Pulmonary Pseudoneoplasms
Eunhee Yi, MD; Marie-Christine Aubry, MD

Context.—Not uncommonly, a surgical pathologist will be requested to review excised material, with a clinical diagnosis of cancer, in which no malignancy can be identified. Often, sampling may be the issue. However, different nonneoplastic processes may mimic cancer clinically and not be recognized histologically. These are commonly referred to as pseudoneoplasms and can involve the lung, pleura, and mediastinum.

Objective.—To review the most commonly encountered pseudoneoplasms of the thoracic cavity in surgical pathology and discuss the main differential diagnosis.

Pseudoneoplasm or pseudotumor is defined in the medical dictionary as “a nonneoplastic enlargement that resembles a true neoplasm” or “a circumscribed fibrous exudate of inflammatory origin.” This term encompasses a wide variety of morphologic abnormalities, with varying amounts of fibrosis and inflammation, which all have the propensity to mimic cancer clinically and histologically. This review article will focus on the most common lesions encountered in the thoracic cavity, including organizing pneumonia, nodular lymphoid hyperplasia, apical scar, round atelectasis, and sclerosing (fibrosing) mediastinitis and hyalinizing granuloma. However, no review on this topic would be complete without discussing the prototype of pseudoneoplasms of the lung, inflammatory pseudotumor. Inflammatory pseudotumor is now considered a heterogeneous group of lesions that encompasses a true neoplasm, the inflammatory myofibroblastic tumor.

INFLAMMATORY PSEUDOTUMOR

Inflammatory pseudotumor (IPT) is characterized by a proliferation of fibroblasts and myofibroblasts mixed with varying numbers of plasma cells, lymphocytes, macrophages, and other inflammatory cells. Historically, IPT has been believed to be a reactive lesion simulating a neoplasm, as the name implies. However, in the past 10 years or so, the pendulum has swung so that almost all IPTs have been regarded as true neoplasms, notably the inflammatory myofibroblastic tumor (IMT). In fact, the current World Health Organization classification of lung tumors adopted the name myofibroblastic tumor as the term for a tumor composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils and listed IPT as a synonym for IMT, along with other names including plasma cell granuloma, plasma cell pseudotumor, inflammatory myofibrohistiocytic proliferation, and omental mesenteric myxoid hamartoma. However, it should be remembered that clinicopathologic descriptions of IPT in the literature encompass both neoplastic and nonneoplastic conditions. Also, a personal review of the original cases that Drs Bahadori and Liebow used in their seminal study on plasma cell granulomas of the lung, available at Averill A. Liebow Pulmonary Pathology Collection at University of California, San Diego, confirmed the heterogeneous nature of IPT or plasma cell granuloma.

The neoplastic subset of IMT or IPT usually shows evidence of clonal cytogenetic abnormalities involving 2p23 that encodes ALK gene and typically occurs in children and young adults. Those that are not neoplastic are distinguished by the generally older age of the patients and the ill-defined or irregular contour of the lesion due to a prominent organizing pneumonia component and fibrosis at the edge of the tumor. The interchangeable use of the term IPT with IMT (connoting a neoplasm) could create confusion by implying all IPT represent neoplasms. In this review, IPT refers to the broad category and IMT to the subset showing neoplastic properties, unless a direct quotation is made from the cited literature. Although the main focus of this article is on pulmonary pseudoneoplasms, pertinent issues on IMT as a neoplasm are also reviewed. Inflammatory pseudotumors in extrapulmonary sites are also discussed to highlight the controversies surrounding this entity.

Inflammatory pseudotumors in different age groups or in different locations represent diverse clinicopathologic entities. The concept of IPT in locations other than the lung has also undergone an evolution similar to that in the lung; the group of lesions formally referred to as IPT in multiple sites is now mostly referred to as IMT. But, while
Figure 1.  

a. Inflammatory myofibroblastic tumor (IMT). An IMT excised from a 30-year-old woman shows a myofibroblastic cell proliferation with increased inflammatory infiltrates including many plasma cells (hematoxylin-eosin, original magnification ×200). This case revealed a cytogenetic abnormality involving 2p23 and diffuse cytoplasmic positivity for ALK-1 immunostaining (inset [original magnification ×200]). b. In contrast, a nonneoplastic inflammatory pseudotumor, excised from a 65-year-old man, demonstrates bland-appearing spindle cell proliferation in a mixed inflammatory background (hematoxylin-eosin, ×200). ALK-1 immunostain was negative in this case (not shown).
IPT occurring in the pediatric age group is mostly a neoplasm with frequent ALK positivity and might properly be referred to as IMT. IPT in adults may include more nonneoplastic processes with much less frequent ALK positivity.\(^3\) Zen et al\(^4\) have also suggested that there is a subset of IPTs that represents an IgG4-related disease. Some IPT cases may be related to an infection or may represent postinfectious sequelae, as some studies\(^5,6\) but not all,\(^7,9\) have found an association with human herpesvirus or Epstein-Barr virus. Inflammatory pseudotumor in the lower urogenital tract has been postulated to be a reparative process with a morphologic resemblance to nodular fasciitis.\(^10\) However, several recent studies have also reported neoplastic-appearing, ALK-1–positive IMTs involving the urinary bladder,\(^11,12\) again raising the possibility that some IPTs are reactive and some are neoplastic IMTs. Meis et al\(^13\) documented a tumor, closely simulating IPT in the mesentery and retroperitoneum, under the name of inflammatory sarcoma on the basis of its behavior as a low-grade malignancy. Coffin et al\(^14\) later discussed the relationship between IMT and inflammatory fibrosarcoma with a historic review of these entities. Kutok et al\(^16\) reported that IPT of the lymph node and spleen is a biologically distinct entity from IMT and based their conclusion on the absence of ALK expression in their 13 cases (9 involving lymph nodes and 4 involving splenic lesions). In a recent study on IMT of the central nervous system (CNS),\(^17\) 5 of 6 IMTs in the CNS, characterized by neoplastic-appearing spindle cell proliferation, were positive for ALK protein overexpression and/or 2p23 rearrangement, while 18 “nonneoplastic-appearing” IPTs were negative for both tests. The authors emphasized that the neoplastic IMTs in CNS should be distinguished from nonneoplastic IPTs for proper clinical management.\(^8\)

In 1995, Snyder et al\(^2\) first reported clonal changes in IPT of the lung involving 2p23, the encoding site for ALK gene, and a subsequent report by Griffin et al\(^22\) demonstrated recurrent involvement of 2p23 in IMTs of various body sites, suggesting the role of ALK outside of its previously well-recognized realm of lymphomas. Indeed, these observations were followed by the discovery of TPM3-ALK and TPM4-ALK fusion oncogenes in IMTs that transform, in vivo, both mesenchymal and lymphoid human cell lineages, as well as chlairthin heavy chain gene, CLTC.\(^16,17\) Yousem et al\(^18\) reported that 3 of 9 pulmonary IPTs showed involvement of 2p23 by fluorescence in situ hybridization; in 1 case, null-cell type ALK-1–positive anaplastic large cell lymphoma was present in the cervical lymph node 2 years before the discovery of lung mass.

In IMT, ALK immunopositivity is a highly sensitive and specific indicator of a 2p23 abnormality and is thus a useful surrogate for molecular or cytogenetic testing. Overall sensitivity of ALK in IPT is approximately 50%, although it varies greatly depending on the age of patients. Chan et al\(^19\) reported ALK expression in 5 of 61 IPT cases involving various sites (8.2%). All of their positive cases included patients younger than 40 years (range, 0.5 to 37 years), with the rate for ALK positivity becoming 21.7% only when those patients in their cohort who were 40 years or younger were considered. Another study on ALK expression in IMT in various sites\(^20\) reported that 44 of 73 cases (60%) were ALK positive, with 6 of 13 pulmonary IMT cases (46%). As mentioned earlier, it is not clear whether these series encompassed only neoplastic or both neoplastic and nonneoplastic-appearing subsets when the term IPT or IMT was used. However, it seems quite clear that not all neoplastic IMTs stain positive for ALK.

Sensitivity and specificity of ALK immunoreactivity are limited for IMT with the differential diagnosis of other soft tissue tumors. A study on ALK expression in 135 cases including 10 cases of IMT and 125 cases of its mesenchymal mimics reported the following results\(^21\): cytoplasmic ALK positivity in IMT (4 of 10; 40%), malignant peripheral nerve sheath tumor (4 of 10; 40%), rhabdomyosarcoma (6 of 31; 19%), leiomyosarcoma (1 of 10; 10%), and malignant fibrous histiocytoma (1 of 11; 9%). Alveolar rhabdomyosarcomas (4 of 16; 25%) displayed a distinctive dot-like cytoplasmic positivity.\(^21\) No staining was observed in nodular fasciitis, desmoids, infantile myofibromatosis, infantile fibrosarcoma, synovial sarcoma, leiomyoma, or myofibrosarcoma.\(^22\) Another study\(^22\) also reported ALK expression in a wide variety of non-IMT soft tissue tumors, although with low-level expression in most non-IMT mesenchymal tumors as compared to the diffuse positivity in IMT. Therefore, ALK positivity is still useful in differentiating IMT from its mimickers, which are part of the differential diagnosis in a practical setting. The possible prognostic significance of ALK expression in IMT has been explored and concluded as being unclear at this time.\(^21\)

While morphologic findings of neoplastic IMT are relatively distinctive (Figure 1, a), a wide range of histopathologic features can be seen in the broad category of IPT (Figure 1, b), reflecting its heterogeneous nature. The pulmonary IMTs with neoplastic characteristics typically form a well-demarcated but nonencapsulated, usually solitary, mass that replaces the underlying lung tissue. On the other hand, IPTs with nonneoplastic features have ill-defined or irregular outlines without obliterating the underlying alveolar parenchyma completely. Inflammatory infiltrates in nonneoplastic IPTs are proportionally more prominent. The central portion of these lesions tends to show abundant plasma cells and lymphocytes, cavitation, and less conspicuous proliferation of fibroblasts and myofibroblasts.

Matsubara et al\(^24\) and Gal et al\(^25\) have proposed morphologic subtypes including organizing pneumonia variant, fibrohistiocytic variant, and plasma cell granuloma/ 

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Figure 2. a, Organizing pneumonia. A well-delineated nodular lesion composed of alveolar-filling fibroblastic plugs characteristic of organizing pneumonia (hematoxylin-eosin, original magnification ×40). b, Computerized tomography scan of the chest shows a spiculated opacity in the left lower lobe, suggestive of malignancy. The wedge resection of this lesion showed only focal organizing pneumonia without any evidence of malignancy.

Figure 3. a, Nodular lymphoid hyperplasia. An excised nodular lesion is composed of numerous germinal centers with fibrosis. b, Prominent lymphoid follicles and plasma cells within the nodular hyperplasia. The reactive nature of these infiltrates should be proved by a careful evaluation with immunophenotypic study as well as by histologic examination to rule out malignant lymphoma, which would more likely obliterate the underlying alveolar parenchyma, interlobular septa, and pulmonary vessels (hematoxylin-eosin, original magnifications ×40 [a] and ×200 [b]).
Inflammatory myofibroblastic variant for their IPT cases that appeared to represent both neoplastic and nonneoplastic conditions. Coffin et al. have used similar but slightly different terms to describe the microscopic patterns of IPT (probably also encompassing both neoplastic and nonneoplastic processes): fibrohistiocytic, plasma cell granuloma, largely sclerosed or fibroxed, compact spindle cell pattern, hypocellular fibrous, and myxoid/vascular pattern. Their morphologic descriptions seem to indicate that the term fibrous histiocytoma type or histiocytoma type corresponds to the neoplastic subtype. One could postulate that the morphologic features described as “plasma cell granuloma type,” “organizing pneumonia type,” or “lymphoplasmacytic type” are likely to represent a nonneoplastic process on the basis of the morphologic descriptions for these lesions. However, it is difficult to determine the true nature of these morphologic types. It should be also noted that Dr. Liebow used the term plasma cell granuloma for both neoplastic and nonneoplastic-appearing groups. A recent study reported the presence of IgG4-positive plasma cells in plasma cell granuloma type of IPTs of the lung. This study purported that the clinicopathologic similarities between IPT of the lung and sclerosing pancreatitis suggest that IgG4-related autoimmune processes might be involved in the pathogenesis of some pulmonary IPTs. It is especially important because IgG4-related disease is sensitive to corticosteroid therapy. These findings described in the literature are summarized in Table 1.

### Table 1. Reported Terminology for Clinicopathologic Spectrum of Inflammatory Pseudotumor (IPT)

<table>
<thead>
<tr>
<th>Nonneoplastic IPT variants</th>
<th>Neoplastic IPT (IMT)</th>
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<tr>
<td>Plasma cell granuloma type</td>
<td>Fibrous histiocytoma</td>
</tr>
<tr>
<td>Lymphoplasmacytic or plasma cell type</td>
<td>Histiocytoma</td>
</tr>
<tr>
<td>Organizing pneumonia type</td>
<td>Myxoma</td>
</tr>
<tr>
<td>IgG4-related</td>
<td>Inflammatory fibrosarcoma</td>
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<tr>
<td></td>
<td>Plasma cell granuloma</td>
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<td>Inflammatory fibromyxoid tumor</td>
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Abbreviation: IMT, inflammatory myofibroblastic tumor.

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Previous studies have provided detailed morphologic descriptions of IPT or IMT. Mitotic rate in IPT or IMT is low and a myxoid stroma may be prominent. Some lesions contain prominent fibroxanthomatous features with prominent endogenous lipid. Multinucleated giant cells including Touton-type cells are seen in some cases but granulomas and neutrophils are usually inconspicuous or absent. Inflammatory pseudotumor can invade incorporated or contiguous small vessels, particularly veins. Invasion of pulmonary vessels distant from the main mass also occurs, but this is rare. A purported case of IPT with an extension into large pulmonary veins and pericardium led to a patient’s death. Endobronchial involvement as a polypoid lesion occurs in about 10% of IPT cases with or without extension to the bronchial wall. Mediastinal or hilar involvement, pleural penetration, and multifocal lesions have been described. In IPTs, intraluminal calcification occurs in about 15% of cases and focal necrosis or hemorrhage may be present.

Spindle cells of IPT are uniformly positive for vimentin and also for smooth muscle actin in many cases, but they are usually negative for desmin, myogenin, myoglobin, CD117, and S100 protein, in keeping with a myofibroblastic immunophenotype. ALK stains positively in approximately 40% of IMTs, mostly from patients younger than 40 years of age. ALK positivity is much lower in the broader category of IPT. Protein p53 positivity is rare and is reported in association with recurrence and malignant transformation. Plasm cells are polyclonal.

Differential diagnoses for IMT or IPT include a variety of benign and malignant spindle cell neoplasms (especially malignant fibrous histiocytoma and inflammatory sarcomatoid carcinoma), infection, and nonspecific fibroinflammatory changes. The most important radiographic differential diagnosis in adults with IPT is primary lung cancer. Inevitably, the distinction of IPT cases with nonneoplastic features from a variety of nonspecific reactive conditions could be difficult and may even be arbitrary. Similarly, the distinction between IMT and inflammatory fibrosarcoma can be difficult, a fact highlighted by their designation as synonyms in the current World Health Organization classification of the soft tissue tumor.

At present, surgery is the principal treatment, although nonsteroidal anti-inflammatory drugs, anti–TNF-α antibody, corticosteroids, and chemotherapy have been reported in a few cases. Inflammatory pseudotumors associated with IgG4-related lung disease respond to corticosteroid therapy.

**ORGANIZING PNEUMONIA**

Organizing pneumonia (OP) occasionally forms a mass-like lesion that can masquerade as a tumor and may result in a surgical resection. This presentation commonly causes concern for malignancy and leads to a surgical resection of the lesion, especially when a needle biopsy is apparently not satisfactory to explain the nodule found on radiologic studies. In this setting, OP may be cryptogenic or secondary to a number of other causes, including infection, radiation treatment, underlying malignancy, or drug reaction. Histologically, OP consists of proliferating fibroblasts forming organized plugs within the air spaces (Figure 2, a). This is often accompanied by varying degrees of interstitial chronic inflammation and type II pneumocyte hyperplasia. Organizing pneumonia presenting as a solitary nodule by radiologic imaging (Figure 2, b) often is cause, first, for a computed tomography (CT)-guided needle biopsy. If the needle biopsy shows OP on histologic examination, the patient may still undergo surgical biopsy to rule out malignancy. A recent study at Mayo Clinic reported the clinical and radiologic manifestations of 26 cases diagnosed by surgical lung biopsy as OP from 1997 to 2004. All patients presented with a unifocal opacity detected on chest radiography or CT scans. At the time of presentation, only 10 patients (38%) had symptoms, including cough, shortness of breath, or chest pain. Contrast-enhancement CT scan or positron emission tomography scanning was performed for 11 patients and the results were positive in all. Surgical procedures included wedge resection for 21 patients (81%), segmentectomy for 3 patients (11%), and lobectomy for 2 patients (8%). Three cases of focal OP were related to infections, but the remaining cases were cryptogenic. Follow-up over a median interval of 11 months (range, 1 to 71 months) yielded no recurrence of OP.

The radiologic features of focal OP are often indistin-
NODULAR LYMPHOID HYPERPLASIA

Pulmonary nodular lymphoid hyperplasia (NLH), a term first coined by Kradin and Mark, refers to 1 or more nodules or localized pulmonary infiltrates consisting of a reactive lymphoid proliferation. The concept of “pseudo-lymphoma” for reactive localized masses of lymphoid tissue in the lung was initially proposed by Saltzstein in his review of pulmonary lymphoid lesions showing low histologic grade, the presence of numerous lymphoid follicles, and a benign clinical course. Most recently, Abbadanzo et al reported a clinicopathologic study on 14 cases of NLH by applying more modern immunophenotypic and molecular methods to exclude a clonal or neoplastic process.

It has been now well recognized that most localized lymphoid lesions arising in the lung are marginal zone B-cell lymphoma. However, there are some cases that have proved to be polyclonal and reactive in nature. For those cases, the term nodular lymphoid hyperplasia is appropriate and is preferred to pseudolymphoma, as it more accurately reflects its histogenetic characteristics. Abbadanzo et al reported that cases collected at the Armed Forces Institute of Pathology showed patients’ ages ranging from 19 to 80 years (mean, 65 years) with a slight female predominance (ratio of men to women, 3:4). Ten of 14 cases (71%) were found incidentally on routine chest radiographs but some patients were symptomatic with signs of cough, shortness of breath, and pleuritic pain. Most lesions were solitary and subpleural. When the disease was multifocal (5 cases), it was usually unilateral. Five patients (36%) also had concomitant hilar, mediastinal, or paraspinal lymphadenopathy. No recurrence of a pulmonary lesion was documented after surgical resection and all 7 patients with follow-up information were alive, with no evidence of disease in a period from 8 months to 6 years after surgical excision.

Grossly, NLH comprises a well-circumscribed, fleshy or rubbery nodule (or nodules) usually measuring 2 to 4 cm, but larger lesions have been reported. Histologically, lymphoid follicles are typically well developed. Plasma cells are frequently prominent between the follicles (Figure 3, a and b). Most cases show at least mild interstitial fibrosis, but in some cases it is dense and remarkable. Focal and limited lymphangitic spread of lymphocytes and plasma cells around the bronchovascular bundles and interlobular septa may be seen. Despite the frequent subpleural location of NLH, plaque-like lymphoid infiltrates in the pleura are rare. Large airways are usually not particularly involved. Regional lymph nodes biopsied at the same time show reactive follicular hyperplasia.

Immunohistochemistry shows a mixture of B cells (with polyclonal λ light chain expression) and T cells. Bcl-2 stain is negative in germinal centers but positive in mantle zone cells and T lymphocytes within and between germinal centers. Immunoglobulin heavy chain gene rearrangement should be absent, by definition, when molecular genetic analysis is performed.

The most important differential diagnosis for NLH is mucosa-associated lymphoid tissue (MALT) lymphoma but it also needs to be differentiated from lymphocytic interstitial pneumonia, lymphomatoid granulomatosis, and IPT or IMT. Nodular lymphoid hyperplasia differs from lymphocytic interstitial pneumonia in that it is focal rather than diffuse. In contrast to IPT or IMT, spindle cells in the background are absent in NLH. Unlike lymphomatoid granulomatosis, markedly atypical B cells are absent in NLH, which will be negative for Epstein-Barr virus by either immunohistochemistry or in situ hybridization. The distinction from MALT lymphoma is particularly difficult if not impossible without molecular studies. Any significant degree of lymphangitic pattern of infiltrative activity would favor lymphoma. Helpful findings in favor of MALT lymphoma include diffuse infiltrative architecture with invasion of pleura and bronchial cartilage, prominent monocyotic B cells, centrocyte-like (cleaved) atypical lymphocytes, intranuclear inclusions (Dutch bodies), prominent lymphoepithelial lesions, and light chain restriction (demonstrable in approximately 40% of cases). It should be noted that some cases remain unclear even after extensive immunophenotypic and molecular studies. It is appropriate to label such cases as an “atypical lymphoid proliferation” if there are sufficient atypical histopathologic features in favor of malignancy.

APICAL CAP

Apical cap, also referred to as apical scar, is a form of localized pulmonary fibrosis. Although historically, apical caps were thought to be caused by tuberculosis, most often the etiology is unknown. Other rare etiologies include radiation, infection other than tuberculosis, trauma, and vascular abnormalities. In idiopathic cases, the apical cap is a common incidental radiologic finding, reported as unilateral in 11.2% and as bilateral in 12.2% of 258 adults undergoing routine chest radiographs. A similar frequency is reported in an old autopsy series. The prevalence of apical caps increases with age and is usually found in patients older than 45 years but may be recognized in younger individuals. The prevalence is similar between men and women. Radiologically, these lesions are described as soft tissue densities, with sharply demarcated smooth or undulating margins, measuring on average of 5 to 6 mm in height. However, radiologic variations of apical caps can result in diagnostic challenges, in particular with apical carcinomas (Pancoast tumor). Therefore, apical caps are occasionally biopsied, thus the need, as a surgical pathologist, to be aware of their morphologic appearance.

Although usually present in the upper lobes, apices of lower lobes can also be involved. The gross and histologic features of apical caps are very characteristic and descriptions from autopsy and surgical series are very similar. Grossly, the apical cap is a slightly depressed, gray-white opaque plaque lesion, which on cross section appears triangular (Figure 4, a). Pleural thickening is usually present, opaque and white, with sharp lateral margins. The underlying lung parenchyma appears gray-white and usually contains black anthracotic streaks. Histologically, at low power, the triangular shape is apparent with the broad base extending along the pleural surface (Figure 4, b). In smokers, the peripheral lung parenchyma often displays emphysematous changes with respiratory bronchiolitis. The lesion comprises mostly areas of dense fibrosis,
Figure 4. Apical cap. a, Cross section of gross lung specimen showing the typical triangular-shaped scar located beneath slightly thickened pleura. The scar is gray-white with focal areas of anthracosis. b, Low-power photomicrograph of an apical scar. The pleural thickening is mild, dense, and eosinophilic, which contrasts with the basophilic appearance of the triangular pulmonary scar. c, High-power photomicrograph highlights the composition of the apical scar with collapse of the pulmonary elastic framework and increase in elastic fibers, which are usually fragmented (hematoxylin-eosin [b and c], original magnifications ×20 [b] and ×400 [c]).

which appear to have obliterated the air spaces with the underlying elastic framework intact. However, the elastic framework is collapsed and fibers are typically increased and fragmented (Figure 4, c). This most distinctive feature distinguishes apical caps from other types of pulmonary scars. Metaplastic ossification or dystrophic calcification of the area of fibrosis is frequently noted in surgically resected fibrotic caps. Necrosis is not usually present. Chronic inflammation is usually mild and acute inflammatory reactions absent. Granulomas are an uncommon finding, seen in only 15% (7 of 48) of autopsy cases reported in 1970 and in a single case (1 of 13) from a recent surgical series.66,69 When present, they are located in the adjacent lung parenchyma and the cap itself is not involved. These findings further support causes other than tuberculosis as the etiology. Moderate to severe vascular abnormalities, characterized by mural thickening and old fibrotic thrombosis with recanalization of arteries and mural sclerosis of pulmonary veins, located in the immediate adjacent lung parenchyma, are another distinctive feature, seen in more than half of cases. Based on this observation, along with the apical location, the leading hypothesis for the pathogenesis of apical caps is ischemic injury. Another significant feature is the pneumocyte hyperplasia present at the edge of the cap or within entrapped residual air spaces, which can be misinterpreted as carcinoma associated with a scar. Pneumocyte hyperplasia tends to be pleomorphic and nonuniform in contrast to well-differentiated adenocarcinoma, in particular bronchioloalveolar carcinoma, in which the cell atypia is monotonous and regular. Nuclear overlap with loss of polarity and increased nuclear cytoplasmic ratio are other features favoring malignancy.41 Other differential diagnoses include organizing pneumonia (discussed above), arterial infarct, and silicotic nodule. Infarcts share some histologic features with apical cap lesions, notably a pleural-based location, triangular shape, and the presence of arterial vascular abnormalities. However, infarcts are more commonly located in the lower lobes, may be of varying age, and will show varying amounts of hemorrhage and organization with proliferating fibroblasts. Furthermore, the elastic framework is often not well preserved in an infarct, in contrast to the prominent elastosis of an apical cap. Silicotic nodules are typically spherical and well-demarcated and comprise concentric collagen fibers with interspersed dust-laden macrophages.

ROUND ATELECTASIS

Round or rounded atelectasis is known by many other terms including folded lung, shrinking pleuritis with atelectasis, atelectatic pseudotumor, and pleura, a reflection of its appearance, location, and presumed pathogenesis.42–47 Patients with round atelectasis are predominantly men (>90%) and are often smokers, with a mean age of 60 years (range, 20 to 83 years).42–47 Patients are usually asymptomatic, with incidental discovery of a mass on routine chest radiograph. When symptoms occur, they most often include cough, dyspnea, and fever with fatigue or weight loss. Rarely, hemoptysis and chest pain have been reported. Although most cases have been attributed to asbestos exposure, other potential etiologies comprise tuberculosis, Dressler syndrome, cardiac failure, uremia, and trauma.42–47 Occasionally, a specific etiology may not be elicited from the clinical history.

Two main theories for the formation of round atelectasis
have been proposed. The original theory suggests that round atelectasis is the result of the mechanical influence of a pleural effusion on the lung, with compression and folding of the lung and fixation in this position by a pleural fibrinous exudate; as the effusion resolves, the normal adjacent lung hyperexpands to fill the space and thus engulfs the atelectatic lung. The second theory proposes a fibrosing mechanism by which a primary localized inflammation of the pleura becomes progressively fibrotic and contracts, leading to folding of the pleura and collapse of the underlying lung.

Both theories could explain the typical radiologic findings. On plain chest radiograph, round atelectasis is described as a rounded mass, 2.5 to 5 cm in dimension, although lesions up to 10 cm have been reported. The most common location is the posterior surface of the lower lobe (approximately 75% of the lesions). It is pleural based and associated with pleural thickening. The most characteristic and specific feature (reported specificity of 92%) is the curvilinear displacement of the vessels and bronchi towards the center of the mass described as the “comet tail” sign. Chest CT with contrast usually confirms the diagnosis and precludes the need for further treatment. However, the comet tail sign is not always present (reported sensitivity of 83%), and a number of variants have been reported with CT; therefore, these lesions may appear clinically suggestive of lung cancer or mesothelioma, particularly in older men who are smokers and with a history of exposure to asbestos.

Morphologic features are distinctive. Grossly, the visceral pleura appears thickened and fibrotic, and sections of the underlying lung reveal no apparent parenchymal abnormality that would correlate with the radiologic findings. Prominent folding of the pleura with invagination into the underlying lung is seen underneath the area of fibrosis. Histologically, the pleural fibrosis is superficial to the elastic and interstitial layer of the pleura, which is of normal thickness but characterized by prominent wrinkling and infolding (Figure 5, a). The infolding is deep and usually related in superimposition of the wrinkled pleura (Figure 5, b). These distinctive features of round atelectasis separate it from simple pleural fibrosis. The fibrosis is mostly acellular with mild chronic inflammation. The appearance of the underlying parenchyma is variable; it often appears collapsed but otherwise unremarkable. Focal nonspecific fibrosis and sclerosis of vessels can be seen. Asbestos bodies can occasionally be identified. Some authors have suggested that round atelectasis is part of a spectrum of pleural fibrotic diseases, from localized pleural fibrosis without associated round atelectasis to diffuse pleural fibrosis, both of which may be associated with pulmonary atelectasis, including involvement of an entire lobe.

When observed, round atelectasis remains stable although cases of spontaneous regression, as well as progression, have been reported. In patients undergoing surgical excision, no further lesions develop on follow-up.

SCLEROSING (FIBROSING) MEDIASTINITIS AND HYALINIZING GRANULOMA

Sclerosing mediastinitis and hyalinizing granuloma share similar histologic features and are both thought to be immunologically derived. Sclerosing mediastinitis involves predominantly the mediastinum and hilar regions and can extend to the lung parenchyma, while hyalinizing granuloma occurs within the lung parenchyma without contiguous involvement of the mediastinum. Some patients may manifest both lesions concomitantly and may also have features of other fibrosing disorders, such as retroperitoneal fibrosis.

Sclerosing Mediastinitis

Sclerosing mediastinitis is a rare condition thought to result from many etiologies, an abnormal immunologic response to histoplasmosis being the most prominent one in the United States (Table 2). It affects predominantly young adults (mean age varies between 30 and 45 years) and men slightly more than women. Distribution of the fibrosis and varying degrees of compression of the mediastinal and hilar structures determine the type and severity of the clinical presentation (Table 3). Venous infarcts have received much attention, as they can be the first manifestation of sclerosing mediastinitis and present in a surgical lung biopsy of a patient with localized infiltrates.

Radiologically, sclerosing mediastinitis is divided between 2 types: focal, the most common, and diffuse. The focal type presents mainly as a localized and calcified mass in the paratracheal or subcarinal compartments of the mediastinum or in the pulmonary hilum. The diffuse
Table 2. Major Causes of Sclerosing (Fibrosing) Mediastinitis

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
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<tbody>
<tr>
<td>Histoplasmosis</td>
<td>Autoimmune conditions (eg, IgG4-related immunopathologic process)</td>
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<tr>
<td>Other fungal infections (aspergillosis, cryptococcosis, blastomycosis, mucormycosis)</td>
<td>Sarcoidosis</td>
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<tr>
<td>Tuberculosis</td>
<td>Radiation</td>
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<tr>
<td>Noninfectious</td>
<td>Drugs (eg, methysergide)</td>
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<tr>
<td>Sarcoidosis</td>
<td>Familial</td>
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<tr>
<td>Radiation</td>
<td>Idiopathic</td>
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Table 3. Clinical Manifestations of Sclerosing (Fibrosing) Mediastinitis

- Asymptomatic
- Systemic symptoms
- Fever
- Weight loss
- Chest pain
- Airway involvement
  - Stridor
  - Dyspnea
  - Wheezing
  - Hemothysis
- Pulmonary atelectasis
- Postobstructive pneumonia
- Vascular involvement
  - Superior vena cava syndrome
  - Pulmonary hypertension
  - Arterial or venous infarcts
- Esophageal involvement
  - Dysphagia
  - Esophagobronchial fistula

Type is typically not calcified and presents as a diffusely infiltrating mass, affecting multiple mediastinal compartments. Additional pulmonary findings, such as infiltrates, consolidation, and pleural effusion, are not uncommon. The clinical outcome is variable. Prognosis depends mainly on the location of the area of fibrosis and structures involved. With focal sclerosing mediastinitis, prognosis is excellent but a mortality of 30% was reported for cases with more diffuse involvement.53,54,56,57 Surgery can be done for complete resection or palliation, depending on the extent of the disease. Percutaneous stenting of major hilar structures has also been used for palliation. Most studies show little or no benefit with most medical treatments, including steroids. However, recently Inoue et al64 reported a patient with sclerosing mediastinitis who had elevated serum IgG4 and increased numbers of IgG4-positive plasma cells in the mediastinal lesion. They suggested the possibility of an IgG4-related immunopathologic process similar to sclerosing pancreatitis. This has significant clinical implication as their patient, like those patients suffering from sclerosing pancreatitis, responded well to steroids with regression of the mediastinal mass.

The gross findings for sclerosing mediastinitis are described as tan-yellow, gelatinous masses to gray-white, hard masses that compress or infiltrate mediastinal structures (Figure 6, a). Infiltration of pericardium, pleura, and pulmonary parenchyma can also be seen. Histologically, sclerosing mediastinitis is characterized by dense collagen type.
fibrosis forming lamellar bands with interspersed lymphocytes and plasma cells (Figure 6, b and c). Inflammation tends to be denser at the periphery of the area of fibrosis, with lymphocytes often forming follicles. In cases of fungal or mycobacterial infection, granulomas are sometimes seen entrapped within the area of fibrosis. It can be variably cellular, with some foci showing more prominent proliferation of spindle cells with ample cytoplasm that display a myofibroblastic immunophenotype. Other areas are paucicellular and the fibrosis has a distinct keloid-like appearance. Necrosis, calcification, and metaplastic bone can occasionally be present.

Occasionally, a surgical lung biopsy may be performed for pulmonary infiltrates in association with hilar enlargement of undetermined cause. The histologic findings usually are a manifestation of the occlusion of mediastinal structures and pulmonary veins are most susceptible, resulting in venous infarcts. Since major veins are being occluded, these venous infarcts are multifocal, located near or around peripheral veins in interlobar septa. The lumens of the veins are often occluded by cellular fibrosis. The infarcts are hemorrhagic and organizing pneumonia surrounding the necrosis can be prominent. The intervening lung parenchyma shows varying degree of interstitial thickening by fibrosis and chronic inflammation, mimicking lung parenchyma shows varying degree of interstitial thickening by fibrosis and chronic inflammation, mimicking lung parenchyma.

The infarcts are hemorrhagic and organizing pneumonia surrounding the necrosis can be prominent. The intervening lung parenchyma shows varying degree of interstitial thickening by fibrosis and chronic inflammation, mimicking lung parenchyma. Recognizing the venous infarcts is crucial in suggesting sclerosing mediastinitis as the etiology for the pulmonary infiltrates. The most important differential diagnosis is fibrosing malignant neoplasms such as Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, and desmoplastic malignant mesothelioma. Adequacy of biopsy is very important and diagnosing sclerosing mediastinitis in small biopsy specimens should be made with caution. The presence of nodular collection of eosinophils and histiocytes admixed with the lymphocytes and plasma cells should prompt the search for Reed-Sternberg cells and assessment of additional material in their absence. In sclerosing mediastinitis, the cells are typically fibroblasts or myofibroblasts with expression of vimentin, with or without coexpression of muscle actin antibodies. This is in contrast to mesothelioma, in which cells usually show diffuse expression of keratin antibodies.

Hyalinizing Granuloma

Hyalinizing granuloma occurs in young to middle-aged adults, with a mean age of 40 to 45 years, with slight predominance in men. Symptoms are usually mild and include cough, dyspnea, and pleuritic chest pain. The radiologic presentation is that of solitary or multiple lung nodules, which may progress and thus mimic cancer. However, the clinical course is benign. Approximately 15% of patients have or will develop sclerosing mediastinitis.

Hyalinizing granulomas form discrete firm nodules, which histologically are identical to sclerosing mediastinitis, and mostly include thick, densely eosinophilic keloid-like bundles of collagen with a lamellar arrangement, often in a storiform pattern. Calcification, metaplastic ossification, and necrosis are rare. The main differential diagnosis is amyloid nodules. Amyloid is more amorphous, and calcification and ossification are common. A foreign body giant cell-type reaction is often present and, most importantly, histochemical stains, such as Congo red, will stain positively for amyloid.

CONCLUSION

Many lesions involving the lung, pleura, and mediastinum have the propensity to mimic cancer clinically. This article briefly overviewed the most commonly encountered lesions in our surgical pathology practice. To know their existence and include them in one's differential diagnosis is the key to their detection and in the helpful correlation with clinical and radiologic findings.

References