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1. Pathology of the pleura

Pleural disorders are always in the shadow of lung diseases. The discussion of these diseases has been neglected in relation to other diseases although the symptoms of pleural effusion always accompany lung as well as heart diseases.

Inflammation of the pleura may be acute or chronic, of nonspecific or specific type. Prolonged, chronic effusion causes reactive changes on mesothelial cells that can be histologically misdiagnosed as malignancy. Tuberculosis inflammation causes pleural effusion characterized by the presence of large numbers of lymphocytes and a small number of mesothelial cells. Tuberculous pleuritis is the most common form of extrapulmonary tuberculosis [1].

Malignant pleural effusions are a consequence of lung cancer spreading to visceral or parietal pleura. Pleural mesothelioma also causes effusions [2, 3].

The most accurate differential diagnosis between primary lung cancer and pleural mesothelioma is immunohistochemical diagnosis [4–7].

Pleural tumors originate from mesenchymal cells of the epithelial type and submesothelial cells of the mesenchymal type. The most common pleural mesenchymal tumor is a solitary fibrous tumor of the pleura. The biological behavior of this tumor of the pleura is predicted by the proliferation marker, protein Ki-67, and when its index is more than 4 mitoses at 2 mm$^2$ or >4/10 high power fields, it may be considered as a malignant alteration that creates dilemmas about the treatment [8, 9].

We will pay particular attention to reactive mesothelial cells as well as to tumors of the pleura.

Figure 1.
Cellular pleural effusion with mass of reactive mesothelial cells.
Reactive mesothelial cells are difficult to distinguish morphologically from malignant mesothelial cells both on biopsy and on effusion \(\text{(Figure 1)}\) \([8, 9]\). Recently, a monoclonal antibody, bap-1, which is mainly expressed in reactive mesothelial cells has been used \(\text{(Figure 2)}\). It is also expressed in malignant mesothelial cells but not in malignant cells of another origin, such as lung adenocarcinoma \([10]\).

According to the latest WHO classification of pleural tumors \([8]\), they are divided into mesothelial tumors, mesenchymal tumors, and lymphoproliferative disorders.

2. Classification of pleural tumors

- Mesothelial tumors
  - Diffuse malignant mesothelioma
  - Epithelioid mesothelioma
  - Sarcomatoid mesothelioma
  - Biphasic mesothelioma
  - Desmoplastic mesothelioma
  - Localized malignant mesothelioma
  - Other tumors of mesothelial origin
  - Well-differentiated papillary mesothelioma
  - Adenomatoid tumor
• Lymphoproliferative disorders
  ○ Primary effusion lymphoma
  ○ Pyothorax—associated with lymphoma

• Mesenchymal tumors
  ○ Epithelioid hemangioendothelioma
  ○ Angiosarcoma
  ○ Synovial sarcoma
  ○ Monophasic
  ○ Biphasic
  ○ Solitary fibrous tumor
  ○ Calcifying tumor of pleura
  ○ Desmoplastic round cell tumor

We will consider the most common types, in the group of mesothelial tumors—pleural mesothelioma and in the group of mesenchymal tumors—solitary fibrous tumor.

Pleural mesothelioma is divided into the most common, monophasic, epithelioid type (Figure 3); sarcomatoid type (Figure 4); biphase, epithelioid/sarcomatoid (Figure 5) and the rarest, difficult-to-diagnose, desmoplastic type (Figure 6). Epithelioid mesothelioma is diagnosed and differentiated from carcinoma that involve pleura with monoclonal antibodies: podoplanin (D2-40) (Figure 7), HBME-1 (Figure 8), cytokeratin 5 (Figure 9), calretinin (Figure 10), and WT-1 (Figure 11). By using several of these antibodies, epithelioid mesothelioma can be diagnosed with great certainty. Sarcomatoid mesothelioma can be diagnosed by using the following antibodies: cytokeratins, vimentin, HBME-1, and Fascin, but this type can be differentiated from pulmonary sarcomatoid carcinoma only by clinical findings [4–8].

Figure 3.
The most frequent type is epithelioid malignant mesothelioma.
Figure 4.
Mixed, epithelioid/sarcomatoid type of malignant mesothelioma.

Figure 5.
Sarcomatoid type of malignant mesothelioma.

Figure 6.
Desmoplastic malignant mesothelioma is a rare type and difficult for pathological diagnosis.
Introduction to Pathology of the Pleura
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Figure 7. Podoplanin (D2-40) is characteristic antibody for diagnosis of epithelioid type of malignant mesothelioma.

Figure 8. HBME-1 is useful antibody for diagnosis of epithelioid type of malignant mesothelioma.

Figure 9. Cytokeratin 5 is dominant antibody for diagnosis of epithelioid type of malignant mesothelioma.
Solitary fibrous tumor is fibroblastic neoplasm, consisting of primitive connective tissue cells, which can therefore mimic morphological picture of neurofibroma or hemangiopericytoma with zones of hypercellularity (Figure 12) and hypocellularity (Figure 13). However, solitary fibrous tumor is characterized by immunophenotype of tumor cells. These cells express vimentin, CD34, bcl-2, and Stat-6 (Figure 14). The proliferation index of these cells is low in benign phase, less than 2 mitosis/10 HPF (Figure 15). If this tumor recurs and proliferation index is elevated, it is advised that tumor is treated as a sarcoma [11, 12].

Rare mesenchymal tumors are epithelioid hemangioendotheliomas which can be bilateral, both in the lungs and in the pleura. Monophasic and biphasic types of synovial sarcoma are also rare. These tumors have a specific immunophenotype, where epithelioid hemangioendothelioma (Figures 16–18) expresses vascular markers, while synovial sarcoma expresses (Figures 19 and 20) itself as synovial sarcoma of the joints but with a specific genetic mutation [13–15].
Figure 12.
Hypercellular zone of solitary fibrous tumor of pleura.

Figure 13.
Hypocellular zone of solitary fibrous tumor of pleura.

Figure 14.
Stat-6 is a characteristic antibody for diagnosis of solitary fibrous tumor of pleura.
Diseases of Pleura

Figure 15.
High Ki-67 proliferative index (>4/10 high power fields), is a sign of malignant alteration of solitary fibrous tumor of pleura.

Figure 16.
Small cleft covered focally by with "signet ring cell" appearance in epithelioid hemangiendothelioma.

Figure 17.
Fli-1 expression in cells confirmed endothelial cells.
Figure 18.
ERG expression also confirmed endothelial origin of the tumor cells.

Figure 19.
Small spindle cells in sarcomatoid type of synoviosarcoma.

Figure 20.
Tle-1 is expressed in synoviosarcoma.
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