor from GIST. Although muscle markers such as actin and desmin can occasionally be encountered at least focally in GIST, it is rare to find such strong immunoreactivity for muscle markers in such tumors compared with glomus tumor. Additionally, GIST is characterized by the strong expression in the tumor cells of CD34, bcl-2 and c-kit (CD117), the latter being highly distinctive of this lesion and not present in glomus tumor cells.[10] It may be more difficult to separate GIST from glomus tumor by electron microscopy due to some of the overlap in features displayed by the two, a circumstance which led some authors to postulate a close histogenetic relationship between these two conditions.[11]

Other conditions that could more remotely enter in the differential diagnosis include gastric carcinoid, and metastases from clear cell neoplasms from other organs. Gastric carcinoids can also show a monotonous proliferation of round cells with abundant cytoplasm displaying a prominent "organoid" growth pattern within the wall of the stomach; however, the tumor cells will characteristically display a "salt-and-pepper" chromatin pattern, and the lesions will be much more infiltrative and ill-defined than glomus tumor. By immunohistochemistry, the tumor cells in gastric carcinoid will be strongly positive for neuroendocrine markers such as chromogranin and other peptide hormones, and will also express low-molecular weight cytokeratins.[12]

Metastases to the stomach are rare and usually seen in advanced stages of most tumors but rarely can occur as the first manifestation of disease. A case of malignant glomus tumor that presented initially as a polypoid, bleeding mass in the stomach was circulated in the AMR slide seminar and later reported in the literature.[13] The gastric lesion was initially misinterpreted as an hemangiopericytoma, and was later identified as a metastasis of glomus tumor upon review of the clinical history and further study by ultrastructure and immunohistochemistry. Very rarely, renal cell carcinoma can also present as a polypoid mass involving the mucosa and the wall of the stomach. Although the tumor can also be composed of monotonous clear cells with bland-appearing nuclei, the cell borders are usually not as clearly defined as in glomus tumors, and the lesion will be more infiltrative and less well-demarcated. Immunohistochemical stains will help to distinguish the two by demonstrating cytokeratin and EMA reactivity in the cells of renal cell carcinoma, as opposed to actin and myosin in the glomus tumor cells.

Clinical Behavior and Treatment:

Glomus tumors of the stomach are universally benign and surgical excision is the only treatment required. Although well-documented examples of malignant glomus tumors (glomangiosarcoma) have been reported in other locations, so far there have been no reported cases of gastric glomus tumors showing aggressive behavior.

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QUESTIONS

1. Glomus tumor of the stomach is a morphologic variant of:
   - **A.** Vascular tumor.
   - **B.** Hemangiopericytoma.
   - **C.** Smooth muscle tumor.
   - **D.** PEComa.
   - **E.** GIST.
2. The most important histologic differential diagnosis of glomus tumor of the stomach is:
   - **A.** Metastatic epithelioid melanoma.
   - **B.** Epithelioid angiosarcoma.
   - **C.** Hepatoid carcinoma of the stomach.
   - **D.** MALToma.
   - **E.** Epithelioid GIST.

***Mark the appropriate letter.**

1. Il tumore glomico dello stomaco è una variante morfologica di:
   - **A.** Tumore vascolare.
   - **B.** Emangiopericitoma.
   - **C.** Tumore muscolare liscio.
   - **D.** PEComa.
   - **E.** GIST.
2. La diagnosi istologica differenziale più importante per il tumore glomico dello stomaco è rappresentata da:
   - **A.** Metastasi di melanoma epitelioide.
   - **B.** Angiosarcoma epitelioide.
   - **C.** Carcinoma epatoide dello stomaco.
   - **D.** MALToma.
   - **E.** GIST epitelioide.

***Contrassegnare la lettera giusta.**

SURGICAL PATHOLOGY -SESSION IX. THORAX

CASE PRESENTATIONS (6 cases)

Case 38. Lung metastasis of giant cell tumor of bone

(C. Moran)

Case 39. Lung metastasis of Ewing's sarcoma

(*S. Ramon y Cajal*)

Case 40. Pleural mesothelioma

(*C. Moran*)

Case 41. Chester-Herdheim disease –lung involvement

(*S. Suster*)

Case 42. Acute interstitial pneumonia (Hamman-Rich syndrome)

(*N. Weidner*)

Case 43. Large cell neuroendocrine carcinoma of the lung

(*C. Moran*)

Case 38. (S)02-4396(BX10)

Contributor: Cesar Moran, M.D., Department of Pathology, M. D. Anderson Cancer Center, Houston, Texas, USA.

CLINICAL HISTORY

A 35-year-old woman presented with a solitary right upper lobe mass. A surgical resection of the mass was done.

PATHOLOGIC FINDINGS

The lobectomy specimen revealed a well-circumscribed, intraparenchymatous tumor that measured 5 x 4 x 3 cm., unrelated to the pleura or bronchial branches. Cut section was somewhat gritty, and showed a tan brown, homogeneous, rubbery tissue showing very sharp circumscription from the surrounding pulmonary parenchyma. The mass was unencapsulated and contained a gritty thin shell of bone in the periphery. The remainder of the surrounding lung tissue appeared unremarkable.

Histologic examination showed a dense cellular proliferation containing an admixture of bland-appearing, osteoclast-type multinucleated giant cells against a background of round to oval mononuclear cells. The giant cells contained up to 20 bland-appearing nuclei displaying similar characteristics to the mononuclear cells in the stroma, and were surrounded by abundant eosinophilic cytoplasm. The mononuclear cells showed round to oval, vesicular nuclei with small chromocenters and a rim of indistinct lightly eosinophilic or amphophilic cytoplasm. In some areas, the cells showed focal spindling reminiscent of fibroblasts. Rare mitotic figures could be seen (max. 2 per 10 HPF). The tumor was well-vascularized and showed a thin rim of mature lamellar bone at the edges of the lesion. Occasional cavernous vascular lakes rimmed by osteoclastic giant cells were also seen.

Special Studies:

The most important special study in this case was a telephone call to the patient's personal physician (not the surgeon!). As it turned out, the patient had a history of a giant cell tumor of her tibia removed 4 years earlier, which had recurred locally once. Special stains were done for the sake of completeness; the giant cells stained strongly positive with PAS and were immunoreactive for FVIII-RA. The mononuclear stromal cells stained only for vimentin; stains for actin, desmin, alpha-1-antichymotrypsin, myogenin, cytokeratin, S-100 and HMB45.

DIAGNOSIS

Metastasis of giant cell tumor of bone to the lung.

DISCUSSION

Metastases of giant cell tumor of bone to lung are extremely rare and constitute another example of the phenomenon of "benign metastasizing tumors", such as benign metastasizing leiomyoma. A total of approximately 140 cases have been reported so far in the world literature, the majority as case reports.[1-3]

Metastases from giant cel tumors of bone (GCTB) can occur at any age; the most common primary site is the distal radius.[2,3] The prevalence of this occurrence in a large series was 3% of all patients with a diagnosis of GCTB.[3] The interval between the onset of the tumor and the detection of the lung metastasis is around 4 years.[2,3] However, cases showing late metastases of up to 27 years have been reported.[4] Lung metastasis as the initial

manifestation of the disease is extremely rare. The majority of patients (~80%) have experienced a local recurrence before the onset of the metastasis.

Clinically the patients can present with signs and symptoms of pulmonary obstruction, chest pain or dyspnea depending on the size and location of the lesion. On chest X-rays and CT scans, pulmonary metastases of GCTB appear as rounded nodular opacities of homogeneous density, ranging from 0.5 to 8 cm. in greatest diameter. The lesions are multiple in up to half of the cases. The peripheral regions of the lung are involved in about 85% of cases and the basilar regions in approximately 62%.[3] A rare case of endobronchial metastasis from GCTB has been described by cytologic evaluation, but was never confirmed histopathologically.[5] Although the histological features appear to always be the same in both the primary and metastatic lesions, metastases to the lungs from GCTB appear to occur more frequently in lesions in which the primary tumor was classified as Grade III according to Campanacci's radiographic grading system (i.e., interruption of the cortex with soft tissue extension).[6,7]

The histological appearance of GCTB is usually identical to that seen in the primary lesion. The vast majority of cases reported to date have shown the features associated with benign GCTB; however, a case of benign GCTB with osteosarcomatous transformation ("dedifferentiation") in a lung metastasis has been described.[8] The lesions are amenable to diagnosis by fine needle aspiration cytology (FNA) when the history of previous GCTB is known. The aspirates usually contain a dual population of cells, consisting of mononuclear tumor cells forming sheets of cohesive perivascular clusters, and multinucleated osteoclastic tumor cells that often were seen to be closely attached to the mononuclear cell clusters.[9]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for these tumors involves basically primary lung tumors of lung infiltrated by osteoclast-like giant cells,[10] as well as metastases of tumors containing osteoclast-type giant cells.[11] The most common primary tumors of lung that can harbor a prominent osteoclastic component include adenocarcinoma, sarcomatoid carcinoma, and the giant cell variant of malignant fibrous histiocytoma (MFH).[10] In addition to the giant cells, common characteristics of these tumors include the overt malignant nature of the neoplasm and the presence of a histologically malignant mesenchymal component. Metastatic tumors that can harbor a prominent osteoclastic component include MFH, osteosarcoma, leiomyosarcoma, malignant melanoma and osteoclastoid adenocarcinomas derived from a variety of organs, including breast, thyroid, pancreas, colon and salivary glands.[10,11] Strict clinicopathologic correlation is always indicated when confronted with a tumor rich in osteoclast-type giant cells in the lung to rule out the possibility of an occult or late metastasis.

For the most part, the differential diagnosis of the above conditions with GCTB is quite simple and straightforward. The admixture of osteoclastic type giant cells with bland-appearing nuclei admixed with a monotonous background of mononuclear cells is quite distinctive and should permit easy recognition. Absence of significant cytological atypia, abnormal mitoses, necrosis or nuclear pleomorphism will allow separation from the majority of lesions included in the above list. When in doubt, immunohistochemical stains may be of aid to identify specific markers of differentiation, including epithelial (sarcomatoid carcinoma, metastatic osteoclastoid carcinoma), melanocytic (metastatic melanoma), and mesenchymal (leiomyosarcoma, etc).

TREATMENT AND PROGNOSIS

The treatment of lung metastases from GCTB is generally surgical followed by chemotherapy. In the study by Bertoni,[7] four out of seven patients were alive and free of disease after an average follow-up of 9 years following lobectomy. In another study, overall mortality rate directly due to GCTB and its metastasis was 23%.[3] A study of the growth rate of lung metastases of GCTB showed a much longer doubling time for these tumors than for other types of metastases to the lungs, consistent with their slow growth and indolent behavior.[12] Spontaneous regression of lung metastases from these tumors, although rare, has also been well-documented in the literature.[2,13]

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QUESTIONS

1. Metastatic giant cell tumor of bone to the lung is least likely to be confused histologically with:
   - **A.** Malignant fibrous histiocytoma, giant cell type.
   - **B.** Sarcomatoid carcinoma.
   - **C.** Pulmonary sclerosing hemangioma
   - **D.** Leiomyosarcoma with osteoclast-type giant cells.

E. Metastatic malignant melanoma.

2. Histologically, giant cell tumor of bone metastatic in the lung is most likely to show:
   - **A.** Benign-appearing mononuclear stromal component and benign-appearing multinucleated giant cells
   - **B.** Benign-appearing mononuclear stromal component with malignant, anaplastic giant tumor cells.
   - **C.** Benign-appearing multinucleated giant cells with highly atypical, malignant-appearing mononuclear stromal cell component.
   - **D.** Benign-appearing giant cells with atypical spindle cell stromal component.
   - **E.** Malignant-appearing mononuclear stromal cells and bizarre neoplastic giant cells.

***Mark the appropriate letter.**

1. Il tumore a cellule giganti dell'osso metastatico al polmone si confonde con minor probabilità con:
   - **A.** Istiocitoma fibroso maligno del tipo a cellule giganti.
   - **B.** Carcinoma sarcomatoide.
   - **C.** Emangioma sclerosante del polmone.
   - **D.** Leiomiosarcoma con cellule gigantidi tipo osteoclastico.
   - **E.** Melanoma maligno metastatico.
2. Istologicamente il tumore a cellule giganti dell'osso metastatico al polmone molto probabilmente presenta:
   - **A.** Componente stromale mononucleata di aspetto benigno e cellule multinucleate di aspetto benigno.
   - **B.** Componente stromale mononucleata di aspetto benigno con cellule tumorali giganti maligne, anaplastiche.
   - **C.** Cellule giganti multinucleate di aspetto benigno con una componente stromale mononucleata marcatamente atipica di aspetto maligno.
   - **D.** Cellule giganti di aspetto benigno con componente stromale atipica a cellule fusate.
   - **E.** Cellule stromali mononucleate di aspetto maligno e cellule neoplastiche giganti bizzarre.

***Contrassegnare la lettera giusta.**

Case 39. 01B4107

Santiago Ramon y Cajal, M.D., Department of Pathology, Clinica Puerta de Hierro, Madrid, Spain

CLINICAL HISTORY

A 22-year-old male with a tumor arising from the right scapula which was resected and diagnosed as Ewing sarcoma. He was treated with chemo and radiotherapy. One year later, a new scapular tumor appeared and bilateral pulmonary nodules were detected. Scapula and right pulmonary nodules were resected, and radiotherapy was administered. We submit representative slides from a scapular tumor for seminary purposes.

PATHOLOGIC FINDINGS

Both scapular mass and pulmonary nodules were grey-white, friable and with extensive necrotic areas.

MICROSCOPICALLY

All the lesions presented a diffuse growth pattern with large areas of necrosis (probably due to chemo and radiotherapy) and (in non-necrotic areas) consisted of uniform small round cells with scanty pale cytoplasm, indistinct cell borders and homogeneous nuclei with finely dispersed chromatin. PAS stain was positive in cytoplasms of tumoral cells and reticulin stain was only positive around blood vessels, but not around tumoral cells.

IMMUNOHISTOCHEMICALLY

Tumor cells expressed vimentin and cytokeratin (in a minority of cells). CD99 was positive. Leu-7, leukocyte common antigen, surface immunoglobulin, lysozyme, alpha-1-antitrypsin, myosin, myoglobin, desmin and factor VIII-related antigen were negative. A t (11; 22) was detected and, by performing RT-PCR technique, a type 2 EWS-Fli1 fusion was diagnosed. These features were present both in scapular tumor and lung nodules.

Our studies confirmed the previous diagnosis, reported at the time of the initial surgery, of Ewing sarcoma of the scapula with multiple lung metastases.

DISCUSSION

In this case, small cell osteosarcoma and mesenchymal chondrosarcoma can be easily ruled out due to the absence of matrix and the age of the patient. Large cell lymphoma can be confused with a large cell variant of Ewing sarcoma. Our case did not have a sufficient number of large cells to misdiagnose it as a large cell lymphoma and PAS, reticulin and immunohistochemical stains (without the expression of leukocytic markers) assist in making the correct diagnosis.

Distinction from metastatic neuroblastoma can be made if we take into account the age of the patient (neuroblastomas occur in the first years of life), the microscopic features (presence, in neuroblastomas, of Homer Wright rosettes, fibrillary intercellular background and tapering cytoplasmic processes) and immunohistochemical profile (neuroblastomas exhibit marked staining for neuron specific enolase, neurofilaments, synaptophysin, vimentin, and with Leu-7).

Ewing sarcoma and neuroectodermal tumor of bone are closely related, because it is thought that they are included in a spectrum of tumors with different degrees of neuroectodermal differentiation. Ewing sarcoma is the least differentiated of them. Despite this close relationship a differential diagnosis must be made between them. Several studies have suggested a higher frequency of metastases at diagnosis, an adverse response to treatment, and a resultant poorer prognosis for tumors with clear-cut neural differentiation, such as neuroectodermal tumor of bone, compared to Ewing sarcoma (1, 2). Immunohistochemically, neuroectodermal tumor of bone expresses some neuroectodermal differentiation in the form of positive staining for neuron specific enolase, synaptophysin, or Leu-7.

More than 85% of tumors diagnosed as Ewing sarcoma or Primitive Neuroectodermal Tumor (PNET) harbor the translocation t (11; 22)(q24; q12). In this rearrangement, the distal portion of FLI1 gene is juxtaposed to the proximal portion of EWS gene, thereby creating a functional EWS-FLI1 gene. These genetic changes have made it possible to understand the relationship between these entities, as a spectrum of lesions, and are now considered a specific diagnostic feature of these tumors (3). Interestingly, the type of EWS-Fli1 fusion can be helpful for prognosis. Recent works indicate that EWS-Fli1 fusion type 1, which is more frequently seen, is associated with a better prognosis than other fusion transcripts, including type 2.

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QUESTIONS

1. The molecular study of the EW-FLI1 fusion transcript in the Ewing family of tumors is important for:
   - **A.** Diagnosis.
   - **B.** Prognosis.
   - **C.** Differential diagnoses with other small cell tumors.
   - **D.** To study minimal residual disease.
   - **E.** All the above aims.

   ***Mark the appropriate letter.**

2. All the Ewing's sarcomas are located in bone. **True or false.** _____.

1. Lo studio molecolare del trascritto di fusione EW-FLI1 nella famiglia dei tumori di Ewing è importante per:
   A. Diagnosi.
   B. Prognosi.
   C. Diagnosi differenziale con altri tumori a piccole cellule.
   D. Studio della malattia minima residua.
   E. Tutte le finalità di sopra elencate.
   ***Contrassegnare la lettera giusta.**

2. Tutti i sarcomi di Ewing si localizzano alle ossa. **Vero o Falso.** _____.

Case 40. (S)01-45478D.

Cesar A. Moran, M.D., Professor of Pathology, Department of Pathology, M.D. Anderson Cancer Center, Houston, Texas, USA.

CLINICAL HISTORY

A 58 year old man presented with chest pain and pleural effusion of several weeks' duration. Radiographic findings revealed thickening of the left pleura but no mass lesions in the lung. Past medical history was unremarkable except for surgery for an incarcerated hernia 5 years previously. An open lung biopsy was done, followed by a left extrapleural pneumonectomy.

PATHOLOGIC FINDINGS

The biopsy specimen showed fragments of markedly thickened parietal and visceral pleura with attached chest wall skeletal muscle. The thickened pleura showed dense areas of collagenization with interspersed cellular areas containing a mixed population of oval to spindle fibroblast-like cells and scattered inflammatory elements, including small lymphocytes and plasma cells. The oval and spindle cells in the collagenized areas showed large vesicular nuclei with dispersed heterochromatin and occasionally prominent eosinophilic nucleoli. Mitotic figures were very rare and extremely difficult to demonstrate. More importantly, the spindle cells were singly scattered throughout the stroma and did not form any clearly recognizable solid or nodular masses. The spindle proliferation, however, did appear to extend focally into the fibroadipose tissue at the interphase between the pleura and the chest wall. No areas of necrosis or epithelial glandular formations could be identified.

SPECIAL STUDIES

Histochemical stains for PAS and mucicarmine were negative. Immunohistochemical stains showed focal positivity of the spindle cells for CK5/6, AE1/AE3 cytokeratins, vimentin and calretinin. Immunohistochemical stains for pCEA, BerEP4, B72.3, Leu-M1, S-100 protein, HMB45 and EMA were negative. Tissue was not available for electron microscopic examination.

DIAGNOSIS

Desmoplastic malignant mesothelioma.

DISCUSSION

Malignant mesothelioma is an unusual tumor of the serosal surfaces that most often affects the pleura. Such tumors have been closely linked with occupational and other forms of exposure to asbestos, although mesotheliomas arising without a history of asbestos exposure have also been documented.[1] The majority of pleural mesotheliomas are tumors of adults over 50 years of age. Clinically patients may present with a history of chest pain, shortness of breath and pleural effusion. Radiologically, pleural mesotheliomas frequently involve the pleural surface in a diffuse fashion and are not accompanied by an intraparenchymatous lung mass.

Histologically, two main histologic cell types can characterize malignant mesothelioma: 1) round, epithelioid cells, and 2) spindle, sarcomatoid cells. The majority of tumors are composed of round, epithelioid cells that form tubulopapillary structures or grow as solid sheets and are designated epithelial or epithelioid mesothelioma. A subset of tumors will

be composed primarily of spindle, sarcomatoid tumor cells, and these are designated as sarcomatoid mesothelioma. An another subset will show an admixture of both cell types, the latter being designated as biphasic mesothelioma.[2] A variety of other rare and unusual morphologic variants of malignant mesothelioma have also been described.

One unusual variant of mesothelioma that presents a particularly difficult challenge for diagnosis is the desmoplastic malignant mesothelioma (DMM).[3,4] Such tumors are characterized by a histologically deceptive pattern because of the abundance of hyalinized collagen that may obscure the associated tumor cells and mimic a reactive process. This uncommon variant, which accounts for approximately 10% of all malignant mesotheliomas, was first described in 1980 by Kannerstein and Churg.[5] The most definable and striking feature of this variant of malignant mesothelioma is the whorled, paucicellular fibrotic lesion produced by the uniform deposition of collagen fibers that may adopt a storiform pattern or assume a "patternless" pattern. Although the neoplastic proliferation in the majority of cases of desmoplastic mesothelioma is composed of spindle or oval cells, a few cases of biphasic and epithelial mesotheliomas bearing these features have been described.[5,6]

In a recent study by Mangano et al,[4] DMM was characterized by diffuse pleural thickening due to deposition of abundant collagen fibers. Bland cytologic appearance and very low mitotic activity characterized the proliferating spindle cells. The features in their study that favored a diagnosis of DMM included: 1) invasion of the chest wall or lung parenchyma by neoplastic spindle cells; 2) foci of necrosis without associated inflammatory reaction; 3) presence of frankly sarcomatoid areas, and 4) presence of distant metastases (very rare). Other features that were of assistance in arriving at this diagnosis included radiographic findings, particularly irregular pleural thickening, nodular masses, invasion of soft tissue of the chest wall or bone destruction, and the results of p53 immunostains, with staining of more than 105 of spindle cell nuclei favoring a diagnosis of desmoplastic mesothelioma.

Immunohistochemical stains are often used in the differential diagnosis of malignant mesothelioma and other pleural malignancies.[7,8] Current criteria for diagnosis depend heavily on results of immunohistochemical stains. Although in the majority of tumor systems, diagnosis is dependent on support of specific *positive* results of special stains, in malignant mesothelioma diagnosis is mainly dependent on the demonstration of the *absence* of certain stains. More recently, many "specific" mesothelial cell markers have been introduced, although with variable results and sometimes limited specificity.

We recently published a proposal for the minimum criteria for the diagnosis of malignant mesothelioma,[9] which included the following:

- Detailed clinical history (i.e., history of asbestos exposure, duration of exposure, etc)
- Information of radiological studies
- Availability of reasonable biopsy material
- Results of immunohistochemical studies, including a minimum panel of stains: a high molecular weight cytokeratin (AE1/AE3 or CAM 5.2), CK5/6, CEA, B72.3, Leu-M1 and calretinin
- In cases with a spindle cell morphology, cytokeratins, calretinin and other antibodies to rule out specific types of sarcoma are recommended
- Sample fresh tissue for electron microscopy, if available

- All studies should be interpreted in coordination and not in isolation. Careful correlation of clinical, radiographic, histopathologic, immunohistochemical and ultrastructural findings are required to arrive at a definitive diagnosis

The role of immunohistochemical stains in sarcomatoid mesothelioma, and in particular DMM, has not been very well established. In our experience, DMM often coexpresses vimentin and low-molecular weight cytokeratin, and many of the cases we have examined have also stained, at least focally, for calretinin. Interpretation of cytokeratin stains, however, should be made with caution, since submesothelial fibroblasts can also stain positively in fibrous pleuritis.[5] Electron microscopy is most useful for making the distinction between epithelioid mesothelioma and metastatic carcinoma, but will be of very limited value for the diagnosis of sarcomatoid or desmoplastic mesothelioma.[7,10]

DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis for DMM is with chronic fibrous pleuritis (Table I).[3,5] Organizing effusions (fibrous pleuresy) often show zonality with high cellularity and cytologic atypia toward the pleural surface and increasing fibrosis with decreased cellularity and lesser atypia toward the chest wall surface. This type of zonality is often not present in DMM. Fibrous pleuritis also often show a proliferation of elongated capillaries arranged perpendicular to the pleural surface. Necrosis and extensive fibrin deposition are often a feature of benign mesothelial reactions and should be evaluated with care.

An important adjunct to differential diagnosis is the use of keratin stains. Although benign submesothelial fibroblasts present in chronic fibrosing pleuritis may be positive for this antigen, a pattern of infiltration of keratin-positive spindle cells in the fat or into the stroma of adjacent structures is distinctive of malignant mesothelioma.

Table I: Differential Diagnosis of DMM and fibrous pleuresy

Fibrosing Pleuritis	***Desmoplastic Mesothelioma***
Zonation phenomenon (i.e., cellularity is more pronounced towards the side of the effusion and lesion becomes more fibrotic away from the effusion)	No zonation. Bulk of the lesion is paucicellular, but may show abrupt transitions between paucicellular foci and frank sarcomatous areas.
Cells immediately proximal to the effusion may be very atypical	Very little cytological atypia seen at all – majority of the cells look uniformly "bland"
Capillaries perpendicular to the lesion	Capillaries inconspicuous and without any "organization"
Absence of stromal invasion	Stromal invasion
Absence of frankly sarcomatous foci	Presence of frankly sarcomatous foci

The distinction between DMM and fibrous pleuritis requires adequate sampling and strict application of the above criteria. Examples have been described of cases in which the diagnostic features could only be demonstrated in a single block out a many in decortication or autopsy cases.[4] In the present case, the biopsy was followed by an extrapleural pneumonectomy which showed diffuse thickening of the pleural surface with multiple foci of invasion of pulmonary parenchyma establishing beyond a doubt the diagnosis of desmoplastic malignant mesothelioma.

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QUESTIONS

1. Desmoplastic mesothelioma is characterized histologically by:
   - **A.** "Zonation" with increased cellularity towards the side of the effusion
   - **B.** Capillaries organized perpendicular to the lesion.
   - **C.** Absence of stromal invasion.
   - **D.** Highly atypical cells proximal to the effusion.
   - **E.** Paucicellular, uniformly "bland" spindle cell proliferation with very little cytological atypia.
2. The best combination of immunohistochemical stains for the diagnosis of desmoplastic mesothelioma of the pleura is:
   - **A.** CEA, vimentin, EMA, p53 and bcl-2.
   - **B.** Vimentin, low-molecular weight cytokeratin and calretinin.
   - **C.** SMA, desmin, myogenin and S-100 protein.
   - **D.** CK5/6, CEA, BerEp4, B72.3 and Leu-M1.
   - **E.** CEA and calretinin.

***Mark the appropriate letter.**

1. Il mesotelioma desmoplastico è caratterizzato istologicamente da:
   - **A.** Fenomeno di "zonation" con incremento della cellularità verso il lato del versamento.
   - **B.** Capillari disposti perpendicolarmente alla lesione.
   - **C.** Assenza di invasione stromale.
   - **D.** Cellule altamente atipiche prossimali al versamento.
   - **E.** Proliferazione a cellule fusate, monomorfe, di aspetto blando con atipie citologiche molto lievi.
2. La migliore combinazione di immunoistochimica per la diagnosi di mesotelioma desmoplastico della pleura è:
   - **A.** CEA, vimentina, EMA, p53 e bcl-2.
   - **B.** Vimentin, citokeratine di basso peso molecolare, e calretinina.
   - **C.** SMA, desmina, miogenina, e proteina S-100.
   - **D.** CK5/6, CEA, BerEp4, B72.3 e Leu-M1.
   - **E.** CEA e calretinin

***Contrassegnare la lettera giusta.**

CASE 41. 01-3667

Saul Suster, M.D., Professor of Pathology, Director of Anatomic Pathology, The Ohio State University, Columbus, Ohio, USA.

CLINICAL HISTORY

A 50-year-old man was seen for dyspnea and left pleural effusion. The patient had a history of plasma cell dyscrasia with paraprotein in the urine that had been followed for several years. CT scan revealed thickening of the left visceral pleura and interlobular septa with patchy associated fine reticular and centrilobular opacities. Thorough clinical and radiographic examination did not reveal any evidence of disease elsewhere. An open lung biopsy was performed.

PATHOLOGIC FINDINGS

The lung biopsies showed a band-like area of fibrosis involving the visceral pleura of the lung that extended into the interlobular septa and bronchovascular connective tissue. The fibrosis was characterized by a fine, fibrillary pattern of collagen deposition, and was accompanied by a scattered population of histiocytic cells admixed with other inflammatory cell elements. In areas, the connective tissue in the areas of fibrosis appeared slightly edematous. Numerous plasma cells with occasional Russel bodies could be seen scattered throughout. Round to oval vesicular nuclei with scattered heterochromatin and a rim of lightly eosinophilic cytoplasm characterized the histiocytic cells. A few scattered multinucleated giant cells were also present. Prominent vessels were also seen, in some areas imparting a granulation tissue-like appearance to the lesion. Extravasation of polymorphonuclear leukocytes into the lumen of small vessels was prominent. No atypical or malignant cells or well-formed granulomas could be identified. The underlying lung parenchyma was unremarkable.

SPECIAL STUDIES

A PAS stain with diastase showed focal weak cytoplasmic staining within macrophages in the fibrotic portions of the pleura. DNA-in-situ hybridization assay for kappa and lambda light chains did not reveal any evidence of monoclonal light chain restriction in the plasma cells within the lesion. Immunohistochemical stains for CD68 (KP-1 clone) and muramidase showed a faint positive cytoplasmic reaction within the histiocytic cells; a few of the cells also stained focally for S-100 protein, suggesting a hybrid phenotype of both Langerhans cells and macrophages. Stains for CD1a were negative.

DIAGNOSIS

Chester-Erdheim disease of the lung.

DISCUSSION

Chester-Erdheim disease (CED) was first described in 1930 by Chester (a pupil of Dr. Erdheim) under the designation of "lipoid granulomatosis".[1] The disease is quite rare, although in all likelihood, many cases are under or misdiagnosed. In a recent review of the literature, a total of 105 cases could be identified in the literature.[2] CED is a systemic disease that can involve many organs in the same patient, among which the long bones represent the most consistent site of involvement.[3-5] The disease is defined as the development of areas of clearly delimited bilateral symmetrical metaphyseal and diaphyseal cortical sclerosis of the long bones characterized histologically by a mononuclear cell infiltrate composed primarily of macrophages. Radionuclide studies

characteristically reveal an increased uptake of bone-seeking agents. The epiphyseal portions of the long bones are usually spared. The flat bones and axial skeleton may also be involved, although to a lesser extent.

The majority of patients affected by this disease are adults over the age of 40. Extraskeletal manifestations are seen in approximately 50% of cases, including the central nervous system,[6] retro-orbital and periorbital tissues,[7] kidney and retroperitoneum,[8] breast,[9] skin,[1] heart and pericardium,[10] and lung and pleura.[11,12] The disease was initially characterized as a "non-Langerhans cell histiocytosis" of unknown etiology; i.e., a non-neoplastic proliferation of lipid-storing histiocytes. A recent study, however, appears to indicate that the process may be clonal and therefore represent a neoplastic disorder.[13] The relationship of CED with Langerhans cell granulomatosis (histiocytosis-X) is still uncertain. There seems to exist some degree of overlap between the two conditions, and cases in which both diseases were present simultaneously or metachronously have been described.[2,14] The present case also suggests a link between these two disorders by demonstrating a hybrid phenotype for the histiocytes, which expressed both markers of histiocytic cells and of Langerhans cells. A similar case to ours describing brain lesions composed of a mixed Langerhans cell/histiocytic cell infiltrate was reported by Vital.[15]

Pleuropulmonary involvement in Chester-Erdheim disease is an important clinical manifestation of the disease. In the largest single study from the Mayo Clinic on 5 cases with pulmonary involvement, 4/5 patients were women ranging in age from 25-70 years. All patients presented with bilateral and symmetrical sclerotic lesions of bone; in three patients, the skeletal abnormalities were discovered only after lung biopsies. The main symptoms of pulmonary involvement include dyspnea and dry cough. Chest X-rays are characterized by diffuse interstitial infiltrates in both lungs with predominance in the upper zones. CT scans are characterized by diffuse thickening of the visceral pleura and interlobular septa with associated patchy and fine reticular and centrolobular opacities and ground glass attenuation. The prognosis in CED depends on the extraosseous manifestations. Approximately 60% of patients die of the disease, the majority due to respiratory failure of CNS deterioration. Of those who die, one third survive less than 6 months from initial diagnosis. There is no effective treatment for this disease, although immunosuppressive drugs and radiation therapy have been employed with variable results.

The histological findings in CED involving the lung are quite distinctive and are nicely illustrated by the present case. Open lung biopsies are characterized by expansion of the visceral pleura due to a band-like fibrosing process that typically extends into the interlobular septa and along bronchovascular bundles. The area of fibrosis typically contains a histiocyte-rich infiltrate admixed with other inflammatory cells. The histiocytes are only partly lipid-laden; many of the histiocytes may not contain any ingested lipid. The immunophenotype of the histiocytic cells in CED is variable. Staining for KP1 (CD68) is a consistent finding. Although reactivity for S-100 protein is regarded as distinctive for Langerhans cells, many well-documented cases of CED have been reported to show staining with this antigen. In the study by Egan et al,[11] stains for CD1a, a Langerhans cell marker, were consistently negative; however, 2/5 cases showed very strong and widespread immunoreactivity for S-100 protein. A more sensitive way of distinguishing these cells from Langerhans cells is by electron microscopy; ultrastructural examination will usually not disclose any Birbeck granules in CED whereas these are pathognomonic of Langerhans cell histiocytosis (LCH).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of CED in the lung includes mainly other histiocytic disorders. Pulmonary eosinophilic granuloma (Langerhans cell histiocytosis) of the lung is distinguished from CED by the distribution of the infiltrate which is mainly centered around bronchioles. Stellate nodules displaying a polymorphic inflammatory infiltrate that contains Langerhans cells displaying the characteristic cerebriform, convoluted nuclei characterize the lesions in LCH. The cells in LCH also are characterized by strong immunoreactivity for both S-100 protein and CD1a.

An important differential diagnosis of this condition is with sinus histiocytosis with massive lymphadenopathy (SHML) (Rosai-Dorfman's disease). The histiocytes in SHML can be very similar to those seen in CED, but are more often larger with more abundant foamy cytoplasm, and often contain ingested white or red blood cells. Unlike LCH, the histiocytes in SHML are strongly S-100 protein-positive but are negative for CD1a. Lung involvement in SHML differs from that in CED in that the lesions are most often nodular and form tumoral masses affecting the large airways. Rare examples of more diffuse lung disease have been described, and in such cases, distinction from Chester-Erdheim disease may depend mainly on clinical characteristics, such as the presence or absence of bilateral and symmetric osteosclerosis in long bones, as well as the presence or absence of emperiopolesis.

In the present case, the radiological and histological findings are characteristic of CED. However, two features were troublesome for the diagnosis: 1) focal expression of S-100 protein in the proliferating cells, and 2) absence of skeletal lesions. The patient is currently being followed for the possible development of skeletal lesions, a finding that has been previously observed in cases of CED. The immunophenotypic expression of markers not commonly associated with CED may be an expression of the close histogenetic relationship that exists between all the histiocytic disorders and an indication of a close linkage between this condition with both LCG and SHML.

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QUESTIONS

1. The positive immunohistochemical profile most commonly encountered in the histiocytes in Chester-Erdheim disease is:
   - **A.** CD68, CEA, muramidase and bcl-2.
   - **B.** Muramidase, alpha-1-antichymotrypsin, and Leu-M1.
   - **C.** CD68, S-100 protein and CD1a.
   - **D.** Muramidase, S-100 protein and CD1a.
   - **E.** CD68, muramidase and S-100 protein.
2. Which of the following histologic features should be expected in most cases of Chester-Erdheim disease of the lung:
   - **A.** A scattering of bland-appearing lipid-laden macrophages in areas of fibrosis.
   - **B.** Epithelioid histiocytes with abundant cytoplasm containing ingested leukocytes.
   - **C.** Histiocytic cells with convoluted, cerebriform nuclei and prominent eosinophilic nucleoli.
   - **D.** Histiocytic proliferation with scattered small epithelioid granulomas.
   - **E.** Hemosiderin-laden macrophages with abundant granular cytoplasm

***Mark the appropriate letter.**

1. Il profilo immunoistochimico positivo di più frequente riscontro negli istiociti nella malattia di Chester-Erdheim è:
   - **A.** CD68, CEA, muramidasi e bcl-2.
   - **B.** Muramidasi, alfa-1-antichimotripsina, e Leu-M1.
   - **C.** CD68, proteina S-100 e CD1a.
   - **D.** Muramidasi, proteina S-100 e CD1a.
   - **E.** CD68, muramidasi e proteina S-100

2. Quale dei seguenti aspetti istologici ci si dovrebbe aspettare nella magggior parte dei casi di malattia di Chester-Erdheim del polmone:
    - **A.** Presenza di sparsi istiociti lipidofori di aspetto blando, in seno ad aree di fibrosi.
    - **B.** Istiociti epitelioidi con abbondante citoplasma contenente leucociti fagocitati
    - **C.** Iistiociti con nuclei convoluti, cerebriformi e nuclei con prominenti nucleoli eosinofili.
    - **D.** Proliferazione di istiociti consparsi piccoli granulomi epiteioidi.
    - **E.** Siderofagi con abbondante citoplasma granulare.

***Contrassegnare la lettera giusta.**

CASE 42. 30262-1

Noel Weidner, MD. Department of Pathology, University of California, San Diego Medical Center, San Diego, CA, USA

CLINICAL HISTORY

62 y/o female experienced a sudden episode of cough and progressive shortness of breath, which rapidly progressed to ARDS. A HRCT study of the lung revealed a diffuse pattern of bilateral lung involvement characterized by alveolar and interstitial solidification. A wedge lung biopsy was performed.

PATHOLOGY

There was an organizing myxomatous connective tissue proliferation in the alveolar septae. Characteristically, the changes were temporally uniform showing fibromyxomatous thickening of the intervening alveolar walls, which contained a modest inflammatory infiltrate and were lined by reactive, type-2, alveolar-lining cells. Although the size of the air spaces and the degree of interstitial thickening varied from one area to another, the component cellular infiltrate remained constant throughout.

DIAGNOSIS

Idiopathic acute interstitial pneumonia (so-called Hamman-Rich syndrome).

DISCUSSION

Acute interstitial pneumonia (AIP) is synonymous with Hamman-Rich syndrome, but it has also been referred to as acute interstitial pulmonary fibrosis (acute IPF) and accelerated interstitial pneumonia. Histologically, AIP is characterized by diffuse interstitial fibrosis, but it differs from the other interstitial pneumonias in that the fibrosis is active (i.e., myxomatous connective tissue being incorporated into the interstitium with interstitial fibrosis and architectural distortion.), consisting of proliferating fibroblasts and myofibroblasts with minimal collagen deposition. These changes closely resemble the organizing stage of diffuse alveolar damage (DAD), but in AIP the histopathology occurs in previously healthy individuals for which no apparent cause can be found. The changes are temporally uniform and appear relatively acutely, reflecting the reaction to lung injury occurring several weeks previously. The term AIP serves to emphasize the fulminant clinical features. Viewed somewhat alternatively, the changes of AIP also mimic those of the active fibroblastic foci of usual interstitial pneumonia (UIP), except that the process is diffuse and temporally uniform rather than the focal and temporally heterogeneous as found in UIP. In AIP other manifestations of acute lung injury are frequently present including remnants of hyaline membranes within alveolar spaces, small arterial thrombi, and squamous metaplasia with cytologic atypia in bronchiolar epithelium. If the process continues for a sufficient period, usually more than a month, enlarged, restructured air spaces can be formed, and the appearance resembles the honeycomb change in UIP. It differs from the latter, however, in that the walls of the air spaces are composed of fibroblasts as well as collagen, and they are lined by alveolar rather than bronchiolar epithelium. This rapid development of honeycomb change results from partial or complete collapse of some alveoli with subsequent enlargement of others. Ventilator therapy with high pressures also likely plays a role in this change.

The differential diagnosis includes diffuse alveolar damage (DAD). In DAD there is a pattern of diffuse lung injury and repair that is usually associated with acute bilateral interstitial lung disease, clinically labeled adult respiratory distress syndrome (ARDS). DAD has many causes and associations, and a similar histologic picture affecting immature lungs is seen in neonates with hyaline membrane disease (respiratory distress syndrome of infants). Causes of DAD include: (1) infections, (2) radiation, (3) shock, (4) oxygen toxicity, (5) trauma, (6) sepsis, (7) neurologic disease, (8) drugs (especially chemotherapeutics), (9) acute allergic reactions, (10) noxious gases and chemical lung injury, (11) collagen-vascular diseases, (12) idiopathic (i.e., in this latter setting termed AIP), (13) Goodpasture's syndrome, (14) capillaritis, and (15) miscellaneous rare entities. The histologic appearance of DAD varies with time (i.e., the injury, repair, and healed or resolved phases), although overlap between these phases exists. The lung is diffusely involved in DAD, although the severity of damage and repair may vary from one field to the next. In early cases, only portions of the lung may be affected (i.e., regional alveolar damage). During the injury phase there is alveolar and/or interstitial edema with or without alveolar hemorrhage, hyaline membranes (usually arising in alveolar ducts), fibrinous alveolar exudate, mild interstitial mononuclear cell infiltrate, and fibrin microthrombi, rarely with subpleural microinfarcts. A few neutrophils may be present in air spaces. Large numbers of neutrophils should suggest bacterial infection or super infection, which is common in patients who have been on a ventilator or who are terminally ill. The repair phase usually shows epithelial metaplasia and re-growth of type-2 alveolar-lining cells over hyaline membranes and denuded alveolar walls, often bizarre in appearance. Fibroblastic proliferation around fragmented hyaline membranes is seen in the edematous interstitium and/or within air spaces in a pattern of organizing pneumonia (i.e., intra-alveolar organization). Immature squamous metaplasia may be prominent in and around bronchioles. The latter is nonspecific, although more characteristic of virally-induced DAD. The healed phase may show entirely normal lung tissue or nonspecific changes, including increased alveolar macrophages, nonspecific interstitial and septal scarring, mural scarring in airways, and/or metaplastic epithelium within bronchioles or lining alveolar spaces. In some cases, the appearance of the scarring resembles UIP. Prolonged respiratory or oxygen therapy may result in a cystic and honeycombed appearance, analogous to broncho-pulmonary dysplasia in neonates. Most cases are seen in early injury or early repair phase. The degree of fibroblastic proliferation varies from case to case. In some, it is predominantly interstitial, in others predominantly airspace; or it may be mixed. Airspace organization, field for field, may resemble that seen in bronchiolitis obliterans organizing pneumonia (BOOP). Air-space organization in the healing phase is eventually incorporated into the interstitium with overlying proliferative type-2 pneumocytes. Finally, some patients with subclinical UIP may present with a fulminant process simulating AIP except for a background of chronic scarring and honeycombing that may be recognized grossly, on prior chest radiographs, or microscopically.

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QUESTIONS

1. Idiopathic acute interstitial pneumonia has been equated to so-called Hamman-Rich syndrome. **True or False.** _____.
2. The differential diagnosis of acute interstitial pneumonia (AIP) includes diffuse alveolar damage, which like AIP has not known cause. **True or False.** _____.

1. La polmonite acuta interstiziale corrisponde alla cosiddetta sindrome di Hamman-Rich. **Vero o Falso.** _____.
2. La diagnosi differenziale della polmonite acuta interstiziale (AIP) include il danno alveolare diffuso, che come la AIP non ha una causa nota.
   Vero o Falso. _____.

CASE 43. (SS)01-47263.

Cesar A. Moran, M.D., Professor of Pathology, Department of Pathology, M.D. Anderson Cancer Center, Houston, Texas, USA.

CLINICAL HISTORY

A 47-year-old man presented with shortness of breath and chest pain of several weeks' duration. Radiographic studies revealed a right lower lobe pulmonary mass. A lobectomy was performed. The resected lobe of lung contained a 5 cm. subpleural tumor that on cut surface showed an ill-defined, tan white mass with extensive areas of hemorrhage and necrosis. The tumor was unrelated to major bronchi and abutted but did not appear to infiltrate the overlying pleura. Three of five hilar lymph nodes were involved with tumor grossly.

PATHOLOGIC FINDINGS

Histologic examination showed a proliferation of small islands and cords of tumor cells with prominent central areas of comedonecrosis that were separated by abundant desmoplastic stroma. The tumor cells were large, round to oval, with large nuclei containing scattered chromatin and mostly inconspicuous nucleoli. Many of the nuclei appeared to display a coarse chromatin pattern. The cells contained abundant eosinophilic cytoplasm with ill-defined cell borders. There were numerous mitotic figures (average 18 per 10 HPF), with many abnormal mitoses. In some areas, the tumor cells formed small glandular structures; in other areas, islands of tumor cells adopted a somewhat cribriform appearance with clear luminal spaces. Foci of vascular invasion were readily apparent. All five hilar lymph nodes showed extensive metastatic deposits.

SPECIAL STUDIES

Stains for PAS and mucicarmine showed focal cytoplasmic positivity in a few scattered tumor cells. Immunohistochemical stains showed strong positivity of the tumor cells for AE1/AE3 cytokeratin and CK7. Immunohistochemical stains for chromogranin showed numerous positive cells scattered throughout the lesion. Stains for pCEA also showed some patchy, focal positivity. Stains for CK20, TTF-1 and synaptophysin were negative. Tissue was not available for electron microscopy.

DIAGNOSIS

Large cell neuroendocrine carcinoma.

DISCUSSION

Neuroendocrine carcinomas of the lung have been the source of much controversy regarding their terminology, classification, and criteria for diagnosis. While standard classifications of most major lung tumors have remained relatively stable over the years, the terminology and classification of neuroendocrine tumors of the lung has undergone constant and continuous revision. Older classifications separated neuroendocrine lung tumors into three distinct groups: carcinoid tumors, "atypical" carcinoids, and small cell carcinoma and its variants. With further advances in our understanding of these lesions, the spectrum of neuroendocrine neoplasms of the lung has continued to expand.

The current WHO classification of tumors of the lung has merged previous morphologic variants of small cell carcinoma into a single type (i.e., "intermediate" "polygonal cell type" and "mixed" are now regarded as the same as small cell neuroendocrine carcinoma

for prognostic and treatment purposes), and have added a new category of "large cell neuroendocrine carcinoma".[1] In the WHO classification, carcinoid tumors are still regarded as a separate, unrelated class of tumors from neuroendocrine carcinomas.

We believe that all of these lesions form part of a single spectrum of tumors that are closely interrelated, and prefer to generically designate them as "neuroendocrine carcinomas of the lung", with the various types falling into one of three categories depending on their degree of differentiation: 1) well-differentiated neuroendocrine carcinoma (corresponding to typical carcinoid tumor), 2) moderately-differentiated neuroendocrine carcinoma (corresponding to "atypical" carcinoid), and 3) poorly-differentiated neuroendocrine carcinoma (corresponding to small cell carcinoma and other variants).[2] A similar schema was previously proposed by us for neuroendocrine carcinomas of the thymus,[3] and has also been recently adopted for lung tumors in a study from the Massachusetts General Hospital.[4]

In our revised classification, we separate the different types of poorly-differentiated neuroendocrine carcinomas of the lung into three broad categories: 1) small cell neuroendocrine carcinoma (SCNEC), 2) mixed small/large cell neuroendocrine carcinoma, and 3) large cell neuroendocrine carcinoma (LCNEC). The latter tumor type is a relatively new entity that has been the subject of some confusion and debate.[5]

LCNEC is defined by Travis et al[5] as a tumor that shows the following features: 1) a neuroendocrine appearance by light microscopy (organoid, trabecular, palisading or rosette patterns); 2) cytologic features of large cell size, low nuclear to cytoplasmic ratio, polygonal shape, finely granular eosinophilic cytoplasm, coarse nuclear chromatin and frequent nucleoli; 3) a mitotic rate greater than 10 per 10 HPF; 4) necrosis; and 5) neuroendocrine features either by immunohistochemistry or electron microscopy. The problem is that many of the tumors that can be included in this category may not always fulfill all of these criteria.

A great deal of overlap has been demonstrated in lung tumors characterized by a large cell morphology with either light microscopic or immunohistochemical features suggestive of neuroendocrine differentiation. Iyoda et al[6] recently presented a study of these tumors and summarized the problems encountered in their classification. Large cell carcinomas can be classified into four types based on a combination of features, including: 1) LCNEC, which shows both light microscopic and immunohistochemical or ultrastructural evidence of neuroendocrine differentiation; 2) large cell carcinoma with neuroendocrine differentiation by IHC/EM which lacks morphologic features of neuroendocrine differentiation; 3) large cell carcinoma showing a neuroendocrine morphology but lacking IHC/EM evidence of neuroendocrine differentiation; and 4) classical large cell carcinomas lacking both morphologic and IHC/EM features of neuroendocrine differentiation.

The distinction between the first three categories can be extremely difficult to establish in some cases. Moreover, quantitative criteria for separating tumors that show IHC/EM features of neuroendocrine differentiation and that either display or do not display a neuroendocrine pattern of growth by light microscopy have not been established. Also, the definition of what constitutes a "neuroendocrine" pattern of growth by light microscopy can be very subjective. The line that divides true LCNEC from large cell carcinoma displaying neuroendocrine morphologic features (without IHC/EM proof of

neuroendocrine differentiation) and conventional large cell carcinoma with IHC/EM evidence of neuroendocrine differentiation is still debated.

We believe in the existence of primary lung tumors corresponding to the poorly-differentiated spectrum of neuroendocrine carcinomas that are characterized by a predominant population of large tumor cells, and therefore are most adequately designated LCNEC.[2] In reviewing the literature, LCNEC appears to be more common in men with a smoking history, with a predilection for the 6th decade of life.[5,6] The tumors are most often peripherally located and range in size from 2-6 cm. in greatest diameter. Chest CT scans usually show a well-demarcated mass with lobulated edges showing moderate enhancement.[7,8] The tumors are often accompanied by mediastinal and hilar lymph node involvement. An interesting aspect of LCNEC, however, is the fact that a high proportion of tumors is found in clinical Stage I. Despite the early stage, however, such tumors tend to do very poorly. In the largest study of LCNEC on 40 patients, 5-year survival for stage I patients was only 18%, and 5-year survival for all stages was 13%.[9]

Application of immunohistochemical markers is currently regarded as indispensable for the diagnosis of these tumors. In fact, use of a panel of neuroendocrine markers should be routinely employed in all large cell carcinomas of the lung to identify cases that despite lacking a "neuroendocrine" light microscopic growth pattern do express markers of neuroendocrine differentiation. The most commonly employed antibodies include chromogranin-A, synaptophysin, and neuron specific enolase.[5,6,9-11] LCNEC should be positive, by definition, for at least one of the above markers. It should be taken into consideration, however, that up to 60% of cases of carcinoma without morphologic features of neuroendocrine differentiation can also be positive for these markers.[11] LCNEC also co-express cytokeratins, and have been found to mark positively for the thyroid transcription factor-1 (TTF1) in from 50 to 100% of cases.[12,13]

Whether the separation of LCNEC from conventional large cell carcinoma with neuroendocrine differentiation is warranted or not on clinical grounds still remains to be established. A few studies have claimed that LCNEC has a much worse prognosis than conventional, non-neuroendocrine large cell carcinoma; however, the differences may be clinically insignificant since conventional large cell carcinoma is already a high-grade neoplasm with a dismal prognosis. A recent study found that large cell carcinomas with neuroendocrine features (i.e., tumors with positive neuroendocrine markers irrespective of light microscopic growth pattern) appeared to have a significantly worse overall and disease-free survival than large cell carcinoma without neuroendocrine markers.[6] Further studies are probably warranted to validate this conclusion.

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QUESTIONS

1. Large cell neuroendocrine carcinoma refers to a primary lung neoplasm characterized by:
   - **A.** Large cell carcinoma with light microscopic features suggestive of neuroendocrine differentiation but with absence of neuroendocrine markers by immunohistochemistry or on ultrastructural examination.
   - **B.** Large cell carcinoma without morphologic features suggestive of neuroendocrine differentiation but with immunohistochemical or ultrastructural evidence of neuroendocrine differentiation.
   - **C.** Admixture of typical small cell neuroendocrine carcinoma with areas of large cell carcinoma.
   - **D.** Large cell carcinoma with both light microscopic morphologic features of neuroendocrine differentiation and immunohistochemical or ultrastructural features of neuroendocrine differentiation.
   - **E.** Carcinoma with prominent "basaloid" palisading of nuclei despite absence of neuroendocrine markers.
2. The neuroendocrine immunohistochemical markers, chromogranin and synaptophysin, display the following features in large cell neuroendocrine carcinoma of lung:
   - **A.** Are never expressed together with cytokeratin.
   - **B.** Are always expressed together with TTF-1.

C. Both markers must always be expressed to make this diagnosis.
D. Must always be expressed together with cytokeratin-7 (CK7) to make the diagnosis.
E. Either one must be expressed to make the diagnosis.

***Mark the appropriate letter.**

1. Il carcinoma neuroendocrino a grandi cellule si riferisce a una neoplasia primitiva del polmone caratterizzata da:
   A. Carcinoma a grandi cellule con aspetti microscopici suggestivi di differenziazione neuroendocrina ma in assenza di markers neuroendocrini in immunoistochimica o all'esame ultrastrutturale.
   B. Carcinoma a grandi cellule con aspetti istologici suggestivi di differenziazione neuroendocrina ma con evidenza di differenziazione neuroendocrina con le indagini di immunoistochimica e ultrastrutturale.
   C. Associazione di un tipico carcinoma a piccole cellule con aree di carcinoma a grandicellule.
   D. Carcinoma a grandi cellule con aspetti sia microscopici, sia immunoistochimici, sia ultrastrutturali di differenziazione neuroendocrina.
   E. Carcinoma con prominente palizzata "basaloide" dei nuclei a dispetto dell'assenza di markers neuroendocrini.
2. I markers neuroendocrini immunoistochimici cromogranina e sinaptofisina esibiscono i seguenti aspetti nel carcinoma a grandi cellule del polmone:
   A. Non sono mai espressi con le citocheratine.
   B. Sono sempre espressi insieme al TTF-1
   C. Entrambi i markers devono sempre essere espressi per porre la diagnosi.
   D. Devono sempre essere espressi insieme alla citocheratina 7 per porre la diagnosi.
   E. Uno dei due markers deve essere espresso per porre la diagnosi.

***Contrassegnare la lettera giusta.**

SURGICAL PATHOLOGY SESSIONS
-GENERAL LIST OF CASE PRESENTATIONS

DIAGNOSES

JUNE 19

Surgical Pathology -Session I. Urogenital tract I (4 cases)

1) Pseudocarcinomatous epithelial hyperplasia with mural pseudoinvasion in acute and chronic non-tuberculous salpingitis -chlamydia infection (*D. Ben-Dor*).
2) Malignant mesothelioma of the tunica vaginalis testis (*M. Bisceglia*).
3) Malignant Sertoli cell tumor of the testis (*S. Suster*).
4) Primary endometrioid FATWO-like carcinoma of the uterine salpynx (M. Fukunaga).

Surgical Pathology -Session II. Urogenital tract II (4 cases

5) Uterine endometrioid carcinoma with small non-villous papillae (*D. Ben-Dor*).
6) 6-I. Sertoli-Leydig cell tumor of the ovary of intermediate type, with low-grade heterologous gastrointestinal , retiform and questionable hepatoid components. 6-II.Low grade Sertoli-cell tumor of the ovary in a centenarian woman (*G. Falconieri*).
7) Testicular tumor of the adrenogenital syndrome (*M. Michal*).
8) Lymphoepithelioma-like carcinoma of the renal pelvis (*M. Fukunaga*).

Surgical Pathology -Session III. Soft Tissue & Bone (5 cases)

9) Biphasic spindle and epithelioid myoepithelioma of soft tissue, oncocytic type *(M. Bisceglia)*.
10) Acral myxoinflammatory tumor of soft tissue (*K. Cooper*).
11) Clear cell chondrosarcoma of bone (*J. Lamovec*).
12) Low-grade fibromyxoid sarcoma of soft tissue (*M. Fukunaga*).
13) Inflammatory leiomyosarcoma of bone (*D. Ben-Dor*).

JUNE 20

Surgical Pathology -Session IV. Kidney & Adrenal (4 cases)

14) Mixed epithelial-stromal tumor of the kidney (*M. Bisceglia*).
15) Angiomyoadenomatous tumor of the kidney (*M. Michal*).
16) Oncocytic borderline tumor of the adrenal gland (*M. Bisceglia*).
17) Corticomedullary mixed tumor of the adrenal (*M. Michal*).

Surgical Pathology -Session V. Head & neck (5 cases)

18) Diffuse sclerosing variant of papillary thyroid carcinoma associated with clinical signs of Hashimoto's disease *(D. Ben-Dor)*.
19) Synovial sarcoma of parapharyngeal area *(G. Falconieri)*.
20) Epithelioid angiosarcoma of the thyroid *(J. Lamovec)*.
21) Clear cell myoepithelial carcinoma of the salivary gland *(M. Michal)*.
22) Endolymphatic sac papillary tumor -Heffner Tumor (*M. Bisceglia*)

Surgical Pathology -Session VI. Hematolymphoid tissue (4 cases)

23) Cerebral intravascular large B-cell lymphoma (*J. Forteza-Vila*).
24) MALT lymphoma of the small bowel (*S. Ramon y Cajal*).
25) BCL-2 negative non-Hodgkin follicular lymphoma (*J. Forteza-Vila*).
26) Subcutaneous, panniculitis-like T-cell lymphoma (*N. Weidner*).

JUNE 21:

Surgical Pathology - Session VII. Breast (5 cases)

27) Small cell neuroendocrine carcinoma of the breast (*G. Falconieri*).
28) Low-grade, B-cell lymphoma of the breast c/w marginal zone lymphoma with plasmacytic differentiation (*N. Weidner*).
29) Microglandular adenosis of the breast (*J. Lamovec*).
30) Granulocytic sarcoma of the breast (*J. Forteza-Vila*).
31) Extensive atypical ductal hyperplasia of the breast vs. borderline low-grade DCIS-clinging monomorphic variant (*N. Weidner*).

Surgical Pathology -Session VIII. GI/Peritoneum (6 cases)

32) 32-I.CMV vasculitis of the colon with ischaemic ulceration. 32-II. Herpes proctitis superimposed on chronic ulcerative colitis (*K. Cooper*).
33) Extrapulmonary inflammatory myofibroblastic tumor -Inflammatory pseudotumor of the liver (*S. Ramon y Cajal*).
34) (Extrapancreatic) papillary solid/cystic tumor of the omentum (*M. Fukunaga*).
35) Lymphohistiocytoid mesothelioma of peritoneum (*K. Cooper*).
36) Primary melanoma of the esophagus (*S. Suster*).
37) Glomus tumor of the stomach (*S. Suster*).

Surgical Pathology -Session IX. Thorax (6 cases)

38) Lung metastasis of giant cell tumor of bone (C. Moran)
39) Lung metastasis of Ewing's sarcoma (*S. Ramon y Cajal*).
40) Pleural mesothelioma (*C. Moran*).
41) Chester-Herdheim disease –lung involvement (*S. Suster*).
42) Acute interstitial pneumonia (Hamman-Rich syndrome) (*N. Weidner*).
43) Large cell neuroendocrine carcinoma of the lung (*C. Moran*).

SURGICAL PATHOLOGY SESSIONS -GENERAL LIST OF CASE PRESENTATIONS

CONTRIBUTORS

(D. Ben-Dor)

- Pseudocarcinomatous epithelial hyperplasia with mural pseudoinvasion in acute and chronic non-tuberculous salpingitis -chlamydia infection (Urogenital tract I, June 19).
- Uterine endometrioid carcinoma with small non-villous papillae (Urogenital II, June 19).
- Inflammatory leiomyosarcoma of bone (Soft Tissue & Bone, June 19).
- Diffuse sclerosing variant of papillary thyroid carcinoma associated with clinical signs of Hashimoto's disease (Head & Neck, June 20).

(M. Bisceglia)

- Malignant mesothelioma of the tunica vaginalis testis (Urogenital tract I, June 19).
- Biphasic spindle and epithelioid myoepithelioma of soft tissue, oncocytic type (Soft Tissue & Bone, June 19).
- Mixed epithelial-stromal tumor of the kidney (Kidney Adrenal, June 20).
- Oncocytic borderline tumor of the adrenal gland (Kidney & Adrenal, June20).
- Endolymphatic sac papillary tumor (Heffner Tumor) (Head & Neck, June June 20).

(*K. Cooper*)

- Acral myxoinflammatory tumor of soft tissue (Soft Tissue & Bone, June 19).
- I. CMV vasculitis of the colon with ischaemic ulceration. II. Herpes proctitis superimposed on chronic ulcerative colitis (Double case presentation) (*K. Cooper*). (GI & Peritoneum, June 21).
- Lymphohistiocytoid mesothelioma of peritoneum (GI & Peritoneum, June 21).

(*G. Falconieri*)

- Sertoli-Leydig cell tumor of the ovary of intermediate type, with low-grade heterologous gastrointestinal, retiform and questionable hepatoid components. II.Low grade Sertoli-cell tumor of the ovary in a centenarian woman (double case presentation). (Urogenital tract II, June 19).
- Synovial sarcoma of parapharyngeal area (Head & Neck, June 20).
- Small cell neuroendocrine carcinoma of the breast (Breast, June 21).

(*J. Forteza-Vila*)

- Cerebral intravascular large B-cell lymphoma (Hematolymphoid, June 20).
- BCL-2 negative non-Hodgkin follicular lymphoma (Hematolymphoid,June 20).
- Granulocytic sarcoma of the breast (Breast, June 21).

(*M. Fukunaga*)

- Lymphoepithelioma-like carcinoma of the renal pelvis (Urogenital tract II, June 19).
- Low-grade fibromyxoid sarcoma of soft tissue (Soft Tissue & Bone, June 19).
- Extrapancreatic) papillary solid/cystic tumor of the omentum (GI & Peritoneum, June 21)
- Primary endometrioid FATWO-like carcinoma of the uterine salpynx (Urogenital tract I, June 19)

(*J. Lamovec*)

- Clear cell chondrosarcoma of bone (Soft Tissue & Bone, June 19).
- Epithelioid angiosarcoma of the thyroid (Head & Neck, June 20).
- Microglandular adenosis of the breast (Breast, June 21)

(*M. Michal*)

- Testicular tumor of the adrenogenital syndrome (Urogenital tract II, June 19).
- Angiomyoadenomatous tumor of the kidney (Kidney & Adrenal, June 20).
- Clear cell myoepithelial carcinoma of the salivary gland (Head & Neck, June 20).
- Corticomedullary mixed tumor of the adrenal (Kidney & Adrenal, June 20).

(*C. Moran*)

- Large cell neuroendocrine carcinoma of the lung (Thorax, June 21).
- Pleural mesothelioma (Thorax, June 21).
- Lung metastasis from giant cell tumor of bone (Thorax, June 21).

(*S. Ramon y Cajal*)

- MALT lymphoma of the small bowel (Hematolymphoid, June 20).
- Inflammatory pseudotumor of the liver (GI & Peritoneum, June 21).
- Lung metastasis of Ewing's sarcoma (Thorax, June 21).

(S. *Suster*)

- Malignant Sertoli cell tumor of the testis (Urogenital tract I, June 19).
- Primary melanoma of the cardias (GI & Peritoneum, June 21).
- Glomus tumor of the stomach (GI & Peritoneum, June 21).
- Chester-Erdheim disease –lung involvement (Thorax, June 21).

(*N. Weidner*)

- Subcutaneous, panniculitis-like T-cell lymphoma (Hematolymphoid, June 20).
- Low-grade B-cell lymphoma of the breast c/w marginal zone lymphoma with plasmacytic differentiation (Breast, June 21).
- Extensive atypical ductal hyperplasia of the breast vs. borderline low-grade DCIS-clinging monomorphic variant (Breast, June 21).
- Acute interstitial pneumonia -Hamman-Rich syndrome (Thorax (June 21).

NOTES