Case 1. Diagnosis: Metastatic serous carcinoma of female genital tract origin presenting as a pleural effusion. Case presented to discuss mesothelioma and its differential diagnosis.

The most common malignancy in the pleura is metastatic carcinoma, especially lung, breast, and others. Serous carcinoma metastatic from the female genital tract is distinctly unusual.

I. Key considerations in the differential diagnosis of mesothelioma include:

1) Location; the differential for pleural involvement is different from that of peritoneal involvement.
2) Sex; eg. breast carcinoma in women, prostate carcinoma in men.
3) Histologic pattern encountered; epithelioid proliferations, be they benign or malignant, are approached differently (especially regarding immunohistochemical staining) from spindled proliferations.

Situation #1. Reactive mesothelial cells versus mesothelioma. This is primarily a histologic determination although a number of special stains have been touted as helpful. The key feature for the morphologist is finding invasion into lung or chest wall. A diagnosis of malignancy can be made in the absence of invasion, for example, in the presence of a bulky mass in the pleura, or compelling cytologic features.

Situation #2. The proliferation is malignant and the issue is epithelioid mesothelioma versus metastatic carcinoma or other mimic. This is the most common situation and the key points are to tailor the differential and the immunostains used (depending on sex, location, prior history of tumor, etc.) and to use a panel of antibodies since no single antibody will be diagnostic. *(Inconclusive immunostains or an inconclusive panel of immunostains is something that we have to live with and in such situations, each case must be individualized and all of the clinical, radiologic, histologic data re-assessed).*

Situation #3. The pleural process is a spindled proliferation and the issue is fibrous pleuritis versus malignancy, especially sarcomatoid/desmoplastic mesothelioma. Again the key finding is evidence of invasion, either of lung or chest wall. Bland necrosis and frankly sarcomatoid histology are also touted as useful. In this situation, a pankeratin stain is usually the only stain needed. Other mesothelial markers are inconsistently positive. In general, mesotheliomas are haphazard and irregular in their proliferation (and cytokeratin staining), whereas reactive fibrous pleuritis has a regularity and zonation that are readily recognizable.
**Situation #4.** There is malignant spindle cell process in the pleura and the issue is sarcomatoid mesothelioma versus sarcomas and other malignant spindle cell tumors including sarcomatoid carcinoma. This situation is rare and in general each case must be individualized. The most common sarcoma to mimic mesothelioma is angiosarcoma (including both epithelioid hemangioendothelioma and high-grade angiosarcoma).

II. Molecular aspects of mesothelioma may prove useful, both diagnostically and prognostically. 9p21 (p16) deletion is almost universal in sarcomatoid mesothelioma and p16 staining could be useful in this setting. Tumors showing p16 deletion have a significantly worse survival than those lacking such a deletion.

**References:**


**Case 2. Diagnosis:** Fibrotic nonspecific interstitial pneumonia misdiagnosed as usual interstitial pneumonia. Patient alive 22 years later.

I. Usual interstitial pneumonia/UIP is a pattern that can be recognized radiologically and pathologically. Most case of UIP occur in the setting of idiopathic pulmonary fibrosis/IPF but not all. The diagnosis of IPF is based on clinical, radiologic, and pathologic correlation (and in controversial cases multidisciplinary discussion/MDD).

II. The pathologic features of UIP are well known: established fibrosis, typically with honeycomb change, occurring in a patchy distribution that may be paraseptal and subpleural. Activity is confirmed by the presence of fibroblast foci.

Cases become difficult when one struggles with whether or not a process should be considered patchy, whether convincing features of chronicity are present, and the fact that fibroblast foci are not unique to or diagnostic of UIP.

III. UIP represents one of the most common patterns of interstitial pneumonia encountered by the pathologist (hence the term “usual” used by Averill Liebow when the term was first coined). Because of this, the most important decisions for the pathologist are as follows:

1) Is it UIP?
2) Is it idiopathic UIP/IPF?

Since the pattern UIP may be encountered in other situations such as connective tissue diseases, drug reactions, familial pulmonary fibrosis, chronic hypersensitivity pneumonitis, and other rare settings there are some histologic clues that may point toward some of those possibilities: *increased inflammation, scattered granulomas, and germinal centers.*

IV. IPF is a generally fatal disease with no good therapy and a number of treatment trials are underway. More and more pathologists are being involved in such treatment trials and in order to accrue patients, algorithms that include radiologic findings and pathologic findings have been devised and various combinations of *definite, possible, and inconsistent with UIP* determinations by the radiologists and *definite, probable, possible, not UIP* determinations by the pathologist are combined to determine whether or not a patient is eligible. While this approach is useful in clinical trials, applying the terms *definite, probable, possible, not UIP* in routine practice for individual patients is not appropriate.
V. The dogma for histologic diagnosis of most interstitial lung diseases, especially UIP and NSIP, has been that surgical lung biopsy, typically by the VAT’s technique these days, is required. Transbronchial biopsy may be occasionally useful in some other conditions but TBBx is not acceptable for a diagnosis of UIP or NSIP. A new technique, transbronchial cryobiopsy allows for much larger pieces of tissue to be retrieved bronchoscopically and for the architecture to be much better appreciated and these may potentially become useful in diagnosis of UIP and NSIP.

References:


**Case 3. Diagnosis:** Aspiration pneumonia with prominent granulomatous reaction. Case discussion: aspiration as a problem for the pathologist and the approach to granulomas when encountered in lung biopsy material.

I. Aspiration has been grossly under recognized by pathologists. This is probably due to the fact that exogenous material may be scant and easily missed unless specifically sought and the fact that not all cases will in fact show such material histologically.

In a consecutive study of granulomas in biopsy material, 12 percent of the cases were due to aspiration, more than for sarcoid, hypersensitivity pneumonitis, and any specific granulomatous infection.

Aspiration pneumonia typically is a lower lobe relatively localized process although it occasionally may produce bilateral infiltrates.

II. The key histologic finding is exogenous material with or without an associated granulomatous reaction. It is often bronchiolocentric and may be associated with acute bronchiolitis and giant cells containing neutrophils as well as foreign material. Some, but not all foreign material polarizes. Food often does not polarize.

In a very interesting study from Yousem and Faber, it was shown that people with unequivocal aspiration (as documented radiologically or at the time of bronchoscopy) may not show foreign material in biopsy material. All that one may encounter was organizing pneumonia, diffuse alveolar damage, or bronchiolitis.

There are a number of clues to consider aspiration if no foreign material is seen: history of GERD, drugs that alter conscientiousness, relatively localized processes showing abscess, organizing pneumonia, bronchiolitis, granulomas or giant cells.

III. The overall approach to granulomas when encountered in biopsy material depends on a number of factors. The following may be adjunctive clues to etiology: exposure history, anatomic distribution of the granulomas, immune status of the patient, risk factors for aspiration, underlying autoimmune disease, medication history, laboratory results, etc.

Examples of exposure history as useful information: birds, beryllium, aerosolized mycobacteria (hot tub lung), aspiration, Sjogren’s syndrome, and prior medications known to be associated with granulomas, etc.

Specific clues that one can identify under the microscope: anatomic distribution of the granulomas, quantitative features of the granulomas (how many), qualitative features (how well formed, necrotizing, foreign material, etc.), and
findings in the lung tissue away from the granulomas (inflammation, eosinophils, foreign material, fibrosis, etc.).

IV. Radiologic findings are also helpful.
1) Diffuse lung disease: sarcoid, hypersensitivity pneumonitis, miliary infection, berylliosis, Sjogren’s syndrome, etc.
2) Relatively localized uni- or multinodular processes: granulomatous infection, aspiration, vasculitis (WG/GPA), etc.

References:

