AMR Seminar #67

Case – 1

Contributed by: Abbas Agaimy

Clinical history: A 35-year-old woman underwent resection of a uterine mass attached to the uterine wall, clinically consistent with subserosal leiomyoma. There is no other remarkable clinical finding and additional investigations are still ongoing (case diagnosed mid-December, 2014).

Macroscopic features: The specimen was submitted as numerous tissue fragments together measuring > 5 cm and weighing 137 gram. The cut-surface was whitish to brown-yellowish and whorled. Consistency was firm to soft in some areas.

Histological & immunohistochemical findings: Histologically, the tumor showed generally a high cellularity and a remarkably eosinophilic (pink) appearance at low power. While in many areas the tumor was not different from a highly cellular spindle cell smooth muscle tumor of the uterus (Fig. A), there existed several unusual histological features: presence of staghorn vessels (Fig. B), presence of eosinophilic cytoplasmic globules that strikingly mimicked a skeletal muscle appearance (Fig. C), scattered large cells with lobulated multiple nuclei with atypia (Fig. D), foci with rhabdoid-like cytoplasmic inclusions or plasmacytoid (hyaline) cells (Fig. D) and frequent occurrence of nuclei with marginated chromatin, central eosinophilic macronucleoli and perinucleolar halo very reminiscent of the HLRCC renal cancer (Fig. C,D). Irrespective of the atypical features necrosis and significant mitotic activity were absent. Immunohistochemisty showed strong expression of the smooth muscle markers desmin and h-caldesmon, but absence of HMB45. Desmin highlighted the skeletal-like pink globules (Fig. E). Based on the nuclear and overall features, the tumor was stained for fumarate hydratase (FH) and showed complete loss of staining in the tumor cells with retained staining in the vessels (Fig. F). Genetic counseling was recommended and molecular analysis of the FH gene postponed after genetic counseling which is not concluded yet.

Diagnosis: Fumarate hydratase (FH)-deficient uterine smooth muscle neoplasm, highly suspicious for HLRCC.

Comment: HLRCC (synonym: Reed syndrome) is a rare autosomal dominant disease caused by heterozygous inactivating germline mutations in the FH gene, a component enzyme of the Krebs cycle mapping to chromosome 1q42-43. Affected individuals are prone to development very frequently cutaneous leiomyomas, uterine leiomyomata (up to 77% of affected women) and aggressive RCC (up to one third of affected individuals). To date, suspicion or detection of the condition mainly relies on the presence of specific pathomorphological features of the individual tumors, particularly in RCC which usually show in addition to variable papillary growth pattern (thus frequently misdiagnosed as papillary RCC type 2) nuclei with eosinophilic macronucleoli surrounded by a halo as a consequence of significant chromatin margination. Thus in the absence of remarkable cutaneous manifestation, the uterine leiomyoma and RCC can easily be overlooked as related to HLRCC if the pathologist is not aware of the distinctive features of this disease. To date, only very few papers exist on uterine smooth muscle tumors related to HLRCC. Santz-Ortega et al reviewed the clinicopathologic and genotypic characteristics of uterine leiomyomata in 19 women with HLRCC. Patients with uterine leiomyomata and FH mutations were younger (range, 24-47; median, 32; mean, 38 y) and tumors are usually multiple measuring up to 8 cm. Increased cellularity, presence of multinucleated giant cells and atypia were reported as consistent findings. Importantly, most tumors showed morphologic nuclear features similar to those reported in the aggressive RCC in this disease setting, that is nuclei with eosinophilic macronucleoli surrounded by a halo as a consequence of significant chromatin margination. This finding

varies greatly within the tumor and can be focal. Loss of heterozygosity (LOH) at 1q43 was detected as a second hit in 8/10 cases. Most case (13/19) qualified as atypical and 6 as cellular leiomyomata. Mitoses were uncommon and none qualified as malignant on histological basis. History of RCC was found in 5 cases. Another more recent study by Reyes reported 9 cases and added other histological features: higher fibrillarity compared to adjacent normal myometrium, presence of pink globules, presence of staghorn vasculature, epithelioid nuclear appearance and neurilemoma-like pattern. FH deficiency interferes with normal conversion of fumarate to malate leading to abnormal accumulation of fumarate which ultimately lead to formation of 2-succino-cysteine by a process named aberrant succination. This makes 2sc IHC a promising tool for identifying the disease. In the study by Reyes et al, all uterine lesions stained strongly with 2-succino-cysteine (2sc) antibody similar to the RCC in the setting of HLRCC. In my experience however, the FH IHC is rather more easy to perform and to assess. A recent study by the group of Dr. Mentzel showed loss of FH in almost all HLRCC associated cutaneous leiomyomas in contrast to other leiomyomatous lesions of skin and leiomyosarcomas. As of now, I am not aware of a study evaluating FH IHC in uterine smooth muscle tumors (admittedly, I might have missed some papers).

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AMR Seminar #67

Case – 2

Contributed by: Gerald Berry

Clinical History: This 61-year-old man presented with a retroperitoneal mass in 2010 and was diagnosed with CLL following a CT-guided biopsy and subsequent bone marrow biopsy. He declined therapy and remained relatively asymptomatic until late 2013 when he developed fevers, night sweats and shortness of breath. Diagnostic testing at that time including bone marrow biopsy, peripheral blood and FNA of a palpable lymph node all showed CLL and absence of transformation. He presented in January 2014 with upper GI bleeding and endoscopy showed gastric ulcers. He was started on chemotherapy with Rituxan and bendamustine and completed 8 cycles. His adenopathy diminished but an 11-12 cm lesser curvature gastric mass persisted. He underwent total gastrectomy with retrocolic Roux-en-Y esophagojejunostomy in September 2014. He is currently well with NED.

Pathology Findings: The gastrectomy specimen exhibited a 12x13x5 cm solid and cystic appearing mass along the lesser curvature of the stomach. Upon opening the stomach multiple polypoid masses we seen on the mucosal surface measuring up to 8x5x1 cm in greatest dimension. No nodules were seen in the omentum. Microscopic examination showed a spindle/ovoid cell neoplasm arranged in a multinodular fibromyxoid stromal background. A delicate arborizing vascular stromal was apparent. Pleomorphism, mitotic activity and necrosis were absent. The neoplastic elements were found throughout the gastric layers with subserosal nodules. The neoplastic cells reacted against smooth muscle actin and showed focal positivity for desmin but were negative for CD117, DOG1, S100, and a variety of low and high molecular weight cytokeratins.

Diagnosis: Plexiform fibromyxoma of the stomach.

Comment: I know that this lesion has been previously submitted to the group but I thought the gross image was too good to pass up!! The term “plexiform fibromyxoma” was coined Miettinen et al in 2009 for this uncommon but distinctive appearing benign mesenchymal gastric neoplasm that appears to arise in the gastric antrum. Other terms in the literature include “fibromyxomas”, “myxomas”, and “plexiform angiomatoid myofibroblastic tumors”. Its histologic appearance and immunophenotype are different from the more common GIST, Schwannoma and smooth muscle tumor of the stomach. In their paper Miettinen states, “there are more than 150 GISTs of the stomach for every case of plexiform fibromyxoma”. Importantly, despite the gross appearance, they are benign in behavior (3 of the reported patients were NED at 18.4, 19.7 and 19.9 years).

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AMR Seminar #67

Case – 3

Contributed by: Ira Bleiweiss

Clinical History: A 59 year old woman presented with a large mass in the right axilla. The mass was excised.

Pathologic Findings: Obviously this is a lymph node and it is extensively replaced by metastatic poorly differentiated carcinoma with some vague papillary areas, some rare foci of central necrosis (a-la comedo-carcinoma) and numerous psamomma bodies, particularly in peripheral sinuses. Of course in any case of axillary node presentation of metastatic carcinoma, one's first thought is an occult breast primary. In my experience, although of course possible, psamomma bodies are actually pretty rare in metastatic breast carcinoma. Needless to say the ipsilateral breast (in fact the contralateral one too) was worked up and was negative.

So….on to the immunohistochemical workup(s): We first received the case with IHC slides which had been performed in an outside institution using Bouin's solution as a fixative for the tissue in that particular block Those IHC slides were: CK7 positive, CK20 negative, ER positive in a few cells, PR negative, Her2 negative. Based on that and location, the original pathologist presumed that the lesion represented metastatic breast carcinoma.

Since we did not know the immunoreactivity for several antigens of interest, we requested a block of tumor which held tissue fixed in formalin and did further IHC resulting in: ER 75% strongly positive, PR negative, Her-2 negative, and WT-1 strongly positive in all cells. Additional negative stains: breast antigen (GDFP-15), mammoglobin, TTF-1, and thyroglobulin. Therefore we felt this was likely to be of gynecologic origin, such as ovarian, primary peritoneal, or uterine papillary serous.

Within 2 weeks the patient had surgery (TAH/BSO) and had an identical primary tumor in the left Fallopian tube (limited to the tube) and endometriosis as a bonus.

The patient received taxol and carboplatinum and is now alive and without evidence of disease four years after her original diagnosis.

Diagnosis: Metastatic Fallopian tube papillary serous carcinoma with psamomma bodies presenting in contralateral axillary lymph node.

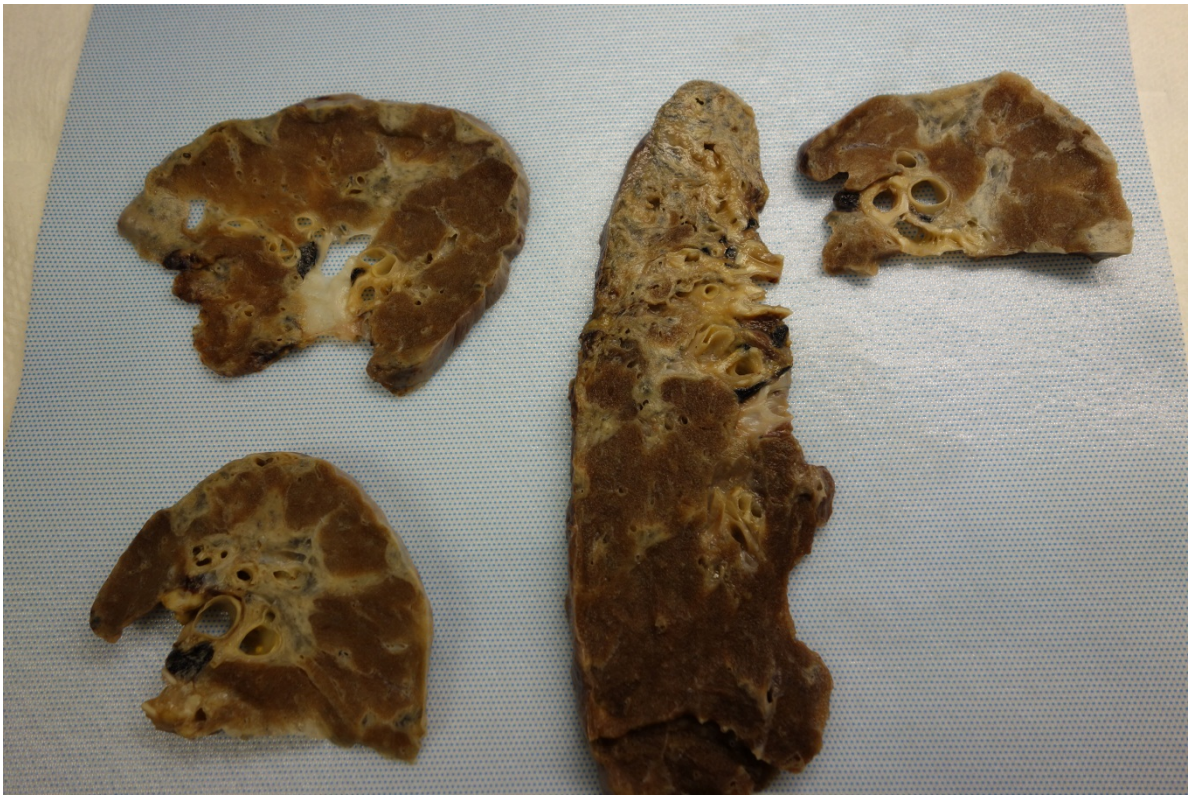
Comment: Not a fancy, tough diagnosis, but not what you expect in an axillary lymph node. Most non-breast metastases in axillary nodes are melanoma of course. I have also seen lung, ovary, and endometrial, but typically in patients with known primaries in those foci.

AMR Seminar #67

Case – 4

Contributed by: Thomas Colby

Case History: (TV13-335) A 62-year-old woman underwent bilateral lung transplant for progressive interstitial lung disease. The patient was said to have had a "long and indolent course with recent decline in pulmonary function leading to transplantation." I don't have specific details but I suspect her history spanned at least 5 to 10 years or more. Radiologically the infiltrates were primarily upper lobe and showed a subpleural predominance similar to that seen in the gross photo of this case below (tissue courtesy Dr. John English in Vancouver).



Histologic Findings: The explants showed a distinctive elastotic fibrosis that appeared to extend from the pleural and subpleural regions into the parenchyma and surrounded some of the bronchovascular bundles. Rare fibroblast foci are present but there is relatively little inflammation and the intervening lung tissue is relatively spared. What this disease looks like is apical cap gone wild.

Diagnosis: The histologic, radiologic, and gross findings are all characteristic of **pleuroparenchymal fibroelastosis (PPFE).**

Comment: Pleuroparenchymal fibroelastosis is one of the new kids on the interstitial lung disease block and included in the recent update on idiopathic interstitial pneumonias (Am J Respir Crit Care Med. 2013 Sep 15;188(6):733-48). PPFE is encountered as an idiopathic process or is encountered in individuals who have had lung transplants (as a cause of chronic restrictive allograft dysfunction) and in patients who have received bone marrow transplants. Drugs have also been implicated as an etiology and it is possible that some of the post bone marrow transplant cases actually represent drug reactions rather than being specifically related to the bone marrow transplant.

While relatively recently recognized in the English literature, PPFE was previously described as “upper lobe fibrosis” in the Japanese literature and actually had been given the name Amitani’s disease for the author who initially described it.

ALL YOU REALLY WANT TO KNOW ON PPFE, INCLUDING NICE PICTURES AND AN EXTENSIVE REVIEW OF THE LITERATURE IS INCLUDED IN THE EDITORIAL BY CAMUS, ET AL. IN EUROPEAN RESPIRATORY JOURNAL 2014;44:289-296.

N.B. For those of you who think interstitial lung disease is a pain in the ass, you are right! “A nearly identical condition (to PPFE) has recently been described in a third of aged donkeys at necropsy.”

EDITORIAL IN
PRESS | CORRECTED PROOF

Pleuroparenchymal fibroelastosis: one more walk on the wild side of drugs?

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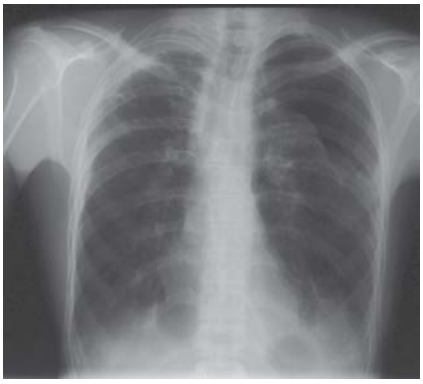
In this issue of the European Respiratory Journal, BEYNAT-MOUTERDE et al. [1] report on six young adults (three of whom were female) who developed a clinical imaging pattern of predominant upper lobe fibrosis with apical pneumothoraces (fig. 1). Presentation in all six patients was similar with cough, dyspnoea, occasional chest pain and weight loss. Imaging was distinctive and showed a cephalad, irregular, pleural-based thickening that encroached on the lung bilaterally. Five patients presented with ‘‘platythorax’’ (fig. 2), a preferential reduction in the anterio-posterior diameter of the chest wall. In all patients, severe restrictive or restrictive-obstructive lung dysfunction progressed to hypoxaemic and hypercarbic respiratory failure, which was fatal in four patients despite intensive care unit support. This outcome was all the more tragic as these four patients had survived previous malignant conditions, including haematological malignancy (n53) and brain tumour (n51).

Pathology in four patients showed a pattern consistent with pleuropulmonary fibroelastosis (PPFE). Due to similar clinical imaging presentation, two additional patients without biopsy were included in the study of BEYNAT-MOUTERDE et al. [1]. There was a history (6 months to 16 years previously) of multi-agent chemotherapy in all six patients; the alkylators cyclophosphamide (n55) and BCNU (bis-chloroethylnitrosourea; n51) were the common denominators in their treatment. BEYNAT-MOUTERDE et al. [1] raised the possibility that alkylating drugs may have triggered or caused PPFE. Issues raised by their study relate to: 1) PPFE as a clinically, radiographically and pathologically separate and recognisable entity; 2) possible aetiological factors at the origin of PPFE, including drugs; and 3) current management strategies.

PPFE (as reviewed recently [2]) is an unusual interstitial lung disease with circumscribed fibrosis of the pleura and subjacent lung, which is of interest to pathologists [3–8], pulmonologists [3, 4, 6–8] and radiologists [3–6, 8, 9]. Although elastosis has also been described in the heart and skin, it appeared to be confined clinically and on imaging to the pleura and lung in cases of PPFE. The condition does not clearly fit into any of the previously described interstitial pneumonias and, thus, is now specifically included in the classification of idiopathic interstitial pneumonias (IIP) under the heading ‘‘rare IIP’’ [2, 10]. The six patients in the study by BEYNAT-MOUTERDE et al. [1] are reminiscent of the 78 cases (59 in the English literature) of PPFE that have been published since the initial reports from Japanese investigators (to whom credit is due), under the term ‘‘upper lobe fibrosis’’ or ‘‘Amitani’s disease’’ [11–13] and by FRANKEL et al. [3]. The three largest series of PPFE included nine [14] 12 [8] and 15 [15] cases, respectively. PPFE emerges as a distinctive array of clinical, imaging and pathological abnormalities affecting the apices and lateral aspects of the lung and pleura bilaterally. The condition has a variable prognosis with substantial mortality

FIGURE 1 a) Frontal chest radiograph in a patient following chemotherapy for acute lymphoblastic leukaemia showing a typical appearance of pleuropulmonary fibroelastosis (corresponding to case 2 in [1]). Note the markedly thickened pleural dome on the right and partial spontaneous pneumothorax on the left. b) Computed tomography scan of same patient showing thickened pleura and left-sided pneumothorax.



[2, 8]. Of potential teleological interest, a nearly identical condition has recently been described in a third of aged donkeys at necropsy [16, 17]. Of note, PPFE affects the dorsal aspect of both lungs in the donkey [17,

18], which is the nondependent part of the lung in quadrupeds. However in humans PPFE affects the lung apices [18].

As the name implies, PPFE is a morphologically descriptive term denoting intense elastotic fibrosis of the visceral pleura and subjacent lung, and collagenous fibrosis abundant in haphazardly arranged elastic fibres (figs 3 and 4). Elastosis is a distinctive form of chronic scarring in the lung that differs from the common scarring seen in idiopathic pulmonary fibrosis (IPF). PPFE lungs contain twice as much elastin compared to IPF [19]. The process may extend into the septa and deeper into the lung (figs 3 and 4) [8, 20]. Elastic fibres

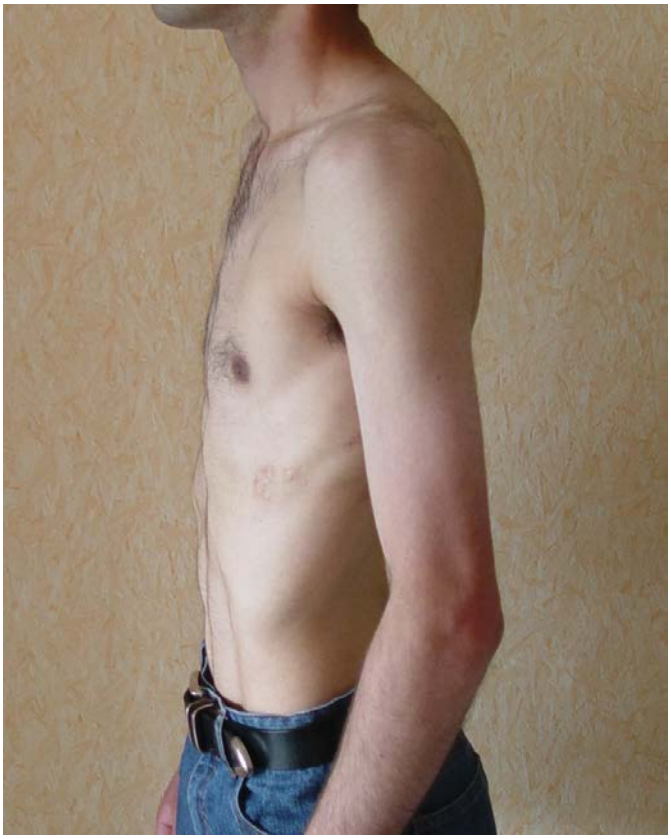
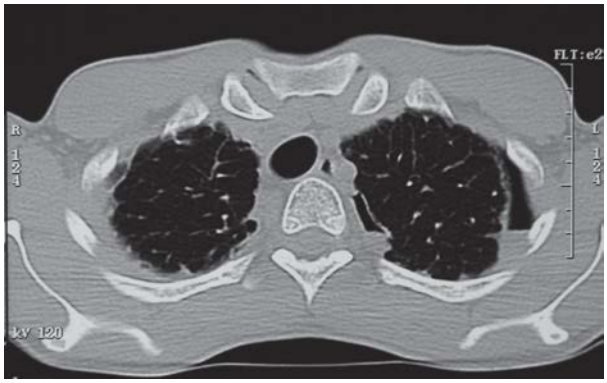


FIGURE 2 Advanced cases may show markedly restrictive physiology and reduced anterio-posterior diameter of the thorax; a trait known as platythorax.



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The Charlesworth Group, Wakefield +44(0)1924 369598 - Rev 7.51n/W (Jan 20 2003)

are best visualised using orcein or Verhoeff van Gieson elastic stain (fig. 4b). The histopathological diagnosis of PPFE can still be considered without performing the specific latter elastic fibre stains, because the features on Haematoxylin and Eosin are characteristic once one is familiar with them. On microscopy, the boundary between the pleuropulmonary fibrotic area and the relatively spared juxtaposed lung is characteristically sharp [2–4, 6–8, 21]. Associated pathological features include an absence of classic honeycombing, inconspicuous fibroblastic foci, a sparse mononuclear lymphocytic infiltrate and moderate interstitial fibrosis in the remaining lung. Diffuse alveolar damage, alveolar haemorrhage [15] and/or obliterative bronchiolitis [6, 15] may be concomitant findings in patients who have had lung or bone marrow/haematopoietic stem cell transplantation [15, 22]. As a generalisation, both the pleural surface and the underlying lung are less affected or appear normal in the lower zones. The changes on gross pathology match those on imaging (fig. 4) [8, 23, 24].

Clinically, idiopathic PPFE affects males and females equally, and preferentially nonsmokers with a proportion of patients being relatively young [2]. Compared to IPF, PPFE patients have a lower body mass index and more severe restrictive lung dysfunction [19]. Onset in childhood is associated with poorer outcome [20, 25], possibly because the restricted fibrotic pleura and lung significantly impede lung growth [20, 25]. Presenting features include chronic dull pleuritic pain with episodes of a sharper quality (which may not reflect pneumothorax in all patients), platythorax [26] (which can be measured on computed tomography (CT) or with a calliper), and small chronic spontaneous uni- or bilateral pneumothoraces [27]. On imaging, the fibrotic pleura and subjacent collapsed and fibrotic lung manifest as a dense irregular peripheral rim [1, 8]. Wedge-shaped pleural-based densities protrude along parenchymal septa toward the hila [8, 9], and the latter tend to be retracted upwards (figs 1 and 3) [24]. Calcifications have not been reported within the thickened pleura [8], which helps to separate PPFE from asbestos-induced pleural thickening; a condition that may also affect the apical pleura, although very rarely [28]. In PPFE, there are usually features of established fibrosis away from the subpleural regions in the more central parts of the upper lobes on CT [8, 24]. Although it may take years for PPFE to develop before patients become symptomatic and seek medical attention [1], some cases develop and progress rapidly. Once PPFE becomes symptomatic, patients may remain stable for a long period of time or progress inexorably to hypercarbic respiratory failure. Then, outcome is poor despite ventilatory support with a 40–66% mortality rate in a few years with or without an identifiable abrupt exacerbation [1, 2, 6, 8, 25, 29]. Spontaneous partial, apical, uni- or bilateral pneumothorax is a marker of abnormality for PPFE, and is present at some point in ~30% of overall patients [2, 30]. This complication was seen in five out of the six patients in the study by BEYNAT-MOUTERDE et al. [1]. Some pneumothoraces are small and may be simply observed [9]. Suggested mechanisms leading to pneumothoraces include cysts present in the apical fibrotic area, altered resistance of the pleura to shear stress, parenchymal bullae in the lung transplant recipient and air trapping upstream to obliterative bronchiolitis. Pneumothoraces rarely absorb spontaneously, and persistent air leak and poor re-expansion of the underlying lung are common [2]. Lung or pleural biopsy must be avoided. Many consider it unnecessary in cases that fit clinically and radiologically for PPFE. In addition, post-operative iatrogenic pneumothorax commonly complicates the procedure [1, 8]. To the extent that the biopsy will provide more than a mere academic diagnosis, it should be considered solely as a companion procedure if surgical cure of pneumothorax is contemplated. While a definitive diagnosis of PPFE traditionally requires histological examination of the pleuropulmonary interface, a sizeable number of the patients will not undergo the procedure. The reasons for refraining from doing so include: very advanced disease; poor ventilatory reserve; lack of perceived benefit as no treatment is available for the condition, especially nowadays; and the fact that the disease can be strongly suspected on clinical and radiological grounds. For those cases where no biopsy is available, a label of ''consistent with PPFE'' has been proposed [2, 8], with the acronym PPFE being reserved for pathologically documented cases [8]. A study in donkeys has shown the potential merit of chest ultrasonography as a noninvasive test to diagnose PPFE (table 1) [17]. Since the disease has now been well defined, it is likely that more and more patients will be diagnosed with PPFE noninvasively.

However suggestive the clinical and imaging presentation of PPFE is, other aetiologies of pleural thickening should be considered [31, 32], including: tuberculosis and tuberculosis pneumothorax treatment; aspergillosis [1, 33], although aspergillosis may complicate the course of established PPFE [33]; other infections; connective tissue disease with rheumatoid arthritis lupus and ankylosing spondylitis [31]; ulcerative colitis [26]; haemothorax; a history of coronary artery bypass graft [34]; exposure to asbestos [35]; and rare or orphan pleural disease [32]. In most of these conditions, pleural thickening has a predilection to involve the lung bases or to predominate on one side, as opposed to PPFE. The differential diagnosis is usually resolved by: reviewing earlier imaging; searching for extrathoracic involvement that is typically absent in PPFE; appropriate laboratory tests for tuberculosis, aspergillosis, other infections and connective tissue diseases; and mineral dust study of bronchoalveolar lavage fluid. Asbestos pleural

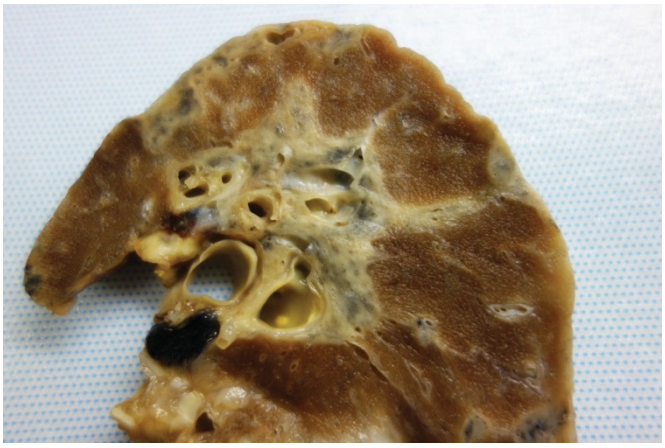


FIGURE 3 Gross pathology of the lung showing grey elastotic fibrosis in the subpleural regions and around the bronchovascular bundles.

thickening is typically more prominent in the parietal pleura and shows the histological characteristic basket-weave collagenous appearance without any admixture of elastotic and fibrotic tissue [36].

The apical cap is a well-known, generally idiopathic lesion of the lung apices that is preferentially found in males of older age [37–39]. The apical cap is in the form of a subpleural pyramidal or spiculated scar spanning 0.7 to 5.2 cm in diameter. Apical caps can be large and simulate a neoplasm [37], but they do not involve the pleura circumferentially like PPFE. On pathological investigation, the cap also corresponds to dense collagen and curls or folded elastic fibres [37–39]. Time may tell whether the apical cap and PPFE share more than morphologic similarity.

Regarding aetiology, the majority of PPFE cases (~ 50%) have been reported as a late complication of bone marrow/haematopoietic stem cell [2, 6] and lung transplantation [2, 6, 40], for which the terms ‘‘upper lobe fibrosis’’ [29, 40] and ‘‘chronic lung allograft dysfunction’’ [41] have been applied. The prevalence of PPFE in lung transplant recipients may be as high as 2% [29]. Rare familial occurrences of consistent with bona fide PPFE have been described in young individuals, mostly females [3, 42]. 10% of PPFE cases developed in patients previously exposed to chemotherapeutic agents, sometimes many years after management of the primary disease [1, 2, 20, 25, 43].

Drugs are a cause célèbre of respiratory injury [44]. Pleural reactions have been known to be a result of respiratory injury since the 1960s [45, 46], accounting for 7% of all respiratory reactions to drugs [44]. Pleural reactions include an effusion with or without pleural eosinophilia, antinuclear-antibody positive effusion (the lupus syndrome), haemothorax, acute pleuritis and pleural thickening [44]. Reactions to ergots (e.g. bromocritptine, ergotamine, lisuride, and methysergide) may result in pleural effusion and/or pleural and pericardial thickening or fibrosis [44, 46, 47]. Individuals with a history of exposure to asbestos may be at a higher risk of developing pleural thickening if exposed to ergot drugs [48, 49]. However, ergot- induced pleural disease differs from PPFE in that pleural thickening usually localises at the lung bases and develops during therapy with the agent; although the pleura rarely returns to a normal state, pleural disease

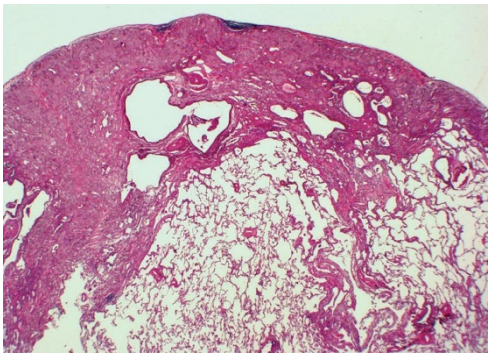
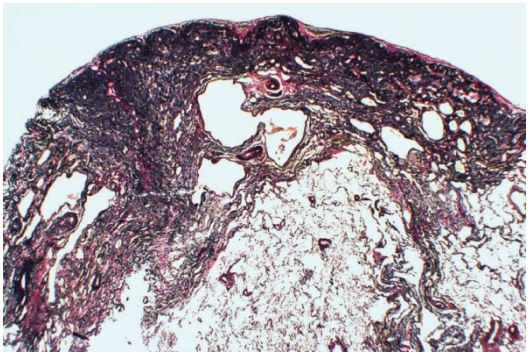


FIGURE 4 Histology staining showing a sharply demarcated zone of subpleural fibrosis with abundant elastic tissue on

B



Elastic tissue stain. a) Haematoxylin and Eosin stain and b) Verhoeff van Gieson elastic stain.

C

TABLE 1 Diagnostic features of pleuropulmonary fibrosis (PPFE)

Symptoms (not of which all may be present)
Dyspnoea Dry
cough Weight
loss Dull chest
pain
Anterior-posterior flattening of the chest wall (platythorax; fig. 3)
May denote advanced disease
Smoking status
85% never-smokers
Significant history
Lung transplant recipient: ~50%
Bone marrow transplant: 6%

EX

Prior exposure to chemotherapy or alkylating agents: 10%
Family history of pulmonary fibrosis: 9%
Idiopathic pulmonary fibrosis in an estimated 10–30%
Imaging: chest radiograph and HRCT
Bilateral apical (upper lobe + pleural dome) thickening invading the lung
Generalised loss of volume
The lower pleural-pulmonary zones are less involved or spared
Interstitial markings may be increased
Hila progressively retracted upwards
Uni- or bilateral spontaneous partial pneumothoraces are common

EO

Chest ultrasound
No data in humans at present
Noninvasive imaging methods have been described in a donkey with PPFE [17]
Pulmonary physiology
Restrictive to markedly restrictive

Obstruction present in some patients
Over time, progressive hypoxaemia and hypercarbia may develop
Bronchoalveolar lavage
No consistent shifts in macrophages, lymphocytes, neutrophils or eosinophils
PET scan
No consistent data at present
Pathology findings
Upper zone collagenous fibrosis of the visceral pleura with haphazardly arranged elastic fibres
Biopsy is not a prerequisite for PPFE diagnosis
Subpleural intra-alveolar fibrosis with a sharp boundary with the underlying lung
Alveolar septal elastosis
Sparing of the parenchyma away from area of pleural thickening
Mild, patchy lymphoplasmocytic infiltrates
Fibroblastic foci are rare or absent

Cases of PPFE and cases which appear to be consistent with PPFE as a result of chronic complications of BCNU treatment [20, 23, 25, 50–52] or cyclophosphamide [3, 43, 53, 54] used to treat breast cancer [3], brain tumours [20, 23, 51] or granulomatous polyangiitis [53] have been previously published, supporting the findings of BEYNAT-MOUTERDE et al. [1]. Studies by O'DRISCOLL and co-workers [20, 25], TAYLOR et al. [23] and HASLETON et al. [51] have detailed the clinical, imaging and pathological features of late BCNU toxicity. The disease develops after a symptom-free interval of 2–12 years. Affected individuals present with the characteristic clinical, imaging and pathological features of PPFE, including pneumothorax and interstitial elastosis [20, 51]. Craniospinal irradiation in those patients with a brain tumour was not thought to contribute to their disease as the dose received to the chest was minimal [20]. Similarly, MALIK et al. [43] reported on five cases of late pleuropulmonary toxicity developing 6 months to 6 years after termination of treatment with cyclophosphamide. Apical pleuropulmonary fibrosis involvement was also observed. Three out of the five patients died due to respiratory failure [43]. The authors reviewed five similar cases from the literature [43]. All the previously reported BCNU and cyclophosphamide cases closely resemble those reported by BEYNAT-MOUTERDE et al. [1].

Although appealing, the nature of an association of alkylating agents and PPFE, either causal or circumstantial, needs be examined carefully [55]. The case against causal association, includes the possibility that PPFE can develop idiopathically or, as some reports suggest, as an abreaction to infectious agents [2], as well as: due to the lack of a clear dose–response curve; development and progression of fibrosis after a free interval of several years after termination of treatment; lack of reversal with drug withdrawal; and absence of robust epidemiological support or absence of a suitable animal model [55]. Current models of pleural fibrosis use transforming growth factor-b1, bleomycin and carbon black instilled in the pleural space as the inciting agents [56, 57]. Conversely, in favour of an association between alkylating agents and PPFE are: the normalcy of pre-therapy chest imaging in the study by BEYNAT-MOUTERDE et al. [1]; the homogenous and consistent reports of the same distinctive drug-associated disease from different countries over the past 35 years [2]; the notion that two separate alkylating agents can produce an association; and the occurrence of PPFE in young individuals [20, 25] in whom fibrotic conditions are relatively rare. Evidence for drug- associated elastosis in organs other than the pleura and lung is extremely scarce, with only one reported case of endocardial fibroelastosis following therapy with adriamycin [58].

Management of this dreadful condition is difficult. Corticosteroids and immunosuppressants offer transitory or no improvement, even less cure; except in a very few cases. Pleuropulmonary biopsy should be undertaken very cautiously, if at all. Experience with decortication is extremely limited [59]. Timely consultation with a transplant team is warranted, as transplantation has been suggested [4, 5] and successfully attempted in a few cases [42, 60].

To conclude, the imaging features of PPFE are very suggestive, if not pathognomonic. PPFE is a probable if not frequent late complication of chemotherapy regimens containing alkylating agents. As greater awareness of PPFE will lead to more frequent and hopefully more accurate diagnosis and reporting, we can only hope this will improve our comprehension of PPFE and its causes, including drug therapy, enabling novel treatment approaches to be identified, thus, improving the currently poor outcome.

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AMR Seminar #67

Case – 5

Contributed by: Ivan Damjanov

(Courtesy of Dr. Rashna Madan)

Clinical History: A 34-year-old morbidly obese woman was admitted complaining of lower abdominal pain. A left ovarian mass measuring 15 cm in diameter was identified during the work-up. She was also found to be pregnant, approximately 16-18 weeks.

Pathologic Findings: We received a 550 g solid lobulated tumor apparently permeating and/or replacing the entire ovary, which on gross examination could not be definitively identified in the tumor mass. The cross section of the solid ovarian mass was whitish yellow with some areas of necrosis. The frozen section was reported as malignant tumor, most likely carcinoma or germ cell tumor or metastasis.

Microscopically the tumor was composed of loosely structured nests of round cells with vesicular nuclei and scant cytoplasm. In some areas, the tumors had either clear of eosinophilic cytoplasm. The tumor nests were often surrounded by fibrous septa, giving the tumor a quasi alveolar appearance. In some areas the cells formed broad solid sheets, whereas in others they formed strands, cords and small groups. There were numerous mitotic figures and areas of necrosis.

Our initial differential diagnosis included a metastasis versus a primary ovarian tumor, such as germ cell tumor or a neuroendocrine tumor or some unusual pattern of clear cell carcinoma. A senior consultant suggested that it might be a hypercalcemic-type small cell carcinoma of the ovary, even though her serum calcium was actually below normal levels. Immunohistochemistry was positive for pancytokeratin and CK7, negative for CK20, PAX-8, WT1, calretinin, p53, OCT3/4, CD30, EMA, chromogranin, MART1, desmin, mammoglobin and inhibin. Second set of staining revealed positive staining for p63 and p16. At that point, we were convinced that this is an unusual squamous cell carcinoma, most likely from the cervix. The in situ hybridization for high risk HPV was strongly positive.

Diagnosis: Squamous cell carcinoma of the cervix, metastatic to the ovary.

Follow up: The tumor metastasized to the uterus permeating the decidual blood vessels and causing a spontaneous abortion. Lung and brain metastases developed during her hospitalization and she was transferred to a facility for palliative care.

Comment: Because of patients' obesity, the cervix was never properly visualized but the Pap smear contained unquestionable squamous cell carcinoma cells. Even though we did not see the primary, we assume that it must have been of the "acantholytic variety", which would have accounted for the loose structured tumor nests in the ovary. It was almost anticlimactic when we realized that it was a squamous cell carcinoma, but we all felt that this was a good lesson in humility. I am not sure if the slide which I chose for you will adequately reflect the excitement we had with this tumor, but at least you will see how many steps and time it took us to recognize "our man in Istanbul".

AMR Seminar #67

Case – 6

Contributed by: Giovanni Falconieri

Clinical History: A 1 day-old female baby undergoes resection of a 1.5 cm nodule of the lateral aspect of the tongue. The tumor is firm, lucent with a slightly lobulated cut surface. Microscopically, H&E stained sections show a cellular proliferation of polygonal cells growing in diffuse sheets underneath a stretched, otherwise unremarkable squamous mucosa. In addition to cytoplasmic granularity, the cells have distinct membranes and small and hyperchromatic nuclei. Mitotic activity is not recognized (Ki67/MIB1 < 1%). The supporting stroma features a rich capillary network and a focal, pericytoid vascular pattern. Immunohistochemistry is positive for NKI-C3 and negative for cytokeratins, S100 protein, desmin, actins, CD34, H-caldesmon.

Diagnosis: Congenital granular cell epulis of newborn.

Comment: In my view this is a good teaching case for residents. Granular cell epulis ("Neumann tumor") is a relatively uncommon lesion of the oral cavity, mostly arising within the gingival tissue of the anterior maxillary alveolar ridge in female newborns. Most published cases are in the form of case reports. Childer and Fanburgh-Smith in 2011 described the largest series detailing10 such cases. Multicentric lesions are rare but not exceptional. Breathing and deglutition difficulty can be early clinical manifestation; prenatal cases of polyhydramnios have been reported. The recommended treatment is surgical excision.

Granular cell epulis should be distinguished from the prototypical granular cell tumor of schwannian cell lineage, considering that congenital examples of this tumor have been reported as well. In contrast to epulis, the overlying squamous mucosa is remarkably hyperplastic in granular cell tumor; in addition, tumor cells are S100 protein positive. The strong immunoreactivity observed for NKI-C3 indicates the lysosomal origin of the cytoplasmic granularity. A relationship between these conditions has been conjectured by some authors.

The case at issue seems to be of interest due to its unusual location since the majority of granular cell epulis occur within the gingival mucosa, and very few cases have been described in the tongue. Lingual lesions do not otherwise differ from orthotopic epulis, i.e. they display a smooth, slightly lobulated surface and good circumscription. The exact origin of granular cell epulis is unclear. The rare but definitive occurrence outside the alveolar ridge apparently supports the claim that granular cell epulis is a proliferation of early mesenchymal rather than dentigerous cells, with ultrastructural features of pericytic and myofibroblastic differentiation and evidence of autophagocytosis.

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AMR Seminar #67

Case – 7

Contributed by: Cyril Fisher

Clinical History: A 40 year old male presented with a six-month history of a progressively enlarging right neck mass, now 8cm diameter, at the common carotid artery bifurcation. Operatively this was a large mass enveloping the internal and external carotid arteries, internal jugular vein, 10th and 12th cranial nerves and sympathetic chain.

Pathologic Findings: Grossly, the specimen comprised a 10x8.5x6cm, 230g soft cystic mass with strips of skeletal muscle and adipose tissue on its surface. Sectioning showed extensively necrotic tumor with approximately 20-40% solid areas composed of medium firm yellow to tan tissue.

Microscopically, this was a partially encapsulated cellular tumor with a focally infiltrative edge. It was predominantly composed of discohesive sheets of large epithelioid or polygonal cells with rhabdoid morphology. The cells were moderately to focally markedly pleomorphic, with binucleate and multinucleate forms. In other areas however, the tumor had a more nested architecture and less frequently the cells were smaller and uniform, with blander morphology and cytoplasm pattern varied from plasmacytoid to focally clear cells. Coagulative necrosis was prominent, and the mitotic index was up to 6 per 10 high power fields. There was perineurial invasion. Native ganglion cells were present within the lesion, and there were surrounding large nerves. No salivary gland tissue was seen.

With immunohistochemistry, the tumor was focally positive for EMA, S100 protein, SMA, calponin, CD10, CD56 and CD34. There was widespread loss of nuclear INI1 expression. The tumor was negative for AE1/AE3, MNF116, CAM5.2, p63, TTF1, calcitonin, desmin, CD31, ERG, CD45, CD79a, CD138, CD30, ALK, CD117, HMB45, melan-A, chromogranin, and synaptophysin.

FISH showed a translocation involving the *EWSR1* gene. There was no evidence of *POU5F1* gene rearrangement. *EWSR1-NR4A3, TAF15-NR4A3, EWSR1-FLI1, EWSR1-ERG, EWSR1-WT1*, *EWSR1-ATF1, EWSR1-CREB1* and *EWSR1-POU5F1* fusion transcripts were undetectable by RQ-PCR.

Diagnosis: Myoepithelial carcinoma of soft tissue with rhabdoid morphology.

Comment: In this (recently published[1]) case the selective epithelial antigen expression, and loss of INI1 suggested a diagnosis of malignant rhabdoid tumour. However, the S100 protein positivity and the *EWSR1* rearrangement exclude these and, with the clear cell areas and other findings, support a diagnosis of malignant myoepithelial tumor.

AMR Seminar #67

Case – 8

Contributed by: Ondra Hes

Case History: 57-year-old Caucasian male was submitted to the hospital because rapid swelling of the right testicle.

Gross Pathology: Huge testicular tumor (necrotic, tan to whitish on gross cut) measuring 13 x 15 x 12 cm was found. Tumor was nearly completely embedded.

Histology: Areas of typical spermatocytic seminoma were found. Population of three cell type (large polymorphic, small lymphocyte-like and intermediate cells) was noted. Mitoses, including atypical ones were numerous. The stroma was loose and edematous. Besides the round cells, a spindle cell neoplastic population was also present in multiple blocks. There was not a sharp border between the seminomatous component and sarcoma (grossly visible). Areas of completely necrotic mass were seen.

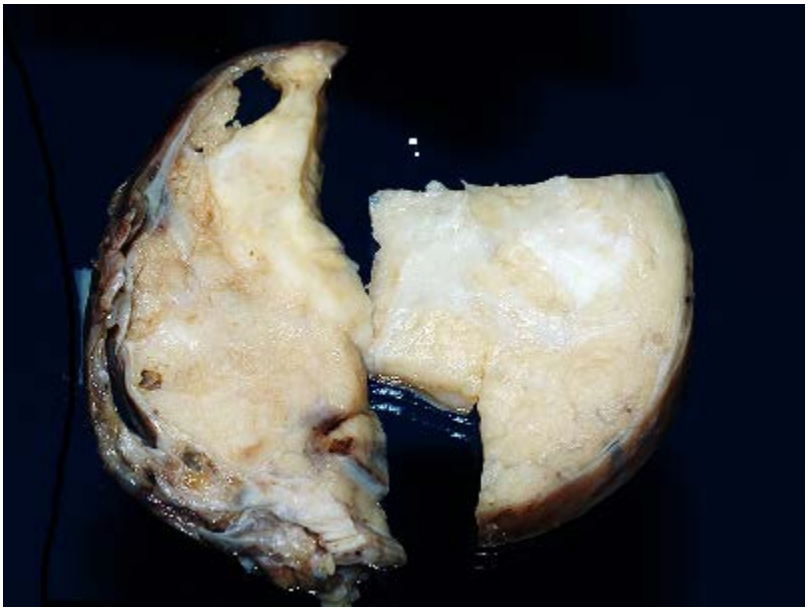
Both seminoma and sarcoma were negative for OCT 3/4, Sall 4, nanog, LIN 28 and glypican 3. Sarcomatous component was negative for S100, smooth muscle actin, and desmin.

Diagnosis: "Spermatocytic seminoma and sarcoma". Sarcomatous component has been diagnosed as undifferentiated sarcoma.

Comments: Spermatocytic seminoma is a very rare testicular tumor, usually constituting less than 1-2% of testicular tumors. Peak incidence is in the fifth-sixth decade, however even younger and older patients are referred. It is essentially a benign tumor, only two metastatic cases (if I am not wrong) have been described (one of them by Dr Josef Matoska from Bratislava - place of AMR meeting in 2015).

Spermatocytic seminoma is typically negative for "classic" germ cell markers like OCT ¾, SALL 4, nanog. PLAP is absent to scant. We haven´t seen a single positive case in our registry (20 spermatocytic seminomas). CD30, alpha fetoprotein, hCG, CEA, EMA, vimentin are usually negative. Cytokeratins are generally negative, only dot-like positivity for CK 18 is sometimes seen. Spermatocytic seminoma showed gain in chromosome 9 and disomic status of chromosome 12p, which is typical for classic seminoma.

The situation is completely different for spermatocytic seminoma with sarcomatous component, which is an aggressive tumor, commonly associated with metastatic spreading at the time of diagnosis. Soma patients have a history of rapid enlargement and pain. Tumors are mostly hemorrhagic and necrotic. The sarcoma is usually well demarcated from the seminomatous component (like in the case of Kum Cooper many years ago). Rarely both components are admixed, like in this case. Sarcoma is usually described as an undifferentiated spindle cell sarcoma, chondrosarcoma or embryonal rhabdomyosarcoma. Metastases are composed of sarcomatoid component.



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AMR Seminar #67

Case – 9

Contributed by: Jason Hornick

Case History: A 21-year-old woman presenting with abdominal pain was taken to surgery with a concern for acute appendicitis and was found to have a mass in the left deep pelvis involving the obturator externus muscle densely adherent to the ischium. The tumor was resected with narrow margins.

Pathologic Features: The 6-cm mass was well circumscribed with a fibrous cut surface. The majority of the tumor was composed of uniform, bland epithelioid cells with round nuclei and moderate amounts of clear cytoplasm arranged in cords and sheets within a densely collagenous stroma. In focal areas, the tumor cells showed a spindled appearance and were arranged in a storiform architecture with variable myxoid stroma (this latter component was only seen in 2 blocks). By immunohistochemistry, the tumor cells showed strong, diffuse cytoplasmic staining for MUC4, whereas keratins, EMA, S100, CD34, KIT, and DOG1 were negative.

Diagnosis: Hybrid sclerosing epithelioid fibrosarcoma/low-grade fibromyxoid sarcoma.

Comment: Sclerosing epithelioid fibrosarcoma is a rare, aggressive fibroblastic neoplasm with a wide anatomic distribution and no age or gender predilection. This tumor is associated with a high rate of both local recurrence and distant metastasis (around 50%), sometimes occurring over a prolonged interval following primary excision. The distinctive histologic appearances may lead to confusion with either metastatic carcinoma (especially lobular breast carcinoma) or perhaps osteosarcoma (if the hyalinized collagen is mistaken for osteoid). Until recently, there were no specific immunohistochemical markers for this tumor type. EMA is positive in a subset of tumors; the lack of reactivity for keratins is most helpful to exclude metastatic carcinoma. The epithelial apomucin MUC4 is positive in 80-90% of cases; this marker is relatively specific for sclerosing epithelioid fibrosarcoma among epithelioid soft tissue tumors (although some carcinomas are also positive). It has recently been recognized that some cases of sclerosing epithelioid fibrosarcoma contain a component of low-grade fibromyxoid sarcoma (and conversely some cases of low-grade fibromyxoid sarcoma contain small foci of sclerosing epithelioid fibrosarcoma). MUC4 was identified as a helpful diagnostic marker for low-grade fibromyxoid sarcoma by gene expression profiling; only very rare cases lack MUC4 expression (<1%).

Given the presence of “hybrid” tumors and the shared expression of MUC4, it is not surprising that these tumor types also share genetic features. Nearly all cases of low-grade fibromyxoid sarcoma harbor either *FUS-CREB3L2* (95%) or *FUS-CREB3L1* (5%) fusions; rare cases contain *EWSR1-CREB3L1* fusions. Conversely, most cases of sclerosing epithelioid fibrosarcoma harbor *EWSR1-CREB3L1* (70%) or *EWSR1-CREB3L2* (10%) fusions, whereas a small subset of cases contains *FUS-CREB3L2* fusions (10-20%). Tumors with a component of low-grade fibromyxoid sarcoma are dominated by *FUS-CREB3L2* fusions. The mechanism for MUC4 upregulation has not been identified.

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AMR Seminar #67

Case – 10

Contributed by: Janez Lamovec
(Case courtesy of Dr. Snježana Pavlović)

History: A 54-year-old woman presented with a tumor in the right breast and a nodule of the subcutaneous tissue of the left thigh. One month before, another subcutaneous nodule of the right lumbar region was excised. Five years previously, she had a facial skin excision performed in another hospital; histology showed malignant melanoma, Clark V, 2.3 in thickness. Excision margins were free of tumor, cervical sentinel lymph nodes were negative (0/2). The tumor recurred in the left breast after two years; it was excised and was morphologically identical with the previously excised tumors. The submitted slide is from the latest recurrence.

Gross pathology: The excision specimen showed unremarkable breast tissue with a solitary nodule of well circumscribed white- grey, focally hemorrhagic neoplastic tissue measuring 1.7 cm in its largest dimension. Excision margins were free of tumor.

Microscopic pathology: The neoplastic tissue features predominantly spindle cell population, mildly to moderately pleomorphic, of different density, mostly randomly distributed, with some fascicular growth focally. Intimately and unevenly admixed are numerous lymphocytes and plasma cells, the former forming some follicles peripherally. Inside the tumor nodule, there are entrapped ducts and lobules of the breast parenchyma. There are several necrotic areas, spindle cell tissue is focally quite collagenized. Mitoses are not numerous. Surrounding breast tissue shows some ductal hyperplasia of usual type.

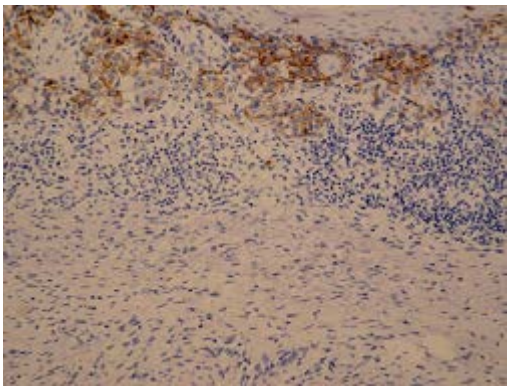
Immunohistochemical results: Neoplastic spindle cells were diffusely strongly positive for S-100 protein (see microphotograph) and negative for Melan-A, MiTF and HMB45. They were also negative for CK5 and CK AE1/AE3. SMA highlighted relatively numerous myofibroblastic cells growing among neoplastic spindle cells, CD34 disclosed abundant meshwork of capillaries.

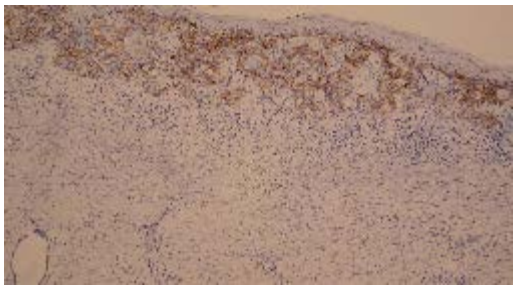
We were able to get blocks of the skin lesion from another hospital: tumor was a malignant melanoma with usual epithelioid morphology in the superficial portion and spindle cell desmoplastic appearance in the deeper portion of the lesion. HMB-45 and Melan-A were positive only in the epitheliod and completely negative in spindle cell component while S-100 protein was strongly positive in both components (see photomicrographs)

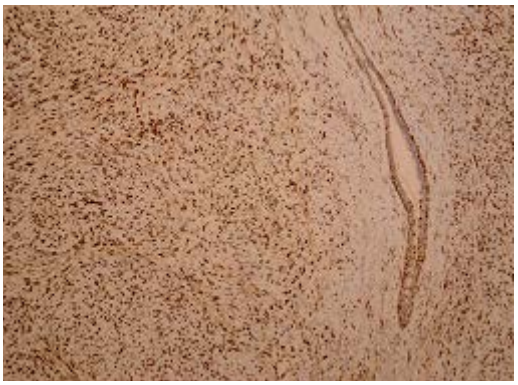
Diagnosis: Metastatic malignant melanoma to the breast.

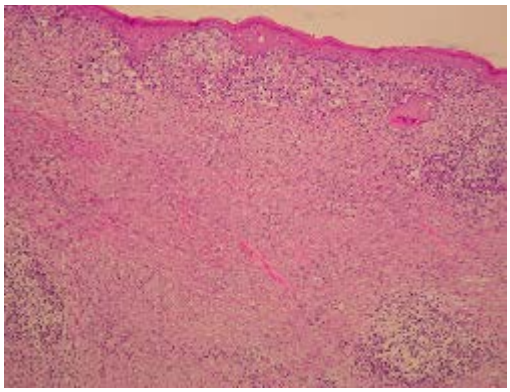
Follow up: The patient is alive with disease, 7 years after excision of the primary lesion.

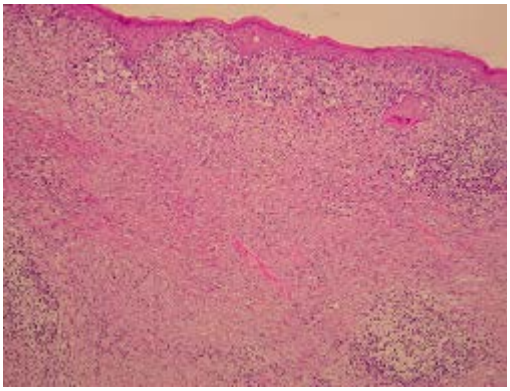
Comment: This is not a difficult case providing the history is known although even in such a circumstance the comparison of primary and secondary lesion is mandatory. It is easy to imagine that one may get a biopsy of the solitary lesion in the breast without any knowledge of the previous history of MM and in such a case and with such a morphology as in the presented case the thought of malignant melanoma may indeed be very remote in spite of the known dictum '' always think of melanoma''. The subject of metastatic malignant melanoma as an isolated breast tumor presented as a simulator of different tumors, including lymphoma has been recently published in Arch Pathol Lab Med 1013; 137: 41-9 by Falconieri G, Bacchi CE et al.

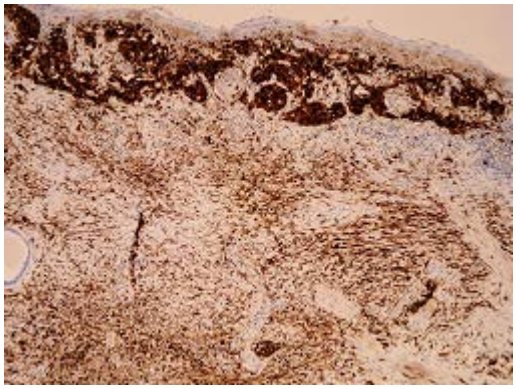












AMR Seminar #67

Case – 11

Contributed by: Michal Michal
(Case M27892/14)

History: A 67-year-old woman with a clinical diagnosis of tumor of the uterine cervix had an abdominal hysterectomy and bilateral adnexectomy. Hysterectomy specimen showed markedly enlarged and dilated lower uterine segment and cervix, filled by a polypoid firm solid white tumor measuring 12 x 5 x 5,5 cm. The tumor partly protruded through the cervical orifice.

Histologically in some areas I found a classical appearance of endometrioid adenocarcinoma. Most of the tumor had, however, the appearance of large mats of myxoid matrix with SM-actin positive bland looking cells with curved nuclei, characteristic of myofibroblasts. These myofibroblastic areas were riddled by glandular structures with squamous cell metaplasia. The referring pathologist suggested a diagnosis of malignant mixed Műllerian tumor (Műllerian carcinosarcoma).

Diagnosis: Endometrioid adenocarcinoma of uterus with fasciitis-like stroma.

Comment: I think that this lesion parallels similar phenomenon in thyroid, where papillary carcinoma with fasciitis stroma has been described (1,2).

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AMR Seminar #67

Case – 12

Contributed by: Michal Michal
(Case M40267/13)

History: A 58-year-old woman underwent a total thyroidectomy for bilateral goiter. Grossly, the right lobe (54x40x23 mm in size) was greyish white and with a compact parenchymatous structure on cut section, with one yellowish nodule sized 15 mm in the largest dimension. The left lobe (58x34x24 mm in size) had the same appearance, but was devoid of nodular lesions. The whole gland was submitted in 48 paraffin blocks. Furthermore, 3 lymph nodes were found and submitted for histological investigation.

Pathologic Findings: Microscopically, the thyroid parenchyma showed signs of Hashimoto's thyroiditis. The nodule in the right lobe described above consisted of three distinct components. The first component had solid cell nests appearance characterized by small polygonal, elongated or spindled cells with distinct borders forming solid structures occasionally with partial cystic transformation. The second part, resembling a branchial cleft cyst, was lined by predominantly squamous epithelium with focal presence of ciliated cells, and surrounded by abundant lymphoid tissue rich in germinal centers. Finally, the third part was identical to Warthin's tumor with its typical two-layers-thick epithelial lining with oncocytes forming the luminal layer. The epithelium was arranged in papillary-cystic pattern and surrounded by dense lymphoid stroma with germinal centers. Imunohistochemically, the lining cells were thyroglobulin and TTF-1 negative, but positive for p63 and Galectin 3. CEA showed only patchy positivity, and Ki-67 was positive only in several individual cells.

Diagnosis: Benign Warthin's tumor of the thyroid.

Comment: Based on morphology and immunohistochemical profile it is apparent the tumor has the same background as solid cell nests, branchial-like cysts (1) and the lesion published recently (2).

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AMR Seminar #67

Case – 13

Contributed by: Markku Miettinen

Clinical history: A 40 year-old woman with multiple uterine leiomyomas of varying sizes undergoes total hysterectomy. Largest leiomyoma was pedunculated measuring 13x10x5 cm. Multiple other leiomyomas measured 0.5-5.5 cm. Section of one leiomyoma is submitted for members' review.

Diagnosis: Uterine leiomyoma associated with HLRCC syndrome.

Discussion: Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome includes occurrence of multiple often painful cutaneous piloleiomyomas (most patients), early onset uterine leiomyomas (common in women), and an aggressive form of renal cell carcinoma, papillary type 2 (approximately in 15% of patients). This hereditary syndrome is caused by germline loss of function mutations in the gene encoding fumarase (FH, fumarate hydratase), a mitochondrial enzyme of the Krebs cycle responsible of converting fumarate to malate. In addition, somatic allelic losses occur in tumors leading into complete silencing of the FH gene in the tumor cells, according to the principles of classic tumor suppressor genes. This mutation leads into activation of pseudohypoxia signaling (with some similarities to SDH deficiency-associated tumor syndrome).

Uterine leiomyomas associated with HLRCC syndrome may have a distinctive appearance with the following features, and the submitted case is typical: There is mild nuclear atypia often manifesting as nuclear enlargement, prominent eosinophilic nucleoli, multinucleation, and eosinophilic cytoplasmic globules. Mitotic activity is not generally prominent. Even atypical mitotic figures can occur. However, leiomyosarcoma is not known to be a common problem in this syndrome, although some uterine smooth muscle tumors in syndromic patients have been diagnosed as such.

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AMR Seminar #67

Case – 14

Contributed by: Elizabeth Montgomery

Clinical History: A 44 year old man with congenital neurofibromatosis type 1 (NF1). His mother died of complications of NF1 and he is blind from bilateral optic gliomas. Over the years he has had both diffuse and plexiform neurofibromas resected. Additionally, he has had numerous gastrointestinal tract polyps that are similar to juvenile polyps in both his colon and stomach as well as multiple colonic tubular adenomas. He had also had high-grade esophageal columnar epithelial dysplasia in Barrett mucosa which was managed endoscopically. These samples are gastric polyps. The endoscopist noted numerous large gastric polyps and she was concerned that carcinoma was present and performed polypectomies on the largest ones.

Diagnosis: Gastric polyposis in association with NF1.

Comment: The histology in this case is far less interesting than the history and the association of such polyps with NF1 and I did not have decent history when these crossed my desk. To me these polyps look very much like gastric juvenile polyps or like gastric hyperplastic polyps. However, some of the slides show adjoining flat mucosa and this lacks gastritis. Very large gastric polyps that appear similar to gastric hyperplastic polyps but unaccompanied by gastritis tend to be syndromic (regular hyperplastic polyps that are large are often accompanied by atrophic gastritis) and it is really impossible to tell which syndrome! To my delight, I learned that Abbas Agaimy had published a lovely paper on NF1-associated gastric polyps and he was gracious enough to entertain some emails about my case. However, during all this, I also learned that a subset of patients with a Lynch-like syndrome displaying biallelic mutations of mismatch repair genes have clinical signs that mimic neurofibromatosis, namely macules that appear similar to café au lait spots. They lack the full set of stigmata of NF1, but of course the spots are a fooler. Their polyps tend to be like those of classic Lynch – and thus not so many gastric ones but more colorectal and small intestinal ones – but there seem to be gastric cancers in some of these people. As such, we performed MSI testing on our case before there was a full history available and the process was microsatellite stable. We also did a CMV stain and it was negative. The polyps in this person seem to be the "real McCoy" as reported by Professor Agaimy in reference 1.

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AMR Seminar #67

Case – 15

Contributed by: Fredrik Petersson

Clinical History:

A subcutaneous 2 cm nodule was excised from the arm of a previously healthy 19 year old man. The cut section was homogeneously tan.

Histology: Sections show a well circumscribed, unencapsulated spindle cell tumor composed of areas of hypocellular myxo-collagenous to fibrotic stroma, as well as more cellular areas featuring short fascicles of bland spindled cells. There is a prominent vascular component composed of small to medium sized variably dilated blood vessels. Many of the small vessels exhibit perivascular cuffing by the spindle cells, often mixed with small lymphocytes. The perivascular cuffing – whorling imparts an onion-bulb like appearance. Mainly in the periphery several small vague nodules are seen. These nodules are cellular and contain crowded small plump spindle cells and also some almost epithelioid immature cells with limited cytoplasm. No significant cellular pleomorphism is seen. Mitotic activity is negligible and there is no necrosis.

Immunohistochemistry: The spindle cells show immunoreactivity for CD34 and EMA. The CD34 expression is much stronger and has a more widespread distribution than EMA (Fig. 1). The areas exhibiting perivascular whorling do not show any consistent staining pattern with areas/cells being both positive and negative for CD34 and EMA (Fig. 1 and 2). There is very focal, patchy weak expression of CD99 and bcl-2 in a seemingly random fashion. S100-protein, desmin and Cam5.2 are negative

Diagnosis: ? Soft tissue perineurioma with extensive CD34-positivity; or (See below) - Angiomatoid fibrous histiocytoma with extensive perineurioma-like pattern and EMA- and CD34 expression???

Comments: When I first saw this case I was puzzled by the seemingly "composite" features of the tumor. On the one hand, the perineuriomatous whorls are obvious, but on the other hand, there also seems to be a more non-descript fibroblastic (SFT-like) component with variable cellularity and prominent collagenization. The immunohistochemically detected much stronger and more widespread expression of CD34 compared to EMA (see pictures) was somewhat puzzling. Hence, I initially contemplated whether this could be a "hybrid/composite" tumor; perineurioma-SFT. However, the expression patterns of CD99 and bcl-2 (and also a subsequent negative STAT6 stain), do not support this possibility. So what about the CD34 expression? Most textbooks state that perineuriomas are composed exclusively of neoplastic cells with perineuriomatous differentiation. The gold standard for establishing "perineuriomatous differentiation" appears to be either IHC or EM. Regrettably I do not have ultrastructural information, but it would have been interesting to see whether there is any difference between areas with different expression patterns of EMA and CD34.

The light microscopical phenotype of "neoplastic perineurial cells" seems to be quite variable, ranging from elongated cells with slender cytoplasmic processes which are seen especially well in reticular variants to the epithelioid appearing tumor cells in sclerosing perineuriomas. In the actual case, especially in the CD34-positive, EMA negative – non-whorled areas, my own impression is that the cells have a less obvious perineuriomatous and more fibroblastic appearance. So, are these fibroblastic appearing, CD34-positive, EMA negative tumor cells which do not form any "perineurial/organoid" structures perineurial cells ? Coming back to the issue of CD34-positivity, most textbooks and

papers state/report that perineuriomas are CD34-negative. In Markku's textbook one can read the following: "At variance with many other studies and with the author's experience, a high frequency (64%) of CD34 positivity was reported." This refers to Dr. Hornick's and Fletcher's study in AJSP (1). This is by far the largest study on perineurioma to date. To recapitulate, 81 soft tissue perineuriomas from a wide variety of sites were studied (intraneural, sclerosing and reticular variants were not included). The range of histopathological patterns was wide - only about 20% of the tumors displayed prominent perivascular whorls (nearly all tumors showed a predominantly storiform architecture and 17 cases demonstrated a more fascicular pattern). Three tumors showed "striking nuclear palisading". Four cases contained "schwannoma-like perivascular hyalinization. 93% of cases were extensively and 7% focally positive for EMA. The staining intensity varied from strong, but "in many cases, staining was relatively weak and only apparent upon examination under high magnification". As mentioned previously, CD34 was expressed by 50/78 (64%) tumors, "usually with extensive positivity". 29% of cases showed claudin-1 expression, and 21% SMA (!). The study also comprised an ultrastructural examination of 6 cases, of which 4 expressed CD34, 2 cases expressed claudin-1 and 1 case expressed SMA. Each of the cases displayed cells typical for perineurioma. The authors insist in the Discussion that perineuriomas are composed exclusively of perineurial cells. Given the heterogeneity of light microscopical appearances and immunohistochemical findings, which is also seen in my case, I think one can make a tentative claim that the cells in perineuriomas exhibit a range of differentiation towards the normal perineurial cells. As we all know, a histogenetic approach to tumor classification carries this general flaw of attributing tumor types features of normal, terminally differentiated cells or tissues. Given the extremely focal nature of any ultrastructural study, it would have been interesting to see whether there were any lesional cells that did ***not*** show the classical ultrastructural characteristics of perineurial differentiation.

Based on the light microscopical features, as presented by Drs Fletcher and Hornick and my case, I think it is plausible to consider the possibility of some tumor cells showing a (myo-)fibroblastic phenotype. This is also suggested by the finding of SMA-positivity in 21% of the cases in Dr. Fletcher's study. On this note, and as mentioned above, it is interesting that the sclerosing perineurioma, contains a predominant cell type that does not exhibit the classical perineuriomatous light microscopical phenotype.

At least two other soft tissue tumors (except for composite peripheral nerve sheath tumors; which in addition would be positive for S100 protein), frequently exhibit immunoexpression of both EMA and CD34; low-grade fibromyxoid sarcoma and superficial acral fibromyxoma. According to the seminal paper on SAFM by John Fetsch and Markku Miettinen (2), the detected immunoexpression of EMA was frequently weak/patchy. The CD34 expression was more widespread, "usually moderate to diffuse with an immunohistochemical score of 3 or 4 (of 4) in 15 of the 21 positive cases". The authors reported a similar pattern for CD99. SAFM is a tumor that so far seems to be exclusively located in fingers/palms/ toes and the histopathological features; "random loose storiform, and focally fascicular growth patterns" seem to differ from the case I have presented. However, the myxoid component may be very limited and a predominantly collagenous stroma was present in 7/37 cases and 15 cases were well circumscribed ("lobular with a pushing margin"). LGFMS may be well circumscribed and the age and location are suggestive of this possibility, but the histological features I see do not make me associate to this possibility.

In a very interesting and recent study from the Cleveland Clinic, authored by Dr Billings (3), the authors describe their experience with angiomatoid fibrous histiocytoma. The study is focused on unusual clinical contexts and morphological patterns; and interestingly they found that 4 out of 27 cases displayed perineurioma-like areas which in one case (12 y/o F; arm) was diffuse (*entire tumor* !) and was associated with stromal sclerosis. 3/3 cases with perineurioma-like areas that were studied had rearranged *EWSR1* and most of these cases were EMA-positive. 56% of the tumors expressed desmin (negative in our case), but I cannot deduce whether desmin expression was present in the perineurioma-like areas. 2/3 perineurioma-like cases expressed EMA. CD34 was not studied. This information kind of haunts me given the fact that my patient is young, there is some intralesional lymphocytes and the tumor was located in the arm. Again, regrettably I do not have any more advanced data on the tumor than IHC, although information on the status of *EWSR1*, would have helped to solve the matter.

Pro forma and for completeness, the vague biphasic appearance with a slightly smaller cell component and spindle cells, could perhaps suggest myofibroma or EBV-associated smooth muscle tumor (of which the latter frequently

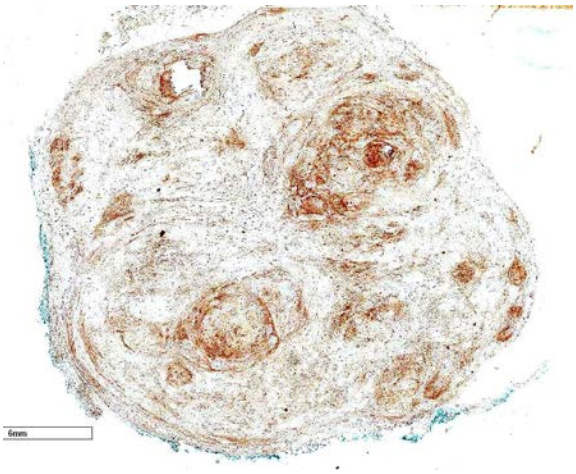
contains intratumoral T- or B-lymphocytes) (4), but taken together the overall features do not fit with these possibilities (I hope the members agree).

On a final note, since I was puzzled by this case I sent it to Michal and this created even more confusion. In his hands there was no expression of either EMA or claudin and STAT6 was negative.

I am eager to hear what the members of the club feel about this case.

Figure 1A-C.

Significant CD34 expression.



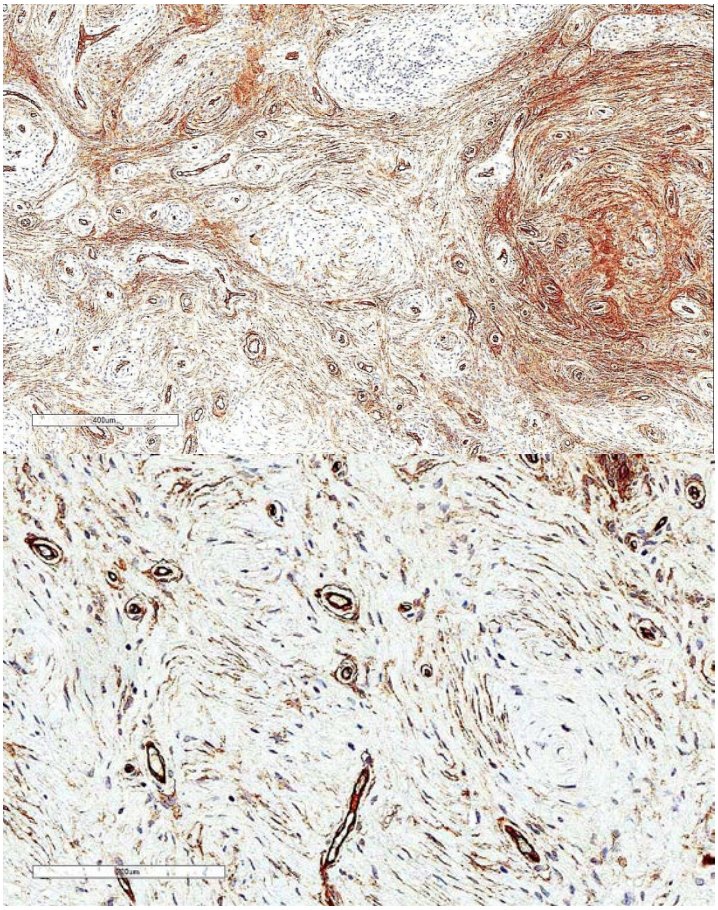
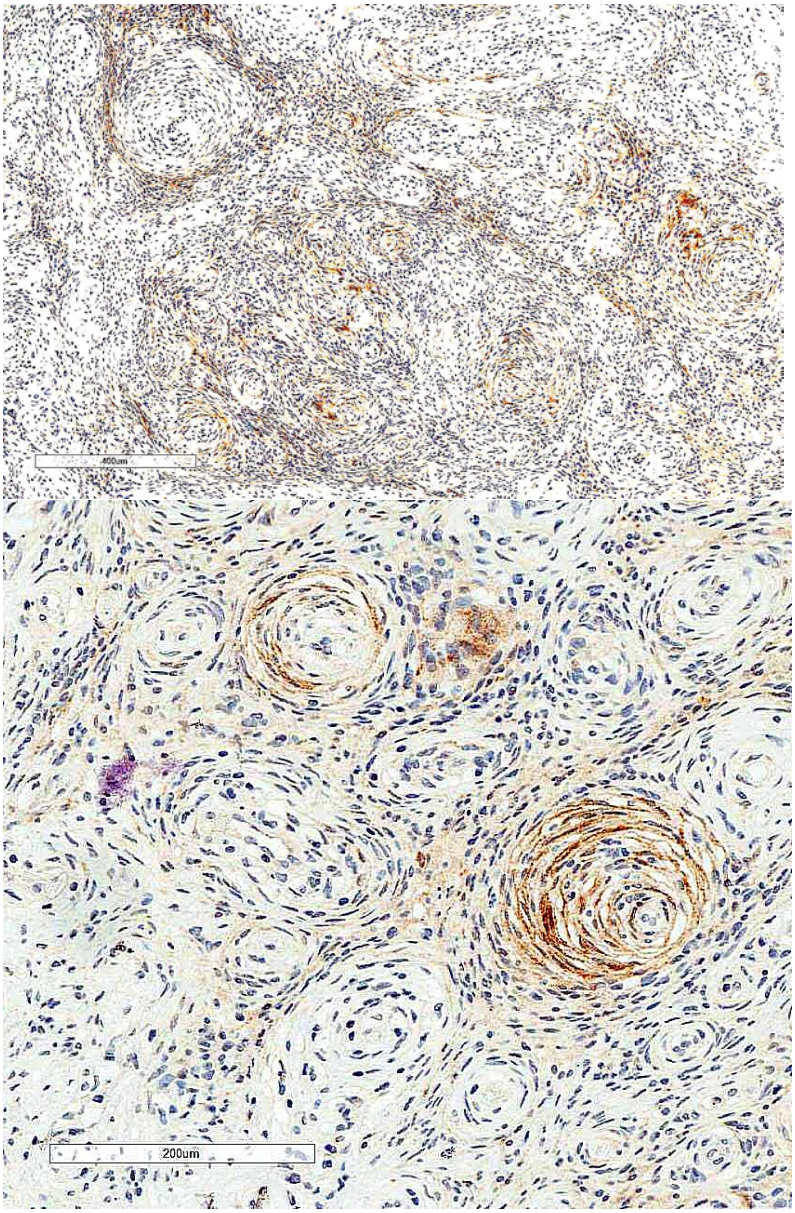
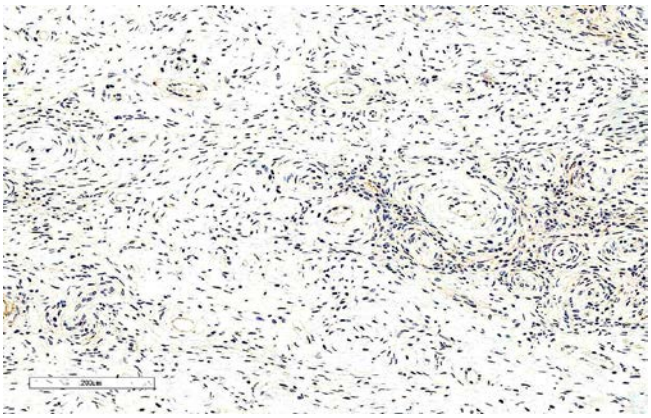


Figure 2A-C. Focal, but distinct EMA expression. Large areas were negative.





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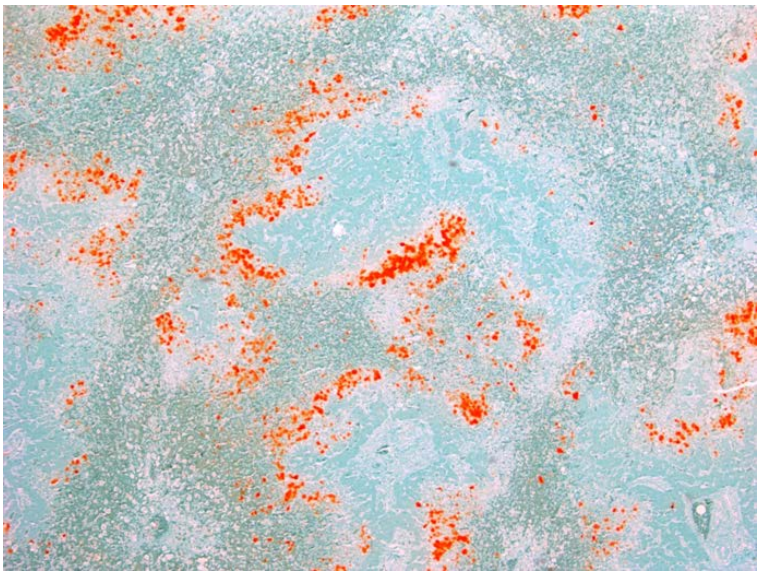
AMR Seminar #67

Case – 16

Contributed by: Murray Resnick

Clinical History: The patient was an 80 year old female with long standing hypertension, ischemic cardiomyopathy, chronic kidney disease, diabetes, hyperlipidemia and previous stroke who presented with overall weakness and low blood pressure. She was treated with fluids and antibiotics for presumed aspiration pneumonia. Initially after a good response her status deteriorated, an echocardiogram revealed severely decreased left ventricular function and her creatinine rose from an initial 2.4 g/dl (normal 0.44-1.03 g/dl) to a 5.22 g/dl. Her phosphorus increased from 6.6 to 8.4 (normal 2.4-4.8) and calcium decreased from 8.9 to 8.1 (normal 8.05-10.5). She then developed hepatic failure AST > 10,000 and ALT >5000 and became encephalopathic. She was made comfort measures only and expired 9 days after admission.

Microscopic features: The liver histology is dominated by features of centrilobular congestion and necrosis with hepatocyte loss estimated as 75%. The portal triads appear relatively spared of significant inflammation. Extensive calcification is evident at the interface between the necrotic and viable hepatocytes. See Alizarin red stain below.



Alizarin Red stain for calcium 4X

Diagnosis: Extensive centrilobular congestion and necrosis with diffuse hepatocellular calcification.

Comments: Calcification in the liver is a rare phenomenon, usually focal and usually secondary to infection, granulomatous disease, neoplasms or other causes. The diffuse extensive calcification seen in this case of ischemic hepatitis is an uncommon finding. Diffuse calcification has been described in liver allograft recipients and is associated with reperfusion injury (1). There have been rare case reports of a similar pattern of injury in patients with chronic renal failure on dialysis and ischemia (ischemic hepatitis) (2-4). Interestingly given this patients hypotension at presentation there may have be an element of reperfusion injury here as well.

Calcification is classified pathologically into two primary categories: dystrophic and metastatic. Dystrophic calcification occurs in injured/necrotic tissue while metastatic calcification occurs in viable tissue due to calcium/phosphorus imbalance. Typically in ischemic or other causes of massive hepatocyte necrosis dystrophic calcification does not occur. It seems logical that the pathophysiology of the calcification seen here may be a combination of dystrophic/metastatic calcification brought on by the massive hypotensive necrosis and acute on chronic renal failure. The fact that the calcium is present at the interface between the viable and dead hepatocytes supports this hypothesis. It is likely that the hepatocytes in this region are more permeable leading to an intracellular influx of calcium and subsequent intracellular calcification (4).

References

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4. Shibuya A. et al. Diffuse hepatic calcification as a sequela of shock liver. Gastroenterology 1985 89:196-201.
5. Pounder DJ. Hepatocellular calcification. Pathology 1985 17:115-118.

AMR Seminar #67

Case – 17

Contributed by: Saul Suster
(Case kindly contributed by Dr. Nathan Dunsmore, Greater Baltimore Medical Center).

Clinical History: The patient was a 55 year old man who presented with a large anterior mediastinal mass. An incisional biopsy of the mass was performed and read initially as "type B1 thymoma". An excision was performed; the specimen consisted of a 17 cm. well-circumscribed mass surrounded by a thin capsule.

Pathologic findings: Histologically the lesion is characterized by the admixture of 2 distinct components: islands and strands of thymic epithelium with abundant Hassall's corpuscles and a hyalinized or fibrotic stroma containing abundant mature fat.

Diagnosis: Thymofibrolipoma.

Comment: Thymofibrolipoma is a rare mediastinal tumor described by Dr. Moran (Moran CA et al. Fibrothymolipoma: A variant of thymolipoma. Arch Pathol Lab Med 118:281-282, 1994). The lesions are usually large and bulky and the prominence of the thymic epithelial component can often lead to an erroneous diagnosis of thymoma, particularly in small biopsy samples. Another diagnostic possibility that can sometimes be entertained in these tumors is that of a thymoliposarcoma (i.e., a liposarcoma originating from the thymus proper). Such cases should be expected to display an atypical adipose tissue component with scattered lipoblasts. I was not able to identify lipoblasts in this particular case and a stain for MDM2 was negative. Although the fibrous component was emphasized in Dr. Moran's article, there can be a spectrum of findings in these tumors and variations within the same lesion. The slide circulated does not show a prominent stromal fibrotic component but the fibrosis is rather subtle due to early collagen stromal deposition with a somewhat myxoid appearance. Although the lesion was initially interpreted as a variant of thymolipoma, the prominence of the epithelial component is such that I believe this corresponds to a separate and distinctive lesion, most likely representing a hamartomatous growth displaying a distinctive biphasic appearance.

AMR Seminar #67

Case – 18

Contributed by: Ady Yosepovich
(Prepared with the help of Cosmin Florescu, MD).

Clinical History: A 32 year-old female patient without other previous medical history presented with a palpable mass in the upper quadrant of the right breast. The mass was noticed 3 months after she gave birth to a healthy child. The ultrasound investigation showed a 2 cm tumor. A core needle biopsy was performed and the histopathological report confirmed the presence of invasive ductal carcinoma. The core needle biopsy of the axilla was benign. The PET CT scan detected a hypermetabolic space-occupying lesion in the right breast, with no evidence of metastatic spread. A lumpectomy and a sentinel lymph node biopsy were performed.

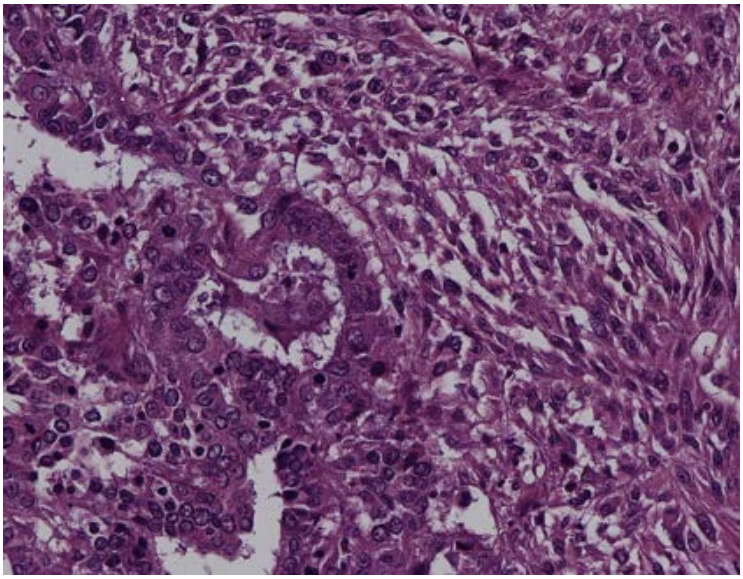
Pathologic findings: A 59 grams lumpectomy specimen was received in the pathology department, measuring 5.2 x 4.8 x 3.2 cm. Cross sections through the specimen revealed a white-grey mass, 3.2 cm in greatest diameter. Histological examination revealed a high-grade tumor composed of areas of high-grade carcinoma, partially with invasive micropapillary features. Abrupt transition to high-grade sarcomatous areas is identified. Additional tumoral areas with sarcomatous features are associated with osteoclast-like giant cells and are rich in pleomorphic large cells. Extensive tumoral necrosis is present. Focally, there is a lobule partially involved by high-grade ductal carcinoma in situ. In addition, there are changes of lactation. The margins are free of tumor. All three axillary sentinel lymph nodes are free of tumor. ER, PR and HER2neu are all negative. Ki67 proliferation rate is above 50%.

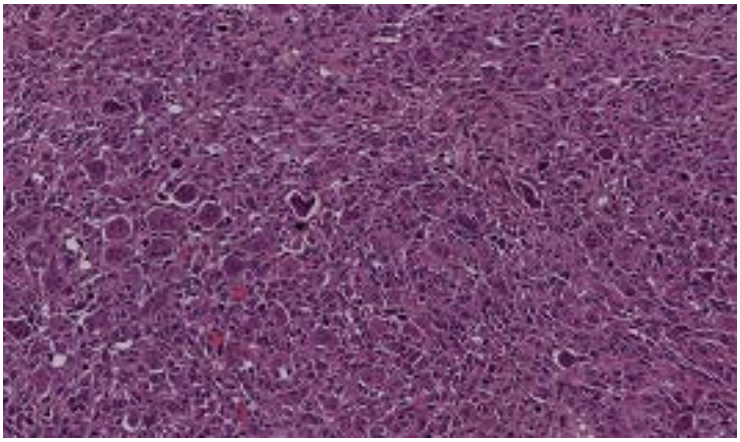
Diagnosis: High-grade metaplastic carcinoma with mesenchymal differentiation (carcinosarcoma) and osteoclast-like giant cells.

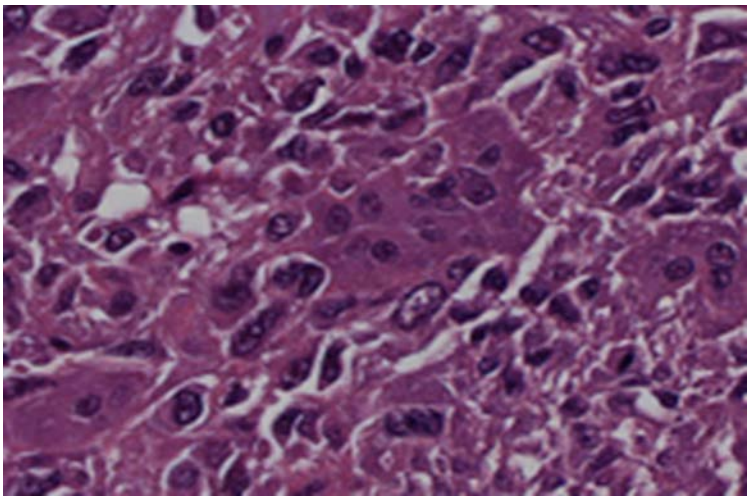
Discussion: This is a rare tumor. There are only few publications describing metaplastic carcinomas of carcinosarcoma subtype that are associated with osteoclast-type giant cells limited only to the mesenchymal part of the tumor. Immunohistochemical studies were performed: MNF116 highlighted the carcinoma areas, CD68 highlighted the giant cells and TRAP positivity supported the osteoclast-like origin of the giant cells.

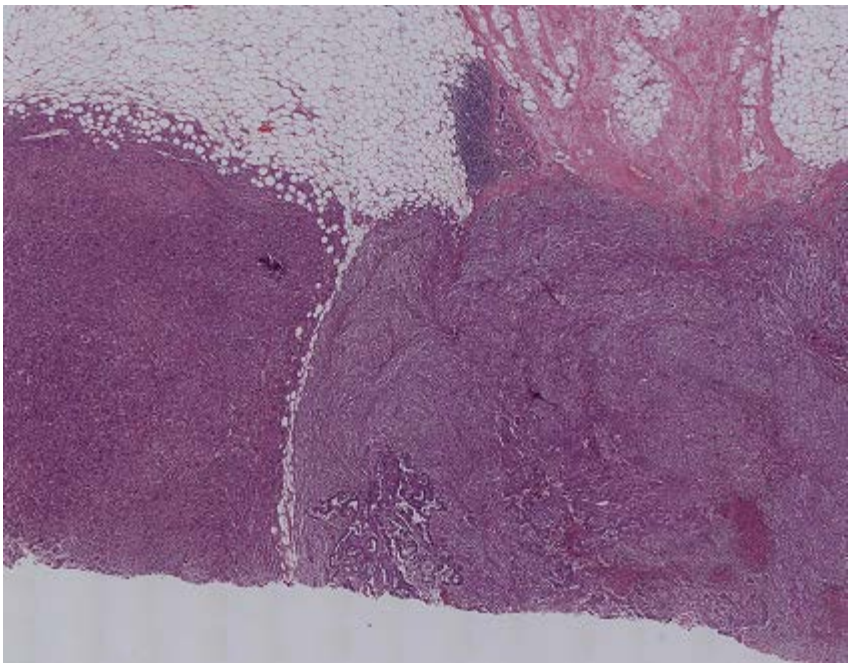
The origin the osteoclast-like giant cells is debatable , but looking closely at those areas one can notice that actually these peculiar cells are engulfing the tumoral cells. It is my hypothesis that tumoral factors are stimulating existing monocytes or macrophages that react and fight against the cancer cells, trying to "eat" them.

I attached a few pictures of this case since I am not sure that all the tumor elements exist in every slide I sent you.









AMR Seminar #67

Quiz Case #1

Contributed by Abbas Agaimy, MD

A 65-year old woman with a remote history of breast carcinoma presented with diffuse enlargement of the thyroid gland, clinically considered metastatic breast cancer. Section submitted is representative for the whole thyroid.

AMR Seminar #67

Quiz Case – #2

Contributed by: Alberto Marchevsky, M.D.

Clinical History: The patient is a 57 year old woman with a past medical history of malignant systemic hypertension associated with end-stage renal disease, cardiomyopathy and secondary pulmonary hypertension. She underwent renal transplantation in 2009 and bilateral lung transplantation in 2009. She had multiple episodes of acute cellular rejection in the renal and lung allografts, MRSA infections and other medical problems that were controlled successfully. In 2011 she developed progressive respiratory failure and underwent a second unilateral lung transplant in October 2011. The slides are from the 2011 right lung explant.