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Lymphomatoid granulomatosis: a practical review for pathologists dealing with this rare pulmonary lymphoproliferative process

E. Tieglavi, G. Rossi, R. Viali, M. Zanelli, A. Cadolisi, M.C. Mengoli, A. Biscagni, A. Cavazza, G. Gardini

Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder predominantly involving the lungs, but poorly-recognized among clinicians and pathologists. It is an Epstein-Barr virus (EBV)-driven disease mimicking severe other diseases on clinical and radiological grounds, generally showing multiple, bilateral nodular, ill-defined infiltrates of the lungs tending to coalesce and/or cavitation. LYG often affects middle-aged males with an underlying immunodeficiency and commonly involves skin and central nervous system during disease progression. Diagnosis requires a generous biopsy and careful histological examination with immunohistochemical staining and molecular demonstration of EBV genome in large atypical B-cells. LYG is graded as I to III based on the number of large EBV-positive B-cells; grades II/III are now considered as a peculiar variant of T-cell rich diffuse large B-cell lymphoma. In this brief review, clinical, radiologic and pathologic features of LYG will be analyzed with focus on differential diagnosis, the most appropriate treatment and prognosis.

About the necessity of improving the current nodal classification in non-small cell lung carcinoma

M. Mika, A. Ayadi-Kaddour, S. Boudaya, A. Margghi, T. Kilani, F. Megni

Background. The classification of lymph node status in non-small cell lung carcinoma has not been revised since 1997. This fact has prompted many authors to point out the limits of this classification.

Methods. We tried to explore the prognostic relevance of the current TNM classification in comparison with the nodal classification based on the ratio of metastatic lymph nodes (LNR) and the nodal classification based on the number of metastatic LNs (nLNs). Additionally, we tried to explore the recommended number of resected LNs. This was done through a retrospective study of 39 cases. We compared the survival curves of patients using the current, RLN and nLNs classifications. In the nLN classification, we grouped patients into three categories: n0 (no metastatic LNs), n1 (1 to 2 metastatic LNs) and n2 (> 2 metastatic LN). In the LNR classification, the total number of the resected LNs was compared to two groups according to the number of LN: < 10 versus ≥ 10 and < 15 versus ≥ 15.

Results. Our results showed that the LNR classification highlighted a difference in prognosis between the n1 and n2 groups. Moreover, survival of patients seemed to be better when the number of the resected LNs was higher.

Conclusion. The ratio of metastatic LNs seems to be an important prognostic factor, but further studies are necessary to standardize this classification.

Intraperineal leiomyoma of the breast: report of a case with emphasis on needle core biopsy-based diagnosis


Objective. We report the clinicopathologic features of a rare case of leiomyoma of the breast parenchyma in a 36-year-old female, diagnosed preoperatively at core biopsy. A complete review of the literature on the topic is provided and differential diagnostic problems are discussed.

Methods. Immunohistochemical and immunohistochemical analyses using a large panel of antibodies were performed in both the core biopsy and surgical specimen.

Results. Ultrasonography revealed a well-circumscribed tumour mass without calcifications. Histological examination of the core biopsy showed proliferation of bland-looking eosinophilic spindle cells arranged in a fascicular growth pattern. Mitoses, pleomorphism and necrosis were absent. Immunohistochemistry, revealing diffuse staining for α-smooth muscle actin, desmin and h-caldesmon, confirmed the leiomyomatous nature of neoplastic cells. Histological and immunohistochemical analyses of the surgical specimen confirmed the diagnosis of leiomyoma.

Conclusions. The present case emphasizes that diagnosis of leiomyoma of the breast parenchyma can be confidently rendered on needle core biopsy. We believe that correct diagnosis is primarily dependent on the awareness that this tumour can arise in this unusual site on rare occasions.

Primary mucinous carcinoma of the thyroid gland: case report with review of the literature

H. Mnif, S. Charni, S. Elhair, M. Ghorbel, T. Sallemi-Boudawara

Primary mucinous thyroid carcinoma (PMTC) are extremely rare lesions that are histologically indistinguishable from mucinous carcinoma of other sites. We describe the clinicopathological, histological and immunohistochemical features of this rare tumour with a review of the literature. We describe a case of thyroid tumour, in 56-year-old Tunisian man, composed of small nests and sheets of malignant epithelial cells associated with extensive extracellular mucin that entrapped the follicular parenchyma of thyroid. Thyroglobulin and thyroglobulin-specific transcription factor 1 (TTF1) were focally positive. Follow-up did not reveal another neoplasm at other sites. Based on these features, we classified this tumour as PMTC. Mucinous carcinoma of the thyroid gland can be a cause of pitfall in differential diagnosis. For correct diagnosis, complete clinical history, restricted histological criteria and immunohistochemical panel are necessary.

Case reports

A solitary polypoid gastric metastasis 20 years after renal cell carcinoma: an event to be considered, and a brief review of the literature


Background. The incidence of gastric metastasis is 2.6%. Although all primary neoplasms can metastasize to the stomach, most originate from melanoma or breast and lung cancer. Their most common endoscopic appearance is a “volcano-like” polypoid mass covered by normal mucosa that may show a central ulceration. Renal cell carcinoma (RCC), clear cell type, is known to spread hematogenously, and isolated metastasis to the stomach is a rare event.

Case presentation. In this report, we describe a gastric recurrence of RCC, clear-cell type, in a 80-year-old patient who underwent nephrectomy 20 years ago. We also performed a brief review of the literature to update the number of cases described to date.

Coexistence of xanthogranulomatous cholecystitis and gallbladder adenocarcinoma: a fortuitous association?

F. Limaiem, B. Chelly, F. Hassan, I. Haddad, S. Ben Slama, A. Lahmar, S. Bourroui, S. Msahi-Rejaia

Xanthogranulomatous cholecystitis is a relatively uncommon variant of chronic cholecystitis, characterized by marked thickening of the gallbladder wall and dense local adhesions. Not only does xanthogranulomatous cholecystitis mimic malignancy, it can also be infrequently associated with gallbladder carcinoma in 0.2% to 35.4% of cases. Herein, the authors report a new case of xanthogranulomatous cholecystitis concomitant with gallbladder adenocarcinoma in a 65-year-old female patient. Because of its overlapping clinical, radiological and macroscopic findings with gallbladder cancer, definitive diagnosis of xanthogranulomatous cholecystitis relies on extensive sampling and thorough microscopic examination of the surgical specimen to exclude the possibility of coexisting tumour. It is still a matter of debate whether xanthogranulomatous cholecystitis is truly a precursor of gallbladder carcinoma if it is just an incidental finding. This aspect needs to be explored in the future with further studies.

Pinkus tumour: an unusual case

S. Sehli-Attafi, M. Jones, B. Facius, Z. Zeramani, S.R. Rommany

Fibroepithelioma of Pinkus is a rare cutaneous tumour. Its classification is controversial and is considered as a variant of either basal cell carcinoma or trichoblastoma I. Its presentation as a multiple tumour is rare. We are reporting such a case occurring in a 55-year-old man presenting with multiple seborrhoeic keratosis-like lesions corresponding histologically to Pinkus tumours. The clinical diagnosis of Pinkus tumour represents a challenge. Histological examination is extremely useful in aiding in the diagnosis of difficult cases.

Mammary myofibroblastoma with leiomyomatous differentiation: case report and literature review

H. Mnif, S. Charni, N. Abid, T. Sallemi-Boudawara

Introduction. Myofibroblastoma of the breast (MFB) is an unusual benign tumour that belongs to the family of benign spindle cell tumours of the mammary stroma. The detection of smooth muscle cells in MFB is explained by its histogenesis from CD34+ fibroblasts of mammary stroma capable of multidirectional differentiation. In this report, we describe a gastric recurrence of RCC, clear-cell type, in a 80-year-old male. The tumour was unusual due to its morphological features, with predominant leiomyomatous differentiation. Immunohistochemical findings, based on the negativity of h-caldesmon, helped in reaching a diagnosis.

Coexistence of xanthogranulomatous cholecystitis and gallbladder adenocarcinoma: a fortuitous association?

F. Limaiem, B. Chelly, F. Hassan, I. Haddad, S. Ben Slama, A. Lahmar, S. Bourroui, S. Msahi-Rejaia

Xanthogranulomatous cholecystitis is a relatively uncommon variant of chronic cholecystitis, characterized by marked thickening of the gallbladder wall and dense local adhesions. Not only does xanthogranulomatous cholecystitis mimic malignancy, it can also be infrequently associated with gallbladder carcinoma in 0.2% to 35.4% of cases. Herein, the authors report a new case of xanthogranulomatous cholecystitis concomitant with gallbladder adenocarcinoma in a 65-year-old female patient. Because of its overlapping clinical, radiological and macroscopic findings with gallbladder cancer, definitive diagnosis of xanthogranulomatous cholecystitis relies on extensive sampling and thorough microscopic examination of the surgical specimen to exclude the possibility of coexisting tumour. It is still a matter of debate whether xanthogranulomatous cholecystitis is truly a precursor of gallbladder carcinoma if it is just an incidental finding. This aspect needs to be explored in the future with further studies.
Lymphomatoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder predominantly involving the lungs, but poorly-recognized among clinicians and pathologists. It is an Epstein-Barr virus (EBV)-driven disease mimicking several other diseases on clinical and radiological grounds, generally showing multiple, bilateral nodular, ill-defined infiltrates of the lungs tending to coalesce and/or cavitate. LYG often affects middle-aged males with an underlying immunodeficiency and commonly involves skin and central nervous system during disease progression. Diagnosis requires a generous biopsy and careful histologic examination with immunohistochemical staining and molecular demonstration of EBV genome in large atypical B-cells. LYG is graded as I to III based on the number of large EBV-positive B-cells; grades II/III are now considered as a peculiar variant of T-cell rich diffuse large B-cell lymphoma. In this brief review, clinical, radiologic and pathologic features of LYG will be analyzed with focus on differential diagnosis, the most appropriate treatment and prognosis.

Clinical Findings

LYG has a predilection for men in a 2:1 ratio and may affect both children and elderly, with the highest prevalence in the forth and fifth decades of life. The
disease more commonly occurs in patients with immunodeficiency or predisposing conditions, such as Wiskott-Aldrich syndrome, human immunodeficiency virus infection (HIV), allogenic organ transplantation, common variable immunodeficiency, X-linked hypo- or agammaglobulinaemia, rheumatoid arthritis, previous history of solid or haematologic neoplasms and chronic treatment with methotrexate (Table I)2. 3. 7-14. 22-27. The mean time from onset of symptoms to diagnosis is about 8 months. 2. 3. 7-14.

It is a common view that LYG may derive from a deficit of CD8 T lymphocytes that cannot control EBV-specific immunity. 3. 7. 8. 10-14. 22. 23. LYG may be localized to the lungs or rather presents as a systemic disease involving skin (50%), central nervous system (25%) and less commonly the kidneys. 3. 7-14. Of note, lymph nodes, bone marrow and spleen are rarely involved. 3. 7-14. Cough, chest pain and dyspnoea are the main pulmonary symptoms, while haemoptysis usually indicates cavitation of the parenchymal nodules. 3. 7-14. 16. 28-30. However, patients with LYG often suffer from systemic symptoms including fever, asthenia, night sweats and weight loss. 11-16. 28-30.

Cutaneous involvement often occurs in the arms and legs with a very heterogeneous manifestation, ranging from an erythematous maculopapular eruption to subcutaneous nodules with non-confluent rash. 11-16. 28-30. Neurologic presentation may present as an isolated peripheral or cranial neuropathy, as a central mass lesion or with seizures. 11-16. 28-30.

Predictors of poor prognosis are central nervous system involvement, high grade, young age at diagnosis (< 25 years), leukocytosis and hepatomegaly. 11-16. 28-30.

**Radiological Features**

The most common radiographic feature is multiple lung nodules, occurring in approximately 80% of cases, pre-dominantly involving the lung bases. 15-21. Lesions can progress rapidly, coalesce and commonly cavitate, mimicking Wegener’s granulomatosis or metastases (Fig. 1) 15-21. 26. Dee et al. 18 described two distinct radiographic manifestations of LYG. In their series of five patients, diffuse reticulonodular opacities correlated microscopically with angiocentric granulomatous infiltra-tion without pulmonary infarction, whereas larger mass-like opacities corresponded to biopsy-proven pulmonary infarcts. 18. There is a wide range in the number (5-60) and diameter of the nodules (up to 6.5 cm), but they generally measure about 1 cm and tend to be located along

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**Table I.** Conditions associated with lymphomatoid granulomatosis.

<table>
<thead>
<tr>
<th>Hematological disorders</th>
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<tbody>
<tr>
<td>Leukemia (acute lymphoblastic, chronic lymphocytic)</td>
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<tr>
<td>Hodgkin lymphoma</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
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<tr>
<td>Myelofibrosis</td>
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<tr>
<td>Wiskott-Aldrich syndrome</td>
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<tr>
<td>Common variable immunodeficiency</td>
<td></td>
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<tr>
<td>Acquired immune deficiency syndrome</td>
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<tr>
<td>Solid tumors</td>
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<td>Renal transplantation</td>
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<td>Autologous stem-cell transplantation</td>
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<tr>
<td>Rheumatoid arthritis</td>
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<td>Sarcoidosis</td>
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<tr>
<td>Biliary cirrhosis</td>
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<td>Chronic hepatitis</td>
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<td>Retroperitoneal fibrosis</td>
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<tr>
<td>Psoriasis</td>
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<tr>
<td>Dermatitis herpetiformis</td>
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</table>

**Table II.** Main pathologic conditions mimicking LYG in the lungs.

<table>
<thead>
<tr>
<th>Infections</th>
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<tbody>
<tr>
<td>Fungal</td>
<td></td>
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<tr>
<td>Mycobacterial</td>
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<tr>
<td>Nocardia</td>
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<tr>
<td>Actinomyces</td>
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<tr>
<td>Paragonomiasis</td>
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<tr>
<td>Autoimmune diseases</td>
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<tr>
<td>Wegener’s granulomatosis</td>
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<tr>
<td>Churg-Strauss syndrome</td>
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<tr>
<td>Microscopic polyangiitis</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>IgG4 syndrome</td>
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<tr>
<td>Neoplasms</td>
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<tr>
<td>Primary lung carcinomas</td>
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<tr>
<td>Metastatic tumors</td>
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<tr>
<td>Lymphoproliferative disease (i.e., leukaemia)</td>
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<tr>
<td>Sarcoidosis</td>
<td></td>
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<tr>
<td>Amyloidosis</td>
<td></td>
</tr>
<tr>
<td>LIP</td>
<td></td>
</tr>
<tr>
<td>COP</td>
<td></td>
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<tr>
<td>Pneumoconioses</td>
<td></td>
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</tbody>
</table>

LYG: lymphomatoid granulomatosis; LIP: lymphocytic interstitial pneumonia; COP: cryptogenic organizing pneumonia.
the bronchovascular bundles and interlobular septa. Less common radiological appearances include coarse linear opacities along the bronchovascular bundles and thin-walled cysts. Nodules can disappear or migrate spontaneously, and may display central ground-glass opacity surrounded by denser consolidation at least 2 mm thick—the so-called “reversed halo sign.” However, this is a non-specific sign, most commonly seen in organizing pneumonia. Differential diagnosis at imaging may be very challenging and includes several other, more common diseases, including metastases, lymphocytic interstitial pneumonia (LIP), sarcoidosis, Wegener’s granulomatosis and cryptogenic organizing pneumonia (Table II). In contrast with other lymphomas involving the thoracic region, mediastinal lymphadenopathy is very uncommon in LYG.

**Immunomorphologic & Molecular Features**

Histology is characterized by poorly-defined pulmonary nodules (Fig. 2A) along the bronchovascular bundles and interstitial inflammatory infiltrates consisting of lymphocytes, plasma cells, histiocytes and intermediate-to-large centroblast-like lymphoid cells (Fig. 2B-C). Vascular and bronchiolar involvement by lymphoid infiltrates is frequently noted. In fact, venous and arteriolar vessels tend to be infiltrated by a mixture of small sized and large atypical lymphocytes justifying the peculiar angiocentric involvement (Fig. 2D). At the periphery of lymphoid proliferation, lung parenchyma commonly shows an acute lung injury with fibrin and hyaline membranes. At immunohistochemistry, there is a background of small T-lymphocytes (CD3+) predominantly with helper phenotype (CD4+) and CD68+ histiocytes intermingled in a population of large B-cells (CD20+, PAX5+, CD79a+) with a high proliferative index by Ki67/MIB-1. In-situ hybridization for EBV-encoded RNA (EBER) reveals a consistent number of EBV-positive large B-cells (Fig. 3D), while molecular analyses generally demonstrate B-cell clonality by immunoglobulin heavy chain gene rearrangement. Despite the misnomer, no granulomas or multinucleated giant cells are generally observed in LYG. According to the WHO classification criteria based on the number of EBV-positive large atypical B-cells, three grades are recognized in LYG. Grade I is very rare and shows a polymorphous infiltrate with minimal angiocentric lesions and fewer than 5 EBV-positive large B-cells per high-power-field (hpf). Grade II has 5-20 EBV-positive atypical B-cells per hpf, while grade III LYG contains aggregates of EBV positive large B-cells (> 20/hpf), prominent angiocentric lesions and necrosis.

**Prognosis & Therapy**

The current view is that LYG is a form of EBV-induced B-cell lymphoma, and so far about 600 cases of LYG have been described in the literature. Despite this, no standard therapy has been established, and treatment is controversial and problematic, basically depending on the disease grade. Several regimens have been considered in the past, from observation to cyclophosphamide plus prednisone or combination chemotherapy with different agents with variable success. However, the outcome is poor and most patients with LYG succumb to the disease after a short period of time. In addition, patients often respond initially, but relapse is very common and the immunosuppressive effects of therapy may actually worsen the condition. During therapy, close follow-up for possible superimposed infections is required. Since this is an EBV-driven process, grade I LYG is often treated with interferon alpha (starting dose of 7.5 x
10^6 U administered subcutaneously 3 times per week, then dose-escalation to best response or complete remission and therapy continued at that dose for a year or longer) 7 10-13. In contrast, grades II and III should be considered high-grade lymphomas, requiring more aggressive treatment including cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with the anti-CD20 monoclonal antibody rituximab (R-CHOP). Etoposide, prednisone, vincristine, cyclophosphamide doxorubicin and rituximab (DAEPOCH-R) are also considered an effective treatment strategy in grade III LYG 7 10-13 30-37.

Of note, patients with grade I LYG can relapse with grade II or grade III disease, but this is sampling-dependant due to the presence of discordant disease at different sites. Re-biopsy should then be highly recommended in patients who are progressing on therapy in order to switch treatment strategies. At a median follow-up time of 5 years, the progression-free survival (PFS) of patients with grade I LYG was 56% with a median time to remission of 9 months 7.10-13. Almost all deaths are recorded in the first 36 months after diagnosis. For grades II-III disease at diagnosis treated with immunotherapy, PFS was 40% with a median follow-up of 28 months 7.10-13.

**Conclusion**

LYG is an angiocentric large B-cell lymphoproliferative disorder due to a defective immune response to EBV and characterized by a mixed polymorphic monoclonal infiltrate with small and large lymphocytes, plasma cells and histiocytes arranged in ill-defined nodules with transmural angiocentric infiltration leading to an angiodestructive process 7.10-13 22 23. The disease generally occurs in middle-aged patients (mean, 40–50 years; range, 2–85 years) with systemic symptoms (fever, malaise, arthralgia, weight loss) mimicking infections (especially tuberculosis and acute histoplasmosis), vasculitides (Wegener’s granulomatosis) or malignancies 7.10-13 16 22 23. Given the rarity of LYG and the non-specific symptoms, correct diagnosis is frequently delayed, requiring a mean time of 8 months from disease onset 14 30. When LYG is restricted to the lungs, fever is the main and often unique symptom, followed by general malaise, weight loss, arthralgia, but clinical manifestations are mainly organ-related (skin, central nervous system, kidney) 7.10-13. Lungs are almost always involved by LYG, but respiratory symptoms may be absent in 20% of cases, while imaging studies invariably show parenchymal nodules, opacities or poorly-defined masses with a peculiar tropism for bronchoalveolar bundles and interlobular septa without mediastinal lymphadenopathy 15-21. Otherwise, LYG may appear as pulmonary cystic disease, pleural-based mass or prominent interstitial process 15 18. Patients with LYG should be investigated for alterations of cytotoxic T-cell function, since a significant association between LYG and immunodeficiencies has been well-demonstrated (i.e. AIDS, Wiskott-Aldrich, post-transplantation, collagen-vascular diseases treated with methotrexate, sarcoidosis, haematologic and solid malignancies, chronic liver and cutaneous diseases, medications) 3 7 8 10-13 24 25 27. Interestingly, recent observations by Yamashita et al. 38 have suggested that some cases of EBV-negative grade I LYG are indistinguishable from pulmonary IgG4-related sclerosing disease, an autoimmune disorder affecting several organs and characterized by elevated serum IgG4 titre, increased IgG4-positive plasma cells in tissues with vascular involvement and dramatic clinical response to steroids.

Diagnosis of LYG requires accurate histopathologic examination on generous biopsies. Bronchoalveolar lavage cytology does not permit a confident diagnosis, basically evidencing a non-specific mixed inflammatory infiltrate. Transbronchial or transthoracic CT-guided biopsies may be diagnostic when sampling a large amount of pathologic tissue and in the hands of expert pathologists. In addition, in the majority of cases reported to date in the literature, diagnosis is performed on surgical specimens and the tissue sampled should be analysed in its entirety, since correct diagnosis mainly depends on careful examination of various areas of the pathologic process coupled to adequate immunohistochemical stains and molecular analysis 22 23. In other words, LYG may actually show grade I and grade III disease in different pathologic areas of the same case. Based on the number of EBV-positive large B-cell counted per high-power-field, LYG is subdivided into three grades 7 8. According to recent observations by Katzenstein et al. 22 and Colby 23, grade I LYG is a formidable challenge to diagnose and probably represent a early or poorly sampled lymphoma. Grades II/III LYG likely raise the suspicion of a malignant lymphoproliferative disease even in the hands of general pathologist. Sharing these complicated cases with more expert colleagues and performing EBER-EBV analysis on multiple sections or blocks is very helpful in discriminating LYG from other mimicking processes.

Differential diagnosis at histology includes other lymphoproliferative (primary or secondary) and inflammatory diseases 22 23. Knowledge of a previous diagnosis of lymphoma (Hodgkin or large B-cell lymphomas) is mandatory before performing a diagnosis of LYG. Since post-transplant lymphoproliferative disorder and iatrogenic immunodeficiency-associated lymphoproliferative disorder are quite similar to LYG, such a diagnosis should be posed with caution in patients receiving organ transplant or those heavily treated with methotrexate or other immunosuppressive agents 7 22. There may be substantial overlap between some indolent EBV-positive angiocentric lymphoproliferative processes (e.g. HIV infection, iatrogenic lymphoproliferative diseases, secondary drug toxicity) and LYG. In these difficult cases, pathologic criteria may be fragile and need prominent integration with clinical and imaging data. The main differential diagnosis is with Wegener’s gran-
PULMONARY LYMPHOMATOID GRANULOMATOSIS

References


Practical Remarks

LYG is an EBV-driven lymphoproliferative disease, ranging from grade I to grades II and III; these latter are considered as a form of diffuse large B-cell lymphoma (T-cell-rich large B-cell lymphoma). LYG primarily occurs in the lungs, less frequently involving skin and central nervous system.

Mean age at diagnosis is 48 years with a male prevalence.
About the necessity of improving the current nodal classification of non-small cell lung carcinoma

M. MLIKA*1, A. AYADI-KADDOUR*1, S. BOUDAYA2, A. MARGHLI2, T. KILANI2, F. MEZNI*1
* Search Unit: 02/SU/08-08; 1 Department of Pathology, 2 Department of Thoracic & Cardiovascular Surgery, Abderrahman Mami Hospital, Ariana, Tunisia

Key words
TNM classification • Ratio of metastatic lymph nodes • Non-small cell lung carcinoma

Background. The current classification of lymph node status in non-small cell lung carcinoma has not been revised since 1997. This fact has prompted many authors to point out the limits of this classification.

Methods. We tried to explore the prognostic relevance of the current TNM classification in comparison with the nodal classification based on the ratio of metastatic lymph nodes (LNR) and the nodal classification based on the number of metastatic LNs (nLN). Additionally, we tried to explore the recommended number of resected LNs. This was done through a retrospective study of 39 cases. We compared the survival curves of patients using the current, RLN and nLN classifications. In the nLN classification, we grouped patients into three categories: nN0 (no metastatic LNs), nN1 (1 to 2 metastatic LNs) and nN2 (> 2 metastatic LN). In the LNR classification, we grouped patients into three categories: rNO (0%), rN1 (≤ 12) and rN2 (> 12). Concerning the total number of the resected LNs, patients were categorized into two groups according to the number of LNs: < 10 versus ≥ 10 and < 15 versus ≥ 15.

Results. Our results showed that the LNR classification highlighted a difference in prognosis between the rN1 and rN2 groups. Moreover, survival of patients seemed to be better when the number of the resected LNs was higher.

Conclusion. The ratio of metastatic LNs seems to be an important prognostic factor, but further studies are necessary to standardize this classification.

Introduction

The TNM staging system for lung cancer, especially for non-small cell lung carcinoma, has not been revised since the first edition of the tumor, node and metastasis classification published in 1997. Initially, this edition remained unaltered in the sixth edition published in 2002, and a revised classification was published in 2009. The new recommendations concerned tumour and metastasis classification. Considering node classification, tumours remained subdivided according to the metastatic lymph node stations, but many concerns have been pointed out by several authors. In fact, the N1 and N2 patient groups seem to be heterogeneous with regards to prognosis. Moreover, patients with multiple-station metastases have been reported to have a poorer prognosis compared with those with single-station metastases in both N1 and N2 patients. With skip metastases have been reported to belong to a more favourable prognostic subgroup. Many authors seem to be disappointed when classifying patients with only hilar lymph node metastasis. In order to answer to some of these questions and in accordance with the TNM staging of major malignancies such as colorectal carcinoma, gastric carcinoma and breast carcinoma, some authors have attempted to highlight the prognostic relevance of including the number of metastatic lymph nodes (LNs). The ratio of metastatic LNs to examined LNs (LNR) has been suggested to be a more favourable prognostic indicator than the number of metastatic LNs in some malignancies. In this study, we explored the prognostic relevance of the current TNM classification in comparison with the nodal classification based on the LNR and the nodal classification based on the number of metastatic LNs (nLN). Moreover, we tried to explore the best prognostic cut-off number of resected lymph nodes.

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Patients and methods

Patients

Between January and December 2008, 53 patients with non-small cell lung carcinoma underwent surgical resection at our hospital. We excluded patients with small cell carcinoma, stage IIb disease and stage IV disease. Furthermore, we excluded patients with induction treatment or with less than six LNs removed because examination of six or more LNs stations is recommended according to the 7th edition of the TNM classification. Finally, 39 patients met these criteria; patient characteristics are shown in Table I. The Abderrahman Mami Hospital review board approved this retrospective study and waived the requirement of patient consent.

All patients underwent physical examination, chest X-ray, bronchoscopic examination and CT-scan of the chest as well as the upper part of the abdomen and magnetic resonance imaging of the brain. A LN > 1 cm in its short axis shown in CT was considered as metastatic.

LN dissection

Mediastinal LN metastasis was not considered as a contraindication for surgery unless the swollen LNs appeared unresectable.

Systemic nodal dissection involves the complete resection of ipsilateral mediastino-hilar LNs. Hilar, interlobar and lobar LNs were resected with affected lung lobes in the hilar LN dissection and remote mediastinal LN station such as subcarinal LNs in the upper lobe tumour, were not resected in selective mediastinal dissection.

Microscopic examination

The LNs stations varying from 1 to 10 were individually removed by surgeons and were either examined extemporaneously or fixed immediately in formalin and cut at their equator, stained with haematoxylin and eosin and examined by light microscopy. Interlobar LNs were resected in combination with the lung, and these nodes were classified into each nodal station. The pathological stage was classified according to the 7th edition of the TNM classification. Hilar lymph node metastasis was classified as N2 stage.

Statistical analysis

The cut-off numbers for each category in the two new nodal classifications (nNC and LNR NC) were defined so that the numbers corresponded with paired categories within the current NC. This was done to compare the prognosis of each category in the two new nodal classifications. In the number NC, we classified patients into three categories: nN0 when there was no metastatic lymph node, nN1 when 1 to 2 lymph nodes were metastatic and nN2 when more than 2 lymph nodes were metastatic. The LNR was calculated by dividing the number of metastatic lymph nodes by the total number of the resected LNs multiplied by 100. In the LNR NC, we classified patients into three categories: rNO when the ratio reached 0, rN1 when the ratio was less or equal to 12 and rN2 with the ratio was superior to 12.

Concerning the total number of the resected lymph nodes, patients were categorized into two groups according to the number of RLNs: < 10 versus ≥ 10 and < 15 versus ≥ 15. The survival period was calculated from the date of surgery to the time of death or the endpoint. Survival curves were calculated using the Kaplan-Meier method and differences in survival were determined by the log-rank test. The comparison of survival was performed using a nonparametric test (Mann-Whitney test). All tests were two sided and p values of less than 0.05 were considered statistically significant. All tests were performed using the Statistical Package for the Social Sciences (SPSS) ver.13 (SPSS Inc, IL, USA).

Results

The most employed surgical procedure was lobectomy with systemic nodal dissection. As shown in Table I, the number of patients in each category and subcategory were quite similar thus allowing their comparison.

Survival and current LN classification

According to the current LN classification, patients were categorized into 3 groups according to the station of the involved LNs. The N0 group contained 26 patients with
a mean survival of 9.8 months. The N1 group contained 4 patients with a mean survival of 9.25 months. The N2 group contained 9 patients with a mean survival of 6.0 months. The largest difference was found between the N0 and N2 groups (p = 0.163). Survival curves are shown in Figure 1.

**SURVIVAL AND CLASSIFICATION ACCORDING TO THE NUMBER OF INVOLVED LNs**

According to this classification, patients were categorized into 3 groups according to the number of the metastatic LNs: nN0, nN1 and nN2. The nN0 group contained 26 patients with a mean survival of 15.94 months. The nN1 group contained 6 patients with a mean survival of 7.33 months. The nN2 group contained 7 patients with a mean survival of 6.71 months. The largest difference was found between the N0 and N1 groups (p = 0.482). These survival curves are shown in Figure 2.

**SURVIVAL AND CLASSIFICATION ACCORDING TO THE RATIO OF INVOLVED LNs**

According to this classification, patients were categorized into 3 groups according to the ratio: rN0, rN1, rN2. The rN0 group contained 26 patients with a mean survival of 15.71 months. The rN1 group contained 5 patients with a mean survival of 14.13 months. The rN2 group contained 8 months with a mean survival of 7.72 months. The largest difference was found between the rN1 and rN2 groups (p = 0.212). Survival curves are shown in Figure 3.

**SURVIVAL AND NUMBER OF RESECTED LNs**

We investigated the prognostic impact of the number of resected LNs. Patients were categorized into 2 representative groups according to the total number of resected LNs: < 10 versus ≥ 10 and < 15 versus ≥ 15 (Fig. 4). The largest difference was found in the total number of
resected LNs categorized between < 10 and ≥ 10 with p value of 0.204, but we also noticed that in both groups survival was better when the number of the resected LNs was higher.

**Comment**

Since 1946, the classification of lung cancer has been modified and the recent recommendations concerned only the Tumour and Metastasis classification\(^1\). In fact, the T1 and T2 stages were subclassified according to tumour size. T2 tumours measuring more than 7 cm were reclassified as T3 tumours. T4 tumours with additional nodules in the same lobe were reclassified as T3 tumours. M1 tumours with additional nodules in ipsilateral lobes were reclassified as T4. T4 tumours with malignant pleural effusion were reclassified as M1a. Finally, M1 tumours were subclassified into M1a and M1b. The N classification was not modified, and classification of LNs metastasis was maintained based on the LN station as shown in Table II. This was based on the idea that LN metastases occur in LNs neighbouring the primary tumour, and then spread to more distant nodes. However, recent studies on skip metastasis and sentinel lymph nodes have assessed that patients with skip metastasis, defined as mediastinal LNs without N1 sentinel lymph nodes have assessed that patients with nodal metastasis were maintained based on the LN station as shown in Table II. This was based on the idea that LN metastases occur in LNs neighbouring the primary tumour, and then spread to more distant nodes. However, recent studies on skip metastasis and sentinel lymph nodes have assessed that patients with skip metastasis, defined as mediastinal LNs without N1 metastasis, showed a better prognosis than patients with non-skip N2 disease\(^7\)\(^-\)\(^-\)\(^14\). From these results, many authors have investigated the impact of the number of resected LNs, the ratio of the metastatic LN or the number of resected LNs (RLN)\(^15\)\(^\)\(^-\)\(^16\). Two studies have reported the usefulness of determining the number of metastatic LNs. Fukui et al. classified nodal categories according to the number of metastatic LNs as 1-3, 4-6 and > 6, and Lee et al. classified them as 1-4, 4-14 and > 14\(^17\)\(^\)\(^-\)\(^18\). Both studies demonstrated that the number of metastatic LNs was a stronger prognostic indicator than current NC based on the location. In addition, Saji and colleagues showed that 4 involved LNs seemed to be a benchmark for NSCLC prognosis\(^19\).

<table>
<thead>
<tr>
<th>Station</th>
<th>Denomination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Highest mediastinal</td>
</tr>
<tr>
<td>2</td>
<td>Upper paratracheal</td>
</tr>
<tr>
<td>3, p</td>
<td>Prevascular, retrotracheal</td>
</tr>
<tr>
<td>4</td>
<td>Lower paratracheal</td>
</tr>
<tr>
<td>5</td>
<td>Subaortic</td>
</tr>
<tr>
<td>6</td>
<td>Para-aortic</td>
</tr>
<tr>
<td>7</td>
<td>Subcarinal</td>
</tr>
<tr>
<td>8</td>
<td>Para-oesophageal</td>
</tr>
<tr>
<td>9</td>
<td>Pulmonary ligament</td>
</tr>
<tr>
<td>10</td>
<td>Hilar</td>
</tr>
<tr>
<td>11</td>
<td>Interlobar</td>
</tr>
<tr>
<td>12</td>
<td>Lobar</td>
</tr>
<tr>
<td>13</td>
<td>Segmental</td>
</tr>
<tr>
<td>15</td>
<td>Subsegmental</td>
</tr>
</tbody>
</table>

On the other hand, Matsuguma and colleagues proposed new nodal classifications for non-small cell lung cancer based on the number and ratio of metastatic LNs. They concluded that the LNR followed by the number of metastatic LNs may be more effective prognostic indicators than the current nodal classification\(^20\). In our study, we observed a more important difference between the subgroups rN1 and rN2 in the LNR classification. Despite the lack of a significant statistical difference between the 2 groups, the survival curves show a tendency towards better prognosis in rN1 group. This classification seems to be more accurate to differentiate the prognosis of these 2 sub-groups. As the number of LNs resected can influence the accuracy of nodal staging, even in current NC, examination of a minimum number of LNs seems to be necessary\(^21\)\(^\)\(^-\)\(^22\). Saji and coworkers retrospectively investigated the prognostic impact of the number of resected LNs and involved LNs in a series of 928 patients with non-small cell lung cancer. They examined many LNs cut-offs and concluded that complete resection including 10 or more LNs influenced survival with favourable prognosis in large number resected LNs\(^19\). This fact was also shown in our study. We studied only 2 groups with a cut-off of 10 and 15 resected LN. We excluded all patients with less than 6 LNs because this cut-off was recommended in the latest TNM classification. Although the fact that our results are not statistically significant because the p value was greater than 0.05, the survival curves showed a trend to better survival in the group with 10 or more resected LNs. These results are not in complete agreement. In fact, the results of the American College of Surgeons Oncology Group showed poorer outcome in patients with a high number of resected LN\(^23\). This is possibly due to the predominance of N1 and N2 stages, which are more likely to be LN-positive at the time of surgery. In fact, in our study, N0 stage was predominant and accounted for 66.6% of the cases. One limitation of our study was the lack of a statistically significant difference either because of the low number of patients included or to the unfairness of the cut-off values used. We believe that in order to determine the most effective cut-off, data accumulated from multiple institutions from several countries should be analyzed. Moreover, a consensus should be achieved concerning the removal of all, some or none of the mediastinal LNs at the time of surgical resection. In fact, practices vary worldwide. In some groups, LN sampling is standard, whereas systematic LN dissection is standard in others. The different practices, especially in case of fragmentation of LNs, may influence the ratio of metastatic LNs and its real prognostic value.

**Conclusion**

Lymph node metastasis has been reported to represent an important prognostic factor in NSCLC. According to the current TNM classification, many aspects concern-
ing the cut-off value of the number of metastatic LNs, the number of resected LNs, the ratio of metastatic LNs, the real prognostic impact of hilar lymph node metastasis and the prognostic importance of single station versus multi-station metastases remain unclear. Additional studies may be necessary in order to improve the ability to indicate the prognostic group of patients. In this regard, the ratio of metastatic LNs seem to be an important prognostic factor, but further studies including large-scale cohort studies with prospective validation analyses and multi-institutional analyses will be necessary in order to standardize this classification.

References

Intraparenchymal leiomyoma of the breast: report of a case with emphasis on needle core biopsy-based diagnosis

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Key words

Breast • Leiomyoma • Differential diagnosis • Spindle cell tumors • Immunohistochemistry

Summary

Objective. We report the clinicopathologic features of a rare case of leiomyoma of the breast parenchyma in a 36-year-old female, diagnosed preoperatively at core biopsy. A complete review of the literature on the topic is provided and differential diagnostic problems are discussed.

Methods. Standard histological examination and immunohistochemical analyses using a large panel of antibodies were performed in both the core biopsy and surgical specimen.

Results. Ultrasonography revealed a well-circumscribed tumour mass without calcifications. Histological examination of the core biopsy showed proliferation of bland-looking eosinophilic spindle cells arranged in a fascicular growth pattern. Mitoses, pleomorphism and necrosis were absent. Immunohistochemistry, revealing diffuse staining for α-smooth muscle actin, desmin and h-caldesmon, confirmed the leiommatous nature of neoplastic cells. Histological and immunohistochemical analyses of the surgical specimen confirmed the definitive diagnosis of leiomyoma.

Conclusions. The present case emphasizes that diagnosis of leiomyoma of the breast parenchyma can be confidently rendered on needle core biopsy. We believe that correct diagnosis is primarily dependent on the awareness that this tumour can arise in this unusual site on rare occasions.

Introduction

Leiomyomas are benign smooth muscle tumours that can potentially occur anywhere, including the breast. Most cases of breast leiomyomas usually arise in the skin or periareolar region, while they are only rarely detected in breast parenchyma. A Pub-Medline-based search reveals only 26 reported cases of leiomyomas of the breast parenchyma. However, we would like to underline that even the most recent review on the topic fails to include the largest series of leiomyomas of breast parenchyma, reported by Jones et al. in 1994. In that paper, the authors described the clinicopathologic features of 11 cases of leiomyomas that occurred within the breast. Thus, to the best of our knowledge, 37 cases of leiomyomas of the breast parenchyma have been reported in the English literature to date, with only one case diagnosed preoperatively by needle core biopsy.

We herein report the clinicopathologic features of a case of leiomyoma of the breast parenchyma, emphasizing needle core biopsy-based diagnosis. Differential diagnosis with spindle cell tumour and tumour-like lesions of the breast is provided. Correct preoperative diagnosis of leiomyoma is crucial for conservative surgical treatment.

Clinical history

A 36-year-old woman presented with a palpable, painless, mobile nodule in her right breast. Ultrasonography revealed a hypoechoic, 2 cm nodular mass with well circumscribed margins and without microcalcifications.
and fibroadenoma was suspected (Fig. 1). There were no skin or nipple abnormalities and no axillary lymphadenopathy was noted. Fine needle core biopsy (FNAB) was performed and a diagnosis of “smooth muscle tumour, likely benign (leiomyoma)” was proposed with the recommendation of evaluating the entire tumour mass after surgical excision. A lumpectomy was performed.

**Materials and methods**

The surgical specimen was fixed in 10% buffered formalin, routinely processed and embedded in paraffin. 4 μm-thick sections were stained with haematoxylin and eosin. Additional sections were cut for immunohistochemical procedures. Immunohistochemical studies were performed with the labelled streptavidin–biotin peroxidase detection system using the Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ, USA). The antibodies tested were: vimentin (dilution 1:100), α-smooth muscle actin (dilution 1:200), desmin (dilution 1:100), h-caldesmon (dilution 1:100), myogenin (dilution 1:100), S-100 protein (dilution 1:500), CD68 (dilution 1:200), CD99 (dilution 1:100), CD34 (dilution 1:50), CD117 (dilution 1:400), pancytokeratins (dilution 1:50), EMA (dilution 1:100), p63 (dilution 1:200), and HMB45 (dilution 1:300; all from DakoCytomation, Glostrup, Denmark). Negative controls for staining were slides stained with omission of the primary antibody.

**Pathologic findings**

The core biopsy specimen showed interlacing bundles of bland-looking deeply eosinophilic spindle-shaped cells, closely reminiscent of leiomyoma (Fig. 2). Mitoses, necrosis and nuclear pleomorphism were absent. Immunohistochemical analyses revealed a diffuse staining for vimentin, desmin, α-smooth muscle actin and h-caldesmon. No immunoreactivity was obtained with any of the other markers tested, including cytokeratins (AE1/AE3), EMA, CD34, S-100 protein, HMB-45, myogenin, CD99, CD68, p63, CD117. Based on morphological and immunohistochemical features, a diagnosis of “smooth muscle tumour, likely benign (leiomyoma) of the breast” was proposed.

The surgically-excised tumour mass presented as an unencapsulated, well circumscribed, 2 cm nodule, firm in consistency and whitish in colour. Histological examination revealed an unencapsulated, well-circumscribed
tumour with the features of a classic leiomyoma, as typically seen in the uterus (Fig. 3). The tumour was composed of interlacing fascicles of spindle-shaped cells with abundant, deeply eosinophilic cytoplasm and elongated nuclei with blunt ends (Fig. 4). Nuclear chromatin was delicate and evenly distributed, and nucleoli were not prominent. Mitoses, nuclear pleomorphism and necrosis were absent. Residual mammary lobules were present at the periphery of the lesion (Fig. 3). Immunohistochemical analyses, revealing a diffuse staining for vimentin, desmin, $\alpha$-smooth muscle actin (Fig. 5) and h-caldesmon, confirmed the leiomyomatous nature of neoplastic cells. Notably, diffuse (> 90%) nuclear staining was obtained with ER/PR. No immunostaining was observed with CD34, bcl-2, CD99, HMB-45, S-100 protein, p63, CD68, CD99, CD117, myogenin, cytokeratins or EMA. Morphological and immunohistochemical features were consistent with the definitive diagnosis of “intraparenchymal leiomyoma of the breast”.

**Discussion**

Although leiomyomas of the breast arising in the muscle-rich subareolar region are relatively common tumours, leiomyomas of the breast parenchyma are extremely rare. Since the first description in 1913, only additional 37 cases have been reported to date.²⁻²⁷ Interestingly, these tumours have been documented exclusively in women with ages ranging from 30 to 60 years (mean age of 47.6 years), usually involving the outer quadrant of the right breast.²⁶ Their size varied from 5 mm to 13.8 cm, and most patients presented a history of painless tumour mass with a duration ranging from 1 month to 26 years.²⁻²⁷ Some cases may present with discomfort, pain, tenderness or may be incidentally detected by screening mammography. On mammography, they appear as dense homogeneous masses with well defined margins without calcifications, architectural distortion, skin or nipple retraction.¹⁰¹¹¹⁶¹⁷¹⁹²⁰ On ultrasonographic examination, leiomyomas present as solid, hypoechoic, homogeneous, circumscribed nodules.¹⁶²¹ Based on these observations, it is noteworthy that radiological features of leiomyoma of the breast are non-specific, and similar to those described in other breast lesions such as fibroadenoma, myofibroblastoma, muscular hamartoma and breast myxoma.²⁸⁻³² Although the histological diagnosis of leiomyoma is usually straightforward due to its typical cytological and architectural features, it may be challenging when this tumour occurs in unusual sites, including breast parenchyma. Additional diagnostic difficulties may arise when, evaluating needle core biopsies, the pathologist is faced with an intraparenchymal spindle cell proliferation. In this regard, leiomyoma can potentially pose differential diagnostic problems with a wide variety of benign and malignant spindle cell lesions. Among benign lesions, especially nodular fasciitis, inflammatory
pressed in myofibroblastoma. Benign peripheral nerve sheath tumours (schwannoma, neurofibroma) enter differential diagnosis with leiomyoma. Nodular fasciitis is a fibroblastic/myofibroblastic pseudosarcomatous lesion of unknown aetiology, which only rarely occurs in the breast parenchyma. Nodular fasciitis usually occurs as a solitary and rapidly growing (1-2 weeks) nodular mass that is successfully treated with local excision alone, with local recurrence extremely rare (1-2%) after complete excision. This lesion showed, at least focally, infiltrative margins, and was composed of pale to eosinophilic spindle-shaped cells with bland nuclei, arranged in short, irregular bundles and fascicles. The stroma is generally fibromyxoid and contains thin-walled vessels, extravasated blood red cells and lymphocytes. As nodular fasciitis typically shows immunoreactivity for α-smooth muscle actin and focally for desmin in some cases, h-caldesmon is a useful marker in distinguishing smooth muscle from myofibroblastic proliferations. Inflammatory pseudotumour is a fibro-inflammatory lesion that can be rarely encountered in breast parenchyma. This reactive lesion is composed of spindle-shaped cells arranged in a fascicular, and less frequently, storiform growth pattern, and embedded in a variable fibromyxoid stroma. Typically, the spindle-shaped cells are admixed with inflammatory cells, especially plasma cells, lymphocytes, and eosinophils. The myofibroblastic nature of the spindle-shaped cells is confirmed by immunostaining with α-smooth muscle actin, along with the lack of desmin and h-caldesmon expression. Although mammary myofibroblastoma may show a wide variety of morphological features, the classic type myofibroblastoma is a benign spindle cell tumour composed of cells closely packed in short, haphazardly intersecting fascicles or clusters of cohesive cells, interrupted by thick, eosinophilic keloid-like collagen fibres. Notably, cells show a variable degree of fibroblastic and myofibroblastic differentiation at the morphological, immunohistochemical and ultrastructural level. Like leiomyoma, myofibroblastoma usually shows a fascicular growth pattern and a diffuse expression of desmin, α-smooth muscle actin and oestrogen/progesterone receptors. Accordingly, there is the possibility of potential confusion between these two tumours, especially when evaluating needle core biopsy. However, unlike leiomyoma, myofibroblastoma exhibits cells with less abundant and eosinophilic cytoplasm, and is also often variably positive for CD34, Bcl-2 protein, CD99 and CD10. H-caldesmon is usually absent or only focally expressed in myofibroblastoma. Benign peripheral nerve sheath tumours rarely arise in the breast parenchyma. Schwannoma and neurofibroma, especially the cellular variant, are easily distinguished by leiomyoma for their diffuse expression of S-100 protein.

Although a wide variety of malignant spindle cell lesions should be potentially included in differential diagnosis, in principle however, only desmoid-type fibromatosis, leiomyosarcoma, malignant myoepithelioma, fibromatosis/nodular fasciitis-like low-grade sarcomatoid/metaplastic carcinoma and fibrosarcoma/malignant fibrous histiocytoma must be distinguished from leiomyoma. Desmoid-type fibromatosis of the breast parenchyma is a relatively rare tumour that can occur sporadically or in the context of genetic syndromes. Unlike leiomyoma, fibromatosis of the breast shows infiltrating borders with entrapment of fat and glandular mammary tissue. It is composed of long, sweeping fascicles composed of bland-looking spindle-shaped cells with slightly to moderate eosinophilic cytoplasm, embedded in a variable, often prominent, fibrous stroma. Fibromatosis, which is usually immunoreactive for β-catenin and α-smooth muscle actin, does not express desmin (occasionally only focal staining), h-caldesmon and CD34. Leiomyosarcoma is the most important malignant tumour that needs to be distinguished from an intraparenchymal leimyoma. This distinction is crucial for appropriate treatment and prognostic information (recurrence rates, potential distant metastases, worse prognosis). At ultrasound examination, leiomyosarcoma frequently appears similar to leiomyoma, exhibiting well-circumscribed margins. However, leiomyosarcoma differs from leiomyoma in that the former has infiltrating margins at microscopic examination and diffuse cytological atypia with high mitotic activity. Necrosis and/or atypical mitoses may be seen. Immunohistochemical analyses are not helpful as both tumours express the same myogenic markers, even if leiomyosarcoma has the tendency to lack h-caldesmon and desmin in the more poorly differentiated tumours. Although differential diagnosis between leiomyoma versus leiomyosarcoma is relatively easy in the surgical specimen, we admit that it may be challenging at needle core biopsy and, thus, histological evaluation of the surgically excised tumour is mandatory. Malignant myoepithelioma is a tumour composed predominantly/exclusively of spindle cells, arranged in haphazardly interlacing bundles, sometimes with a focal storiform pattern. This tumour usually displays cytological atypia and a low to high mitotic activity. Immunocytochemistry, demonstrating the myoepithelial nature of cells (variable co-expression of cytokeratins, vimentin, α-smooth muscle actin, S-100 protein, CD10, p63) is an important ancillary diagnostic tool. Fibromatosis/nodular fasciitis-like low-grade sarcomatoid/metaplastic carcinoma is predominantly/exclusively composed of spindle cells with a minority of neoplastic cells exhibiting a more ovoid/epithelioid morphology, which tend to aggregate in small nests or, more rarely, in pseudo-glandular structures. This variant of metaplastic carcinoma can be easily excluded with the use of immunohistochemistry for low molecular weight keratins which identify epithelial neoplastic cells with both spindle to ovoid/epithelioid morphology. The possibility that a significant number of neoplastic cells are also stained with α-smooth muscle actin is not rare. Lastly, fibrosarcoma/malignant fibrous histiocytoma of breast parenchyma is a category that covers a continuous morphological spectrum of low to high grade lesions sharing features of classic type fibrosarcoma and malig-
nant fibrous histiocytoma. Unlike our case, fibrosarcoma/malignant fibrous histiocytoma is a tumour exhibiting infiltrative margins and a prominent herringbone and/or storiform growth pattern. Immunohistochemistry reveals diffuse staining for vimentin, while α-smooth muscle actin and CD34 may only be focally detected.

The present case emphasizes that diagnosis of leiomyoma of the breast parenchyma can be confidently rendered on core needle biopsy. We believe that correct diagnosis is primarily dependent on the awareness that this tumour can arise in this unusual site, albeit rarely. When dealing with a breast tumour that exhibits bland-looking spindle-shaped cells with deeply eosinophilic cytoplasm, arranged in fascicles, without mitoses and nuclear pleomorphism, pathologists should keep in mind the possibility of leiomyoma, including appropriate myogenic markers in the list of the immunohistochemical panel. Immunohistochemical analysis, revealing a diffuse expression of desmin, α-smooth muscle actin and h-caldesmon, is extremely helpful to confirm diagnosis of leiomyoma at core biopsy, ruling out other benign and/or malignant tumours. However, due to the morphological and immunohistochemical overlap between leiomyoma and leiomyosarcoma, we recommend a diagnosis of “smooth muscle tumour, likely leiomyoma” at core biopsy, suggesting that a final diagnosis can be rendered on the surgically excised nodule.

Various theories have been proposed about the origin of leiomyoma of breast parenchyma. Kaufman and Hirsch suggested that this tumour arises from the smooth-muscle cells that surround capillaries in the subcutaneous tissues of the breast. Diaz-Arias et al. proposed five sources: i) teratoid origin with extreme overgrowth of the myomatous elements; ii) embryologically displaced smooth muscle from the nipple; iii) angiomatosus smooth muscle; iv) a multipotent mesenchymal cell; v) myoepithelial cells. Although the frequent occurrence of leiomyoma near the nipple may be related to the abundance of smooth-muscle cells around the nipple and areola, the histogenesis of lesions occurring within the breast parenchyma still remains controversial.

References
Intraparenchymal leiomyoma of the breast

Primary mucinous carcinoma of the thyroid gland: case report with review of the literature

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Key words
- Mucinous carcinoma
- Thyroid gland
- Differential diagnosis
- Immunohistochemistry

Summary

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Primary mucinous thyroid carcinoma (PMTC) are extremely rare lesions that are histologically indistinguishable from mucinous carcinoma of other sites. We describe the clinicopathological, histological and immunohistochemical features of this rare tumour with a review of the literature. We describe a case of thyroid tumour, in 56-year-old Tunisian man, composed of small nests and sheets of malignant epithelial cells associated with extensive extracellular mucin that entrapped the follicular parenchyma of thyroid. Thyroglobulin and thyroid-specific transcription factor 1 (TTF1) were focally positive. Follow-up did not reveal another neoplasm at other sites. Based on these features, we classified this tumour as PMTC. Mucinous carcinoma of the thyroid gland can be a cause of pitfall in differential diagnosis. For correct diagnosis, complete clinical history, restricted histological criteria and immunohistochemical panel are necessary.

Introduction

Mucinous carcinoma occasionally arises in various organs of the human body, but rarely occurs in the thyroid gland, with only six cases reported in literature. Accordingly, its clinicopathological and histopathological features have not been extensively documented.

We present a case of primary mucinous thyroid carcinoma (PMTC). We describe the clinicopathological, histological and immunohistochemical features of this rare tumour with a review of the literature.

Case presentation

A 56-year-old Tunisian man presented with rapidly enlarging mass in his neck 2 months before admission. He complained of recent dysphagia. On physical examination, there was a palpable and painless nodule in the right lobe of the thyroid and a second nodule in the left lobe. There were palpable bilateral subclavian lymph nodes. There were no other abnormal physical findings. The patient was euthyroid. There was no history of neck irradiation or familial thyroid disease. Results of thyroid function tests, routine blood counts and biochemical tests were within normal limits. Ultrasonography and CT identified hypodense nodules involving both lobes of the thyroid associated with bilateral lymph nodes in the neck and at the mediastinum. There were no lung lesions. The patient underwent a total thyroidectomy with resection of local lymph nodes with no postoperative complications. In final histological examination, both tumours showed a similar appearance with an infiltrative growth pattern entrapped residual atrophic thyroid follicles. Tumours consisted of extracellular mucin around strands, small solid nests (Fig. 1a) and trabeculae of epithelial malig-
nant cells, similar to that of mucinous carcinoma of the gastrointestinal tract. Glandular-like structures were scanty. The mucus positively stained for mucicarmine, Alcian blue (Fig. 1b) and PAS before and after diastase treatment. The cells were of polygonal to round shape with large nuclei and prominent nucleoli, but no cytoplasmic inclusions or nuclear grooves. Mitotic figures were present. The mucus pool merged progressively with solid areas of poorly differentiated carcinoma and glandular differentiation. There were no areas of typical thyroid carcinoma. Common vascular invasions were found (Fig. 1c). The tumours grew in an aggressive manner and invaded the fibrous capsule, neighbouring cervical structures and skeletal muscle of the neck (Fig. 1d). Immunohistochemical study showed immunoreactivity to epithelial markers (CK MNF 116, CK7). Thyroglobulin (Fig. 2a) and thyroid-specific-transcription factor 1 (TTF1) (Fig. 2b) were focally positive in both tumors. CK 20, carcinoembryonic antigen (CEA) (Fig. 2c) and calcitonin (Fig. 2d) were negative. Follow-up did not reveal another neoplasm at other sites. From these features, a diagnosis of PMTC was made. One month later the patient died of disease. Autopsy was not allowed.

Discussion

Mucinous carcinoma occasionally arises in various organs of the human body including the gastrointestinal tract and breast. Diaz-Perez et al. first described PMTC in 1976, although it is extremely rare in this gland, and only 6 cases having been reported in literature. Thus, virtually nothing is known about its epidemiology, and its clinicopathological and histopathological features have not been extensively documented. The reported cases of PMTC are summarized in Table I. These tumours presented as a rapid or slow growing, occasionally painful “cold” thyroid nodules with or without palpable regional lymph nodes. Tumours were well-or poorly-circumscribed grey-brown gelatinous nodules ranging up to several cm in diameter. In the World Health Organization classification system, PMTC is characterized by clusters of neoplastic cells surrounded by extensive extracellular mucin deposition. Tumours usually show focal thyroglobulin, TTF1, low molecular weight cytokeratins and MUC2 immunoreactivity, and are negative for calcitonin. Differential diagnosis would fall between PMTC and others histological types of thyroid carcinoma showing mucin production.
(follicular neoplasm, papillary carcinoma, anaplastic and medullary carcinoma) 4 5 10. In these cases, the tumour is characterized by a pool of mucin that is often extracellular and admixed with areas of typical thyroid carcinoma 3 4. In our case, the tumour did not have typical features of follicular neoplasms such as a fibrous capsule or a distinctive follicular architecture. We failed to demonstrate the nuclear features of papillary thyroid carcinoma such as ground-glass appearance, grooving, or pseudoinclusion. Mucin-producing medullary carcinoma was excluded based on immunohistochemical findings: positivity for thyroglobulin and negative for

![Image](https://example.com/image1)

![Image](https://example.com/image2)

![Image](https://example.com/image3)

![Image](https://example.com/image4)

**Table I. Reported cases of PMTC.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Tumour size (cm)</th>
<th>Treatment</th>
<th>Metastases</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td>M</td>
<td>5 x 4 x 3</td>
<td>Partial thyroidectomy</td>
<td>-</td>
<td>8 years</td>
</tr>
<tr>
<td>40</td>
<td>M</td>
<td>2.8 x 2.5 x 1.5</td>
<td>Left lobectomy</td>
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<tr>
<td>56</td>
<td>M</td>
<td>8 x 6 x 2</td>
<td>Total thyroidectomy</td>
<td>N+</td>
<td>2 years</td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>6 x 2.5 x 1.5</td>
<td>Chemotherapy</td>
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<tr>
<td>82</td>
<td>F</td>
<td>3 x 2 x 2</td>
<td>Radiotherapy</td>
<td>N+</td>
<td>8 months</td>
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<tr>
<td>62</td>
<td>F</td>
<td>-</td>
<td>Total thyroidectomy</td>
<td>Skin +</td>
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</tr>
<tr>
<td>56</td>
<td>M</td>
<td>4 x 3 x 2 (left)</td>
<td>Radioisotope therapy</td>
<td>N+</td>
<td>6 months</td>
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M: male; F: female; N+: lymph node metastases.
Primary mucinous carcinoma of the thyroid gland. We ruled out mucoepidermoid carcinoma as the tumour lacked a squamoid component and mucus cells. Furthermore, a metastasis from a mucinous adenocarcinoma arising in other sites should be considered in differential diagnosis. A key feature that can help in this differential diagnosis is the absence of solid or glandular areas that progressively merged with areas of mucinous stroma and a pool of extracellular mucin. If a PMTC is suspected, immunohistochemical study is necessary to provide a final diagnosis (Tab. II).

Based on the limited follow-up information available, PMTC is a highly aggressive malignant neoplasm typified by rapidly progressive local disease, lymph node and distant metastases. Of the 6 previously reported patients in the literature, 4 had lymph node metastases and 3 had distant metastases to the lung and/or skin. Survival periods ranged from 8 months to 4 years. The prognostic outcome of our present case is similar to that of each of the previously reported cases. Our patient had metastatic tumours in the lymph nodes and died of disease one month after his primary operation.

Histogenesis of PMTC is still controversial. The ultimobranchial body, solid cell nest and intrathyroidal minor salivary gland are suggested to be the origins of mucinous carcinoma. Despite a lack of follicular structure and colloid substance, focal expression of thyroglobulin and TTF1 in this tumour suggests the possibility of a poorly differentiated carcinoma derived from thyroid follicular cells.

In conclusion, mucinous carcinoma is a rare and unusual tumour of the thyroid gland that can be a cause of pitfall in differential diagnosis. For diagnosis of PMTC, histological criteria, an immunohistochemical panel and complete clinical history are necessary.

References

A solitary polypoid gastric metastasis 20 years after renal cell carcinoma: an event to be considered, and a brief review of the literature

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Key words
Polypoid gastric metastasis • Renal cell carcinoma • Snare polipectomy

Summary

Background. The incidence of gastric metastasis is 2.6%. Although all primary neoplasms can metastasize to the stomach, most originate from melanoma or breast and lung cancer. Their most common endoscopic appearance is a “volcano-like” polypoid mass covered by normal mucosa that may show a central ulceration. Renal cell carcinoma, clear cell type, is known to spread hematogenously, and isolated metastasis to the stomach is a rare event.

Case presentation. In this report, we describe a gastric recurrence of RCC, clear-cell type, in a 80-year-old patient who had undergone nephrectomy 20 years before. We also performed a brief review of the literature to update the number of cases described to date.

Conclusion. Metastatic involvement of the stomach should be suspected in any patient with a previous history of renal cell carcinoma, clear cell type, presenting with gastrointestinal symptoms, even if many years after nephrectomy. The peculiarity of our case is due to the very late presentation of the gastric metastasis. Only two cases of very late gastric metastases from RCC, clear cell type, have been described in the literature, todate.

Case report

An 82-year-old man was admitted to the hospital of Garbagnate Milanese with a persistent rectal bleeding. On admission severe anaemia was present. He had a history of weight loss, epigastric pain and weakness. On physical examination neither rebound tenderness nor a palpable mass was observed. Laboratory tests revealed only a low haemoglobin value of 7 g/dl (reference range: 10-14 g/dl). Urine analysis did not reveal the presence of red blood cells. Because of the symptoms and signs, the patient underwent colonoscopy and gastroscopy. Colonoscopy was negative while gastroscopy revealed a 30 mm, irregular, polypoid bleeding lesion with superficial erosions in the upper part of the fundus near the lesser curvature (Fig. 1a). The lesion was removed by snare polipectomy, since the endoscopist did not suspect its histological nature, and to prevent post-polipectomcy bleeding. The excision biopsy was fixed in formalin, paraffin-embedded and stained with haematoxilin and eosin. Microscopically, the

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Primary mucinous carcinoma of the thyroid gland

The polypoid lesion, covered by gastric mucosa, revealed nests of neoplastic cells with a solid pattern of growth (Fig. 1b). The neoplastic population was represented by cells with abundant clear cytoplasm and nuclei were round, hyperchromatic with prominent nucleoli (Fig. 1c). Firstly, in the absence of clinical information, cytokeratin-7, cytokeratin-20, CDX2 and TTF-1 immunostaining were performed to exclude/confirm a gastric origin, and were all negative. Subsequently, clinicians informed us that the patient had a past medical history of left nephrectomy for a RCC, clear cell type, in 1992. A second set of antibodies was tested [CD10, CAM 5.2, epithelial membrane antigen (EMA), vimentin] on the basis of updated clinical information. The neoplastic cells strongly stained with CD10 (Fig. 1d), CAM 5.2, EMA and vimentin. On the basis of the clinical and immunohistochemical data, the diagnosis was consistent with gastric metastasis from clear cell type RCC. Endoscopic margins were free of disease. Computed tomography scan whole body showed no evidence of other metastatic sites.

**Conclusions**

RCC, clear cell type, accounts for 3% of all adult malignancies, and is more than twice as common in males than females with the majority of cases occurring in the sixth decade of life \(^1\)\(^2\). Although the localizing findings of haematuria, pain and a flank mass are the classic triad of presenting symptoms, many patients with renal cell carcinoma lack any of these and have systemic symptoms such as fever, malaise or anaemia. Metastases at the time of diagnosis occur in 25-33% of patients since this neoplasm frequently presents as a metastasis of unknown origin, sometimes in unusual sites \(^3\). The extent of spread of RCC, clear cell type, is notoriously unpredictable with well-documented cases of spontaneous regression of metastases, prolonged course and recurrence 10 years or more after nephrectomy in more than 10% of surviving patients. Gastric metastases from RCC, clear cell type, following radical excision of the primary tumour is extremely rare \(^4\). They may be single or multiple, grossly polypoid or plaque-like, appearing as a submucosal lesion, gradu-
ally ulcerating the mucosa. Immunohistochemical evaluation is mandatory due to the clear appearance of neoplastic cells in the context of gastric mucosa. The most common presenting symptom is abdominal pain, although nausea, vomiting and gastrointestinal bleeding can also be present. Gastrointestinal bleeding is mainly related to acid erosion of the metastatic lesion. Diagnosis is confirmed by upper gastrointestinal endoscopy and histological examination of the lesion. Despite the strong potential for hematogenous metastases of RCC, clear cell type, and due to its rarity, stomach metastases are often not suspected as a cause of gastrointestinal bleeding. This case highlights the importance of clinical information to better treat patients with metastases. Investigation for such metastatic tumours should be performed routinely in the follow-up of patients who have been treated for RCC, clear cell type. To date about 53 cases of gastric metastases from RCC, including the present one, have been reported (obtained by systemic review of publications, including patients with metastasis identified on autopsy). Eslick et al. reported that in their series females are younger than males, and overall patient age is younger than that previously reported in other case series (66 vs. 73 years). Moreover, they argue that on average there is a long interval between nephrectomy and presentation of gastric metastases. They confirmed, as Greendyke et al. stated, that in 25% of new patients with renal cell carcinoma there is radiologic evidence of metastases at presentation. Surgical excision of gastric metastasis is mandatory as these lesions can bleed again after endoscopic coagulation treatment. An isolated metastasis should be treated as a new tumour. This often results in a significantly increased survival with a good quality of life. The peculiarity of our case is due to the very late presentation of the gastric metastasis. Actually, only two cases of very late gastric metastases from RCC, clear cell type, have been described in the literature.

<table>
<thead>
<tr>
<th>References</th>
<th>Age/Gender</th>
<th>Symptoms/Signs</th>
<th>Histological type</th>
<th>Period (years)</th>
<th>Surgery</th>
<th>Outcome</th>
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<td>69/M</td>
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<td>65/M</td>
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<td>RCC</td>
<td>9</td>
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<td>Gastrectomy</td>
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<td>Anemia, epigastric pain</td>
<td>RCC 9.3</td>
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<td>Maeda et al (2009)</td>
<td>49/M</td>
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<td>Mi-Young Kim et al (2012)</td>
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<td>No tumour recurrence at 6 months</td>
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<td>RCC 20</td>
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RCC: Renal Cell Carcinoma clear type; GI: Gastrointestinal; M: Male; F: Female; ?: Data not found.
characteristics of the reported cases, including our, are summarized in Table I. Moreover, our case demonstrates the importance of dialogue between clinicians and pathologists to obtain a rapid and accurate diagnosis of lesions which are histopathologically unlikely to be primary in origin, despite a usual presentation (a gastric fundic polyp). Although the nature of polypoid mass was unknown, the choice of the endoscopic polypectomy seemed to be the best because it helped us to obtain a correct histological and immunohistochemical diagnosis. Correct diagnosis was useful to avoid total gastrectomy (surgical stress) in an older patient, thus preventing worsening of patient’s quality of life. Moreover, our case underlies the importance, in patients with a past history of RCC, clear cell type, of accurate follow-up of the gastrointestinal tract, even many years after nephrectomy for RCC.

References


Coexistence of xanthogranulomatous cholecystitis and gallbladder adenocarcinoma: a fortuitous association?

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Key words
Gallbladder • Carcinoma • Xanthogranulomatous cholecystitis • Surgery

Introduction
Xanthogranulomatous cholecystitis (XGC) is an unusual focal or diffuse destructive inflammatory process of the gallbladder, representing between 0.7 and 13.2% of all gallbladder diseases. The malignant potential of XGC is controversial and the relationship between XGC and gallbladder carcinoma (GBC) is unclear. The coexistence of XGC and GBC is very infrequent and has been reported in 0.2% to 35.4% of cases. Herein, the authors report a new case of xanthogranulomatous cholecystitis concomitant with gallbladder adenocarcinoma in a 65-year-old female patient. Because of its overlapping clinical, radiological and macroscopic findings with gallbladder cancer, definitive diagnosis of xanthogranulomatous cholecystitis relies on extensive sampling and thorough microscopic examination of the surgical specimen to exclude the possibility of coexisting tumour. It is still a matter of debate whether xanthogranulomatous cholecystitis is truly a precursor of gallbladder carcinoma or if it is just an incidental finding. This aspect needs to be explored in the future with further studies.

Clinical history
A 65-year-old female patient with a medical history of hypertension and diabetes was admitted for repeated attacks of right hypochondriac pain and vomiting of 12 days duration. Upon admission, the patient's temperature was 38°C. On physical examination, palpation of the abdomen revealed tenderness in the right upper quadrant and a palpable mass in gallbladder region. In addition, Murphy’s sign was positive. Laboratory findings were within normal range. Abdominal ultrasonographic examination showed multiple gallstones with evidence of gallbladder wall thickening and hydrops. CT scan of the abdomen demonstrated multiple thickenings of the gallbladder wall with intramural hypoattenuated nodules. At the neck of the gallbladder, a focal irregular thickening of the wall was also noted. The gallbladder was excised by laparoscopic cholecystectomy. Macroscopically, the gallbladder specimen measured 11 x 5 cm. The cut section of the gallbladder showed gallstones with a markedly thickened wall and a 2.3 cm protruding lesion in the infundibulum of the gallbladder (Fig. 1a-b). Histological examination of the gallbladder revealed focal ulceration of the mucosa with severe chronic inflammation of the lamina propria and submucosa, associated with mild fibrosis and muscular hypertrophy. Numerous foamy macrophages and scattered multinucleated giant cells were also present, along with occasional cholesterol clefts (Fig. 2a-b). The protruding lesion in the gallbladder infundibulum corresponded to a well differentiated adenocarcinoma that extended to the perimuscular connective tissue on the background of a moderate desmoplastic reaction (Fig. 3a). The tubular glands were lined by cuboidal to tall columnar mild atypical cells resembling biliary epithelium (Fig. 3b). Postoperative course was unremarkable. A present, the patient is still being followed.
Discussion

Xanthogranulomatous cholecystitis is a relatively uncommon form of chronic cholecystitis characterized by a focal or diffuse destructive inflammatory process, with varying proportions of fibrous tissue, acute and chronic inflammatory cells and accumulation of lipid-laden macrophages in areas of inflammation. It often mimics a gallbladder carcinoma, leading to a diagnostic dilemma. Pre- and intra-operatively, it is difficult to diagnose this entity and the final diagnosis is usually based on histological examination of the resected specimen. The malignant potential of XGC is controversial and highly disputed. Several inflammatory conditions have neoplastic potential on long-term follow-up. For example, ulcerative colitis has shown evidence of such neoplastic potential; foci of dysplasia and malignancy arising in this background are well documented. Such evidence is not available for XGC. A recent study supports the inflammatory nature of XGC, but does not show any evidence of a premalignant condition. The association of XGC and GBC remains a matter of discussion. According to some authors, it may simply be that XGC and adenocarcinoma are both complications of cholelithiasis and cholecystitis of a particular duration or degree, or that tissue disruption by a carcinoma facilitates the entry of bile in the stroma.

As in the present case, obstruction of the cystic duct by a neoplasm may also initiate the histiocytic inflammatory process of XGC. The association between XGC and gallbladder cancer has been shown in the literature in small case series and some single case reports. An Indian study reported that only 0.2% of patients with XGC have associated GBC. On the other hand, in an American study, among 40 cases of XGC, five (12.5%) also had GBC. In the United Kingdom, a study of 31 patients with XGC revealed carcinoma in three (9.7%) patients. In a Japanese study, XGC was associated with carcinoma in five cases (3%) among a total of 182 cases of XGC. According to the authors of that study, the inflammatory reaction followed by an associated immunologic cellular response may produce the appearance of cellular changes that degenerate into carcinoma. The possible association of XGC and GBC carries a
potential risk of diagnostic confusion. In fact, pathologists might fail to notice the presence of GBC when it is associated with florid XGC. Furthermore, the existence of florid XGC may lead to errors in determining the exact stage of the malignant spread of GBC as macrophages can be confused with tumour cells. Fine needle aspiration cytology from the gallbladder mass lesions was used in differential diagnosis and found to have an important role in making a preoperative diagnosis of XGC and malignancy. Because of its overlapping clinical, radiological and macroscopic findings with GBC, definitive diagnosis of XGC relies on extensive sampling and thorough microscopic examination of the surgical specimen to exclude the possibility of coexisting tumour. Although rare, it is important to be aware of the possible coexistence of XGC and GBC. At present, it is a matter of debate whether XGC are truly precursors of GBC or if they are merely an incidental finding. This aspect needs to be explored in the future with further studies.

References

Fibroepithelioma of Pinkus is a rare cutaneous tumour. Its classification is controversial and is considered as a variant of either basal cell carcinoma or trichoblastoma. Its presentation as a multiple tumour is rare. We are reporting such a case occurring in a 55-year-old man presenting with multiple seborrheic keratosis-like lesions corresponding histologically to Pinkus tumours. The clinical diagnosis of Pinkus tumour represents a challenge. Histological examination is extremely useful in aiding in the diagnosis of difficult cases.

**Case report**

A 55-year-old man presented to our clinic complaining of multiple small, blackish, nodular lesions clinically suggestive of multiple seborrheic keratoses. A biopsy of one of these lesions was taken.

Histological examination showed an epithelial proliferation arising from the epidermis, composed of thin, branched and anastomosing trabeculae of basaloid cells. The stroma was fibrous (Figs. 1, 2). A diagnosis of fibroepithelial tumour of Pinkus was made.

**Comment**

Fibroepithelioma of Pinkus (FEP) was first described by Herman Pinkus in 1953 as ‘premalignant fibroepithelial tumor of the skin’. Later, it has been considered to be an unusual subtype of basal cell carcinoma (BCC). Other authors have suggested that FEP is a variant of trichoblastoma.

Like BCC, FEP is more frequent in lighter skin types and relatively rare in dark skin types; unlike it, there is no predilection for sun-exposed sites. Prior radiotherapy is a predisposing factor. FEP develops, typically, in persons aged between 40 and 60 years. A few pediatric cases have been reported. Clinically, FEP presents as a skin-colored, pink, red or brown nodule or plaque, with occasional ulceration. They usually are located on the trunk or extremities. However, lesions occurring on the head, abdomen, anus, penis, scrotum and breasts have been reported. Multiple lesions are rare. In fact, only 10 cases of multiple FEP have been described; 9 of these were associated with BCC and previous radiotherapy, demonstrating the role of radiation damage in the onset of disease. Clinical features of FEP can mimic many lesions such as seborrheic keratoses (as in our case), pedunculated fibroma, nevus sebaceous of Jadassohn, papillomatous melanocytic nevus, amelanotic melanoma and neurofibroma. Dermoscopy shows fine arborizing vessels that may be associated with dotted vessels and white streaks.

Diagnosis relies on histological examination that shows that the tumour is superficial and well demarcated at its lower border. It consists of basaloid epithelial, long and thin strands, arising from the epidermis and anastomosing to create a fenestrating pattern. They surround a loose fibrovascular stroma. Nuclear pleomorphism may be present, and staining with Ki-67 shows an increased proliferative index. Merkel cells are quite prominent and their staining by androgen receptor and cytokeratin 20 may aid in diagnosis of FEP. Cyst formation and small follicle-like bulbs may be additional features.

The main differential diagnoses of FEP are BCC, trichoepithelioma and trichoepithelioma. The histological appearance of the tumour is often distinctive. FEP has a
Pinkus tumour: an unusual case

strong histologic resemblance to reticulated seborrhoeic keratosis, but typical horn and pseudohorn pearls are absent and hyperkeratosis is rare. FEP has an indolent behaviour with no metastatic potential. Its treatment is typically surgical including complete excision, electrodessication followed by curettage and Moh’s micrographic surgery. Rarely, intralesional or topical chemotherapy may be useful.

References

Mammary myofibroblastoma with leiomyomatous differentiation: case report and literature review

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Key words
Breast • Myofibroblastoma • Smooth muscle cells • H-caldesmon

Introduction. Myofibroblastoma of the breast (MFB) is an unusual benign tumour that belongs to the family of benign spindle cell tumours of the mammary stroma. The detection of smooth muscle cells in MFB is explained by its histogenesis from CD34+ fibroblasts of mammary stroma capable of multidirectional mesenchymal differentiation, including smooth muscle.

Aims. The purpose of this case is to highlight characteristics of this rare neoplasm. Immunohistochemical features, in MFB with predominant leiomyomatous differentiation, are provided to offer a practical approach to a correct diagnosis.

Case report. We report a right MFB in a 60-year-old male. The tumour was unusual due to its morphological features, with predominant leiomyomatous differentiation. Immunohistochemical findings, based on the negativity of h-caldesmon, helped in reaching a diagnosis.

Conclusion. The detection of leiomyomatous rather than myofibrolastic features in MFB may reflect only the predominant cell types of examined area, and this is not necessarily representative of the remaining tumour which may have a different basic cellular composition. Immunohistochemical expression of h-caldesmon is a reliable marker in distinguishing smooth muscle versus myofibrolastic cellular differentiation in spindle cells lesions of the breast.
histological examination, the tumour was cellular and vaguely nodular with an abundant leiomyomatous appearance (Fig. 1b). The muscular cells were arranged in ill-defined fascicles, haphazardly intermingled with bland-looking, slender, spindle-shaped cells, closely packed in short fascicles or clusters of cohesive cells, interrupted by thick, hyalinised collagen bundles. The latter cells have a varied appearance ranging from fibroblastic-like cells with scanty cytoplasm and elongated nuclei to cells with myoid features consisting of abundant palely cytoplasm. The tumour cells were monomorphic without atypia and mitotic activity (Fig. 1c). There were no areas of necrosis or hemorrhage. The lesion contained scattered islands of adipose tissue or separate adipocytes (Fig. 1d). In the tumour stroma, there were numerous mast cells without lymphoplasmacytic infiltrate. The tumour was well circumscribed and had no infiltration to the adjacent breast tissue. The resection margin was free of tumour. Immunohistochemistry revealed a strongly positive reaction of the leiomyomatous component for actin, desmin and h-caldesmon (Fig. 2a). The second component was positive for vimentin, desmin, CD34 (Fig. 2b) and CD10, while S100 protein (Fig. 2c), h-caldesmon (Fig. 2d), cytokeratins, EMA, CD117 and HMB-45 were negative. The present findings were consistent with a diagnosis of MFB with abundant mature leiomyomatous, heterologous component. The patient made an uneventful recovery and 18 months later remains well with no evidence of recurrence.

Discussion

MFB is an unusual benign tumour that belongs to the family of benign spindle cell tumours of the mammary stroma. The name MFB reflects its cellular composition, comprising neoplastic cells showing a variable fibroblastic differentiation at morphologic, immunohistochemical and ultrastructural levels. The first cases of a benign spindle cell stromal tumour of the breast were reported by Toker et al. in 1981. The term MFB of the breast was first coined by Wargotz et al. in 1987. This tumour is an extremely rare lesion with less than 70 cases reported in literature. Reported cases of MFB...
occur most often in older men aged 40-87 years. Several cases have also been documented in females, suggesting that it can occur in both sexes. It is likely that the increased incidence of MFB reported in women in the last 2 decades could be due to increased mammographic screening. There are no reported cases that indicate relation to gender, race, medical conditions, use of medication or other effects of growth factors. The usual clinical presentation is a unilateral painless lump, not adherent to overlying or underlying structures. Bilaterality and unilateral multicentricity are rare. Radiologically, they are homogenous, lobulated and well circumscribed lesions, typically lacking microcalcification. Ultrasonographic findings cannot often differentiate it from fibroadenoma.

Tumour size ranges from a few mm to 11 cm. By gross examination, MFB is generally a well-circumscribed, firm and rubbery, unencapsulated, round to oval mass. The cut surface usually reveals a solid lesion, with a smooth or lobulated external surface, pale white to greyish, with a variably whorling appearance. In some cases, the cut surface of the tumour may show focal to extensive mucoid- or lipomatous-appearing areas. Cystic degeneration, necrosis and haemorrhage are not features of MFB.

Histopathologically, the classic type MFB is an unencapsulated tumour composed of uniform, bland looking spindle cells haphazardly arranged in short fascicles, separated by thick bands of hyalinized collagen bundles and devoid of mammary ducts and lobules. The spindle cells have abundant eosinophilic cytoplasm, round or oval nucleus with 1-2 small nucleoli. Mitotic activity is absent or rare when present (≤ 2/10 HPF). Prominent mast cells can be seen in tumour stroma, but lymphoplasmacytic infiltration is almost always absent. The morphologic spectrum of MFB has been expanded by the recognition of several morphologic variants, such as the cellular, infiltrative, epithelioid, deciduoid-like, lipomatous, collagenized/fibrous and myxoid variants. Other unusual morphologic features have been described such as the presence of atypical cells, multinucleated Floret-like cells, haemangiopericytoma-like pattern and heterologous components. These latter characteristics have been described as foci of heterologous mesenchymal components, apart from adipose tissue, such as mature leiomyomatous, osseous or...
PULMONARY LYMPHOMATOID GRANULOMATOSIS

References