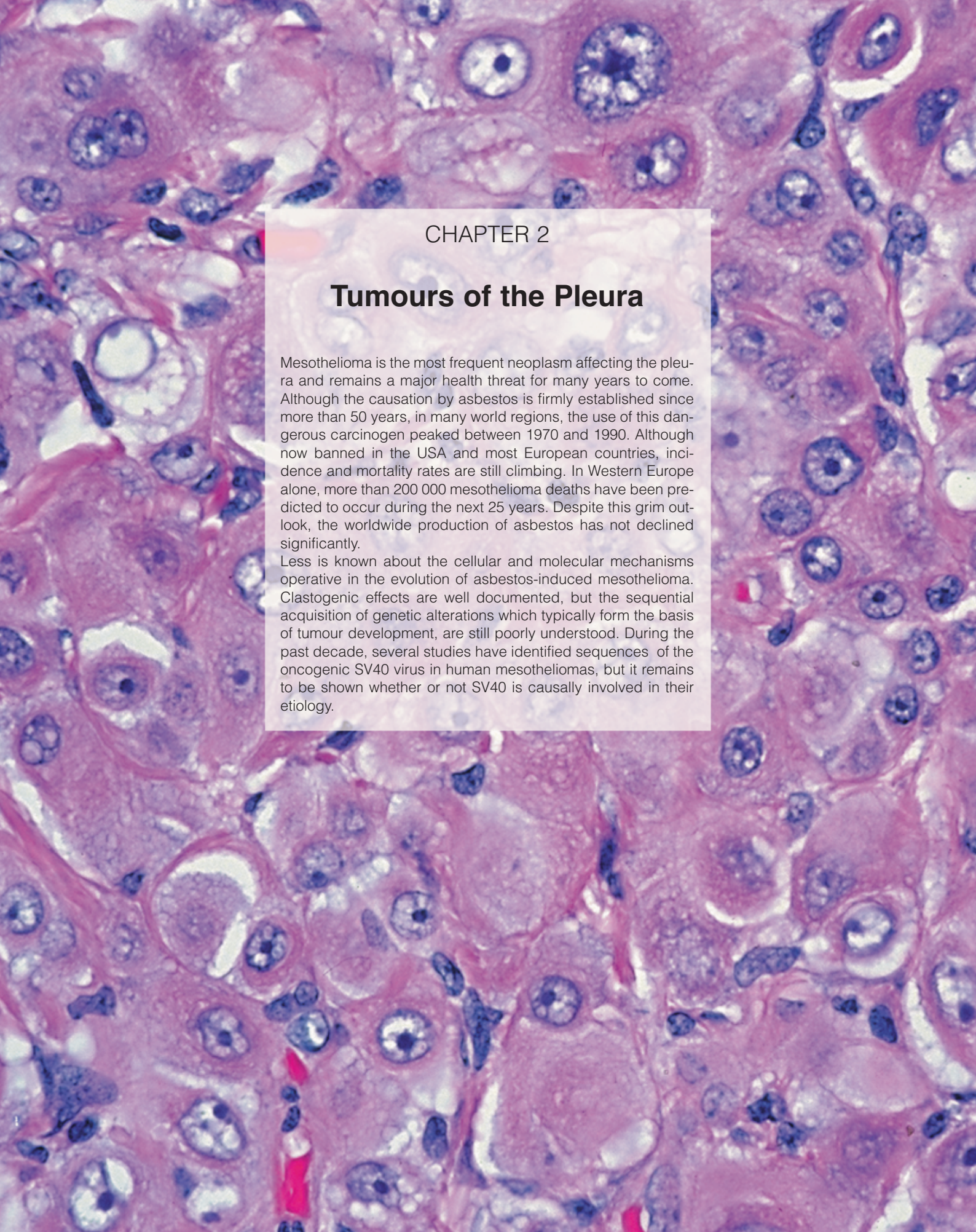


CHAPTER 2

Tumours of the Pleura

Mesothelioma is the most frequent neoplasm affecting the pleura and remains a major health threat for many years to come. Although the causation by asbestos is firmly established since more than 50 years, in many world regions, the use of this dangerous carcinogen peaked between 1970 and 1990. Although now banned in the USA and most European countries, incidence and mortality rates are still climbing. In Western Europe alone, more than 200 000 mesothelioma deaths have been predicted to occur during the next 25 years. Despite this grim outlook, the worldwide production of asbestos has not declined significantly.

Less is known about the cellular and molecular mechanisms operative in the evolution of asbestos-induced mesothelioma. Clastogenic effects are well documented, but the sequential acquisition of genetic alterations which typically form the basis of tumour development, are still poorly understood. During the past decade, several studies have identified sequences of the oncogenic SV40 virus in human mesotheliomas, but it remains to be shown whether or not SV40 is causally involved in their etiology.

WHO histological classification of tumours of the pleura

Mesothelial tumours	
Diffuse malignant mesothelioma	9050/3
Epithelioid mesothelioma	9052/3
Sarcomatoid mesothelioma	9051/3
Desmoplastic mesothelioma	9051/3
Biphasic mesothelioma	9053/3
Localized malignant mesothelioma	9050/3
Other tumours of mesothelial origin	
Well differentiated papillary mesothelioma	9052/1
Adenomatoid tumour	9054/0
Lymphoproliferative disorders	
Primary effusion lymphoma	9678/3
Pyothorax - associated lymphoma	
Mesenchymal tumours	
Epithelioid hemangioendothelioma	9133/1
Angiosarcoma	9120/3
Synovial sarcoma	9040/3
Monophasic	9041/3
Biphasic	9043/3
Solitary fibrous tumour	8815/0
Calcifying tumour of the pleura	
Desmoplastic round cell tumour	8806/3

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {6} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

TNM classification of pleural mesothelioma

TNM classification [1,2]

T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Tumour involves ipsilateral parietal pleura, with or without focal involvement of visceral pleura

T1a Tumour involves ipsilateral parietal (mediastinal, diaphragmatic) pleura. No involvement of visceral pleura

T1b Tumour involves ipsilateral parietal (mediastinal, diaphragmatic) pleura, with focal involvement of the visceral pleura

T2 Tumour involves any ipsilateral pleural surfaces, with at least one of the following:
- confluent visceral pleural tumour (including the fissure)
- invasion of diaphragmatic muscle
- invasion of lung parenchyma

T3* Tumour involves any ipsilateral pleural surfaces, with at least one of the following:
- invasion of endothoracic fascia
- invasion into mediastinal fat
- solitary focus of tumour invading soft tissues of the chest wall
- non-transmural involvement of the pericardium

T4** Tumour involves any ipsilateral pleural surfaces, with at least one of the following:
- diffuse or multifocal invasion of soft tissues of chest wall
- any involvement of rib
- invasion through diaphragm to peritoneum
- invasion of any mediastinal organ(s)
- direct extension to contralateral pleura
- invasion into the spine
- extension to internal surface of pericardium
- pericardial effusion with positive cytology
- invasion of myocardium
- invasion of brachial plexus

Notes: *T3 describes locally advanced, but potentially resectable tumour
**T4 describes locally advanced, technically unresectable tumour

N – Regional Lymph Nodes[3]

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in ipsilateral bronchopulmonary and/or hilar lymph node(s)

N2 Metastasis in subcarinal lymph node(s) and/or ipsilateral internal mammary or mediastinal lymph node(s)

N3 Metastasis in contralateral mediastinal, internal mammary, or hilar node(s) and/or ipsilateral or contralateral supraclavicular or scalene lymph node(s)

M – Distant Metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Stage Grouping

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
Stage IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

1 {738,2045}.

2 A help desk for specific questions about the TNM classification is available at http://www.uicc.org/tnm/.

3 The regional lymph nodes are the intrathoracic, internal mammary, scalene and supraclavicular nodes.

Mesothelioma

A. Churg
V. Roggli
F. Galateau-Salle
Ph.T. Cagle
A.R. Gibbs
Ph.S. Hasleton
D.W. Henderson
J.M. Vignaud
K. Inai
M. Praet
N.G. Ordonez
S.P. Hammar
J.R. Testa
A.F. Gazdar
R. Saracci
R. Pugatch
J.M. Samet
H. Weill
V. Rusch
T.V. Colby
P. Vogt
E. Brambilla
W.D. Travis

Definition

Diffuse malignant mesothelioma: a malignant tumour arising in the pleura from mesothelial cells, and showing a diffuse pattern of growth over the pleural surfaces.

ICD-O Codes

Epithelioid mesothelioma	9052/3
Sarcomatoid mesothelioma	9051/3
Desmoplastic mesothelioma	9051/3
Biphasic mesothelioma	9053/3

Synonyms

This tumour is properly referred to as "diffuse malignant mesothelioma", but is often abbreviated as "malignant mesothelioma" or just "mesothelioma." Care needs to be taken when using these terms, since localized mesothelial tumours exist in the pleura and have different behaviour.

Epidemiology

Pleural mesotheliomas are largely seen in patients over 60 years of age, but the age distribution is wide and occasional tumours are observed in children. In North America tumours in males outnumber those in females by approximately 9:1, but in other countries such as the UK, France and Australia this ratio is lower.

In North America the incidence of mesothelioma in females is about 2-3/million/yr and this number is essentially unchanged over the last 30 years {8}. In men the incidence is now about 20/million per year. The male incidence increased steadily until the early 1990's but appears to have peaked and there is a suggestion that the numbers are decreasing. The experience in North America is distinctly different from that in Australia, France and the UK, where the incidence is considerably higher and number continue to increase. For example, in Australia, the current incidence in 2000 was 60/million in men and 11/million in women {1156}. Within Europe, the mesothelioma burden varies coniderably. For practical purposes the mortality of pleural mesothelioma is 100%. It is possible that some very early stage tumours have been cured by so-called triple modality therapy: extrapleural pneumonectomy followed by chemotherapy and radiation therapy, but this remains to be proven and would only apply to a small number of cases.

Etiology

Asbestos

In most industrialized countries, greater than 90% of pleural mesotheliomas in men are related to prior asbestos exposure. In women in North America only about 20% of tumours are caused by asbestos {1862}. In other countries, particularly the UK and Australia, where extensive use was made of crocidolite, the proportion of mesotheliomas in women related to asbestos exposure is higher. The latency period is typically very long, with a mean of 30-40 years. Asbestos rarely if ever produces mesothelioma with a latency period less than 15 years. From past exposure, future mortality from mesothelioma has been estimated. In the UK, the number of death cases is expected to peak in 2015-2020, with more than 2000 per year {1588}. Another study postulated that in Western Europe approximately a quarter of a miilon people will die from asbestos-induced mesothelioma over the next 35 years, men born around 1945-1950 being at highest risk {1587}.

However, recent European incidence rates have already started to level off {1346,1347}.

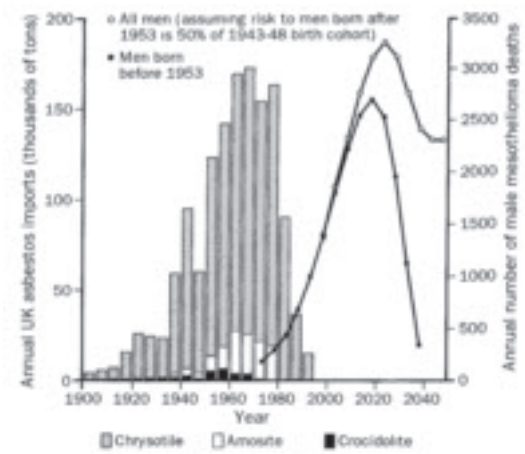


Fig. 2.01 Asbestos imports into the United Kingdom and predicted mesothelioma deaths. The mortality is expected to reach a maximum around the year 2020. From J. Peto et al. {1588}.

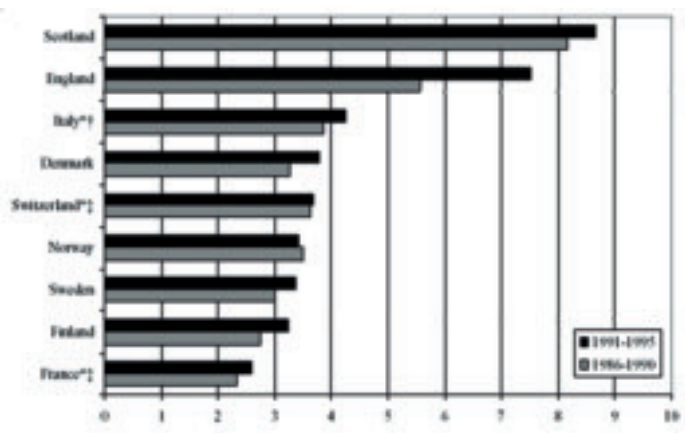
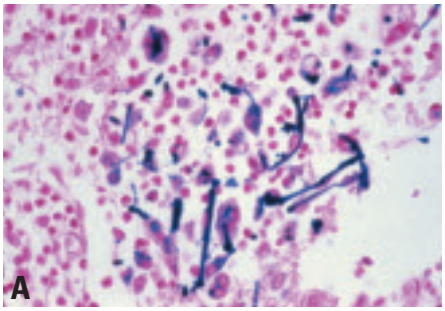


Fig. 2.02 European pleural mesothelioma incidence. Truncated (40-74) age-standardized rates per 100,000 person-years. From F. Montanaro et al. {1347}.



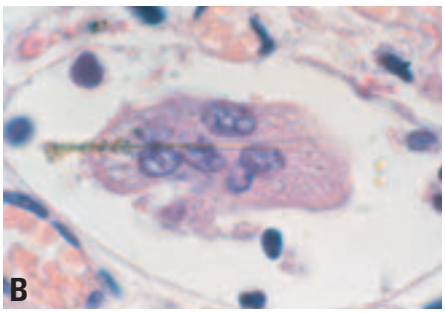
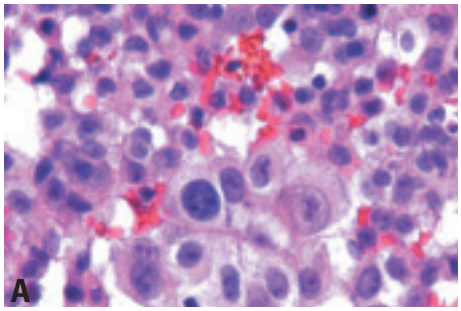
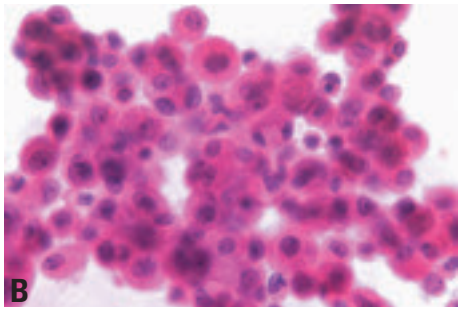
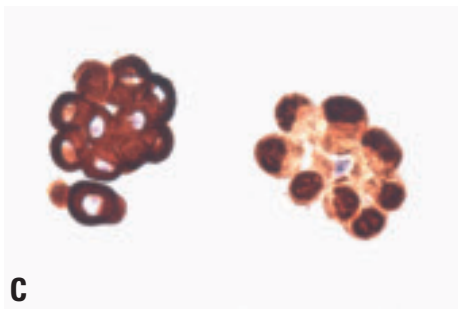


Fig. 2.03 **A** Multiple ferruginous bodies with inflammatory reaction. **B** A ferruginous body within a multinucleated macrophage.







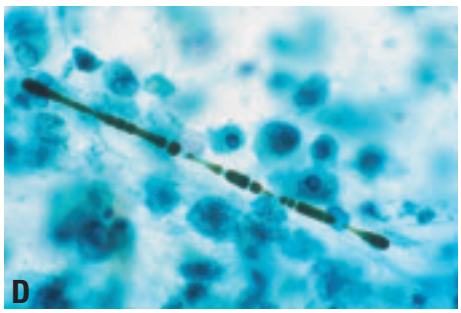


Fig. 2.04 Diffuse malignant mesothelioma - cytology. **A** Group of mesothelial cells with enlarged, slightly irregular nuclei and with multiple nucleoli in some cells. **B** Note bland mesothelial cell appearance of the malignant cells. **C** Immunostain for cytokeratin (left) stains strongly in the cytoplasm of this cluster of cells of diffuse malignant mesothelioma in a pleural effusion. Immunostain for calretinin (right) stains the nucleus of diffuse malignant mesothelioma cells in a pleura effusion. **D** Asbestos body in the sputum of an exposed individual.

Fibre types. There are distinct differences in the propensity of the different asbestos fibre types to cause mesothelioma. Amphibole (amosite and crocidolite) asbestos is considerably more potent than chrysotile, and crocidolite is more dangerous than amosite. The exact ratio among these 3 fibres depends upon the approach used to investigate the problem: a recent report of estimates of cohort, mean fibre exposure suggested a ratio of 500:100:1 (crocidolite:amosite:chrysotile) for relative risk {858}.

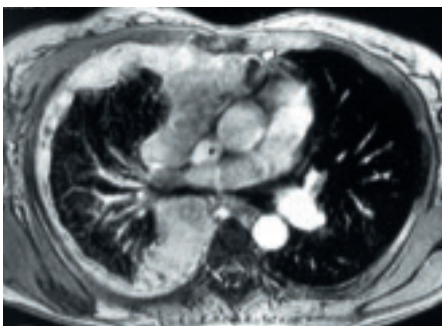


Fig. 2.05 Diffuse malignant mesothelioma. In this CT scan, the pleura shows marked diffuse thickening by mesothelioma, with resulting encasement of the lung.

SV40

Some polio vaccines used during 1955 and 1962 were contaminated with the Simian monkey virus 40 (SV40) and this infection has since spread to millions of people in several world regions, including North America and most European countries Several studies have shown, that some human neoplasms, in particular, mesothelioma, brain tumours, bone sarcomas and non-Hodgkin lymphomas frequently contain sequences of SV40, a highly oncogenic DNA virus in rodents {2085}. For mesotheliomas, this was first reported in 1994 {283} and has been confirmed in subsequent analyses {668}. SV40 induces DNA strand breaks in human mesothelial cells {253} and causes pleural mesotheliomas in hamsters {374}. The viral large T-antigen (Tag) inactivates the function of the tumour suppressor genes *TP53* and retinoblastoma *(RB)* and induces chromosomal aberrations {106,285}. The small t-antigen (tag) may contribute to transformationby binding to the protein phosphatase PP2A {106,668}.

Whether a latent SV40 infection is a causal factor in the development of mesothelioma, remains to be assessed. Epidemiological studies provided no evidence that populations which received the contaminated polio vaccine have an elevated cancer risk {542}.

Other causes

These include the non-asbestos fibre, erionite (seen only in Cappadocia, Turkey), therapeutic radiation, and possibly processes that lead to intense pleural scarring such as prior plombage therapy for tuberculosis.

Pathogenesis

A considerable fraction of inhaled asbestos fibers remain permanently entrapped in lung tissue. The majority of these fibers remain naked, without causing a tissue reaction: these are probably responsible for the clastogenic, and, eventually, carcinogenic effects. A minority of asbestos fibers induce an accumulation of monocytes and become surrounded and encapsulated by multinucleated macrophages. This process is associated with deposition of protein and of haemoglobin-derived iron, resulting in the formation of ferruginous bodies.

Clinical features

Signs and symptoms

The most common presenting symptoms in mesothelioma are dyspnoea, usually due to a large pleural effusion, and chest

wall pain {796}. These may be associated with constitutional symptoms, especially weight loss and malaise. Additional clinical features include chills, sweats, weakness, fatigue, malaise and anorexia {18}. Unusual presentations include spontaneous pneumothorax {943}, mass lesions and/or segmental or lobar pulmonary collapse, and mediastinal invasion with laryngeal nerve palsy or superior vena caval obstruction. Myalgias, aphonia, dysphagia, abdominal distension, nausea and a bad taste in the mouth have also been reported {1189}.

Imaging

On a chest radiograph malignant mesothelioma often manifests as a large pleural effusion that may obscure an underlying pleural mass or thickening. It is not unusual to see associated pleural plaques. The pleural disease may take on a circumferential pattern of involvement with disease extending along the fissural, mediastinal and/or pericardial pleura. The ipsilateral hemithorax may appear contracted. CT scanning and MRI better define the extent of pleural disease, in particular chest wall, diaphragmatic, pericardial, mediastinal lymph node, or pulmonary involvement.

Relevant diagnostic procedures

Malignant pleural mesothelioma (MPM) is usually diagnosed by pleural biopsies obtained by videothoracoscopy (VATS). Occasionally, pleural fluid cytology will yield a sufficient sample for diagnosis although approximately 50% of patients will have cytologically negative fluid. In addition, VATS pleural biopsy provides samples for immunohistochemistry, which is usually required to support a definitive histological diagnosis. Thoracotomy is not required for diagnosis and should be avoided because it increases the risk of tumor implantation into the chest wall and therefore, may affect the technical feasibility of subsequent definitive resection. In patients whose pleural space is fused by locally advanced tumor, tissue can be obtained via a 5cm incision with very limited rib resection and direct pleural biopsy.

Computed tomography (CT) is the standard imaging study for the initial staging of MPM. However, it does not accurately predict the presence or absence of superficial chest wall invasion (i.e. involvement of the endothoracic fascia and intercostal muscles) or full thickness involvement of the diaphragm. Magnetic resonance imaging (MRI) may be slightly more accurate than CT in these areas but not consistently enough to be used as a routine imaging modality. If transdiaphragmatic tumor extension is suspected on CT or MRI, this is best confirmed or disproved by laparoscopy. Positron emission tomography (PET) detects metastatic disease in approximately 10% of patients in whom this is not suspected clinically or seen by CT and is therefore used in some insitutions as a routine part of the initial staging evaluation. The maximum standard uptake value (SUVmax) on PET also appears to have prognostic significance. None of these imaging studies accurately predicts the presence or absence of mediastinal lymph node metastases, an important issue because these are known to have a prognostic impact on survival. Mediastinoscopy can identify some but not all lymph nodes metastases because approximately 25% of these occur in areas that are not accessible by mediastinoscopy (e.g. internal mammary lymph nodes).

Cytology

In industrialized countries, about 1% of malignant pleural effusions are caused by diffuse malignant mesothelioma. Mesothelioma cells in effusions are virtu-

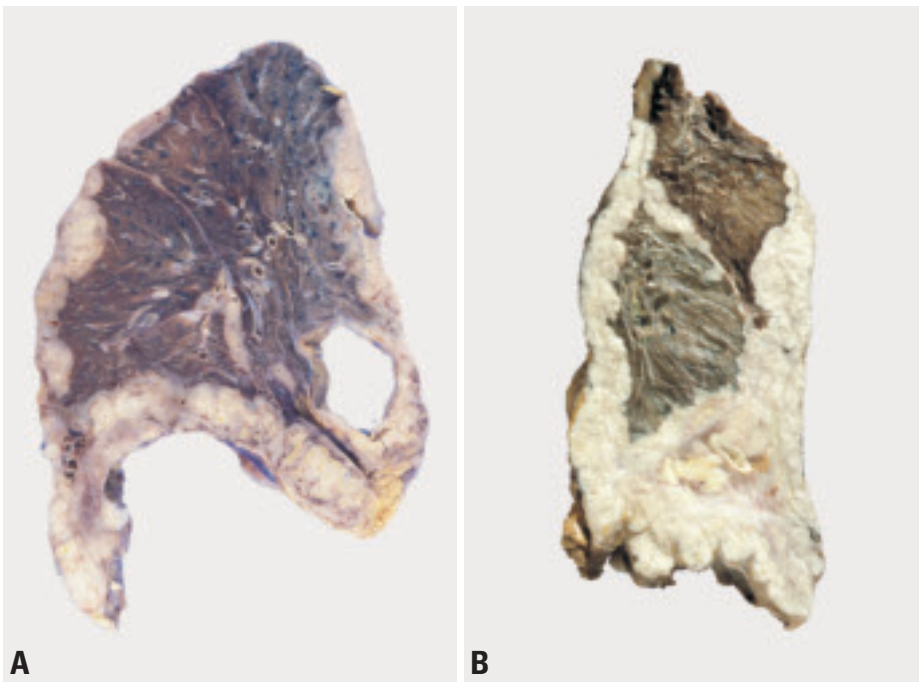


Fig. 2.06 Malignant mesothelioma. **A** Gross image of malignant mesothelioma at autopsy showing the typical appearance of the tumor encasing the lung, and, in this example, the pericardium. **B** Extensive mesothelioma growth with compression of residual lung tissue.

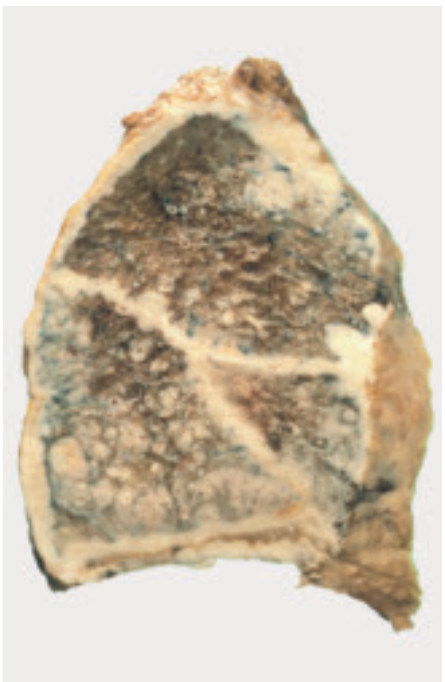


Fig. 2.07. Metastatic pleural adenocarcinoma (pseudomesothelioma). Note infiltration of lung tissue which is typically absent in mesothelioma.

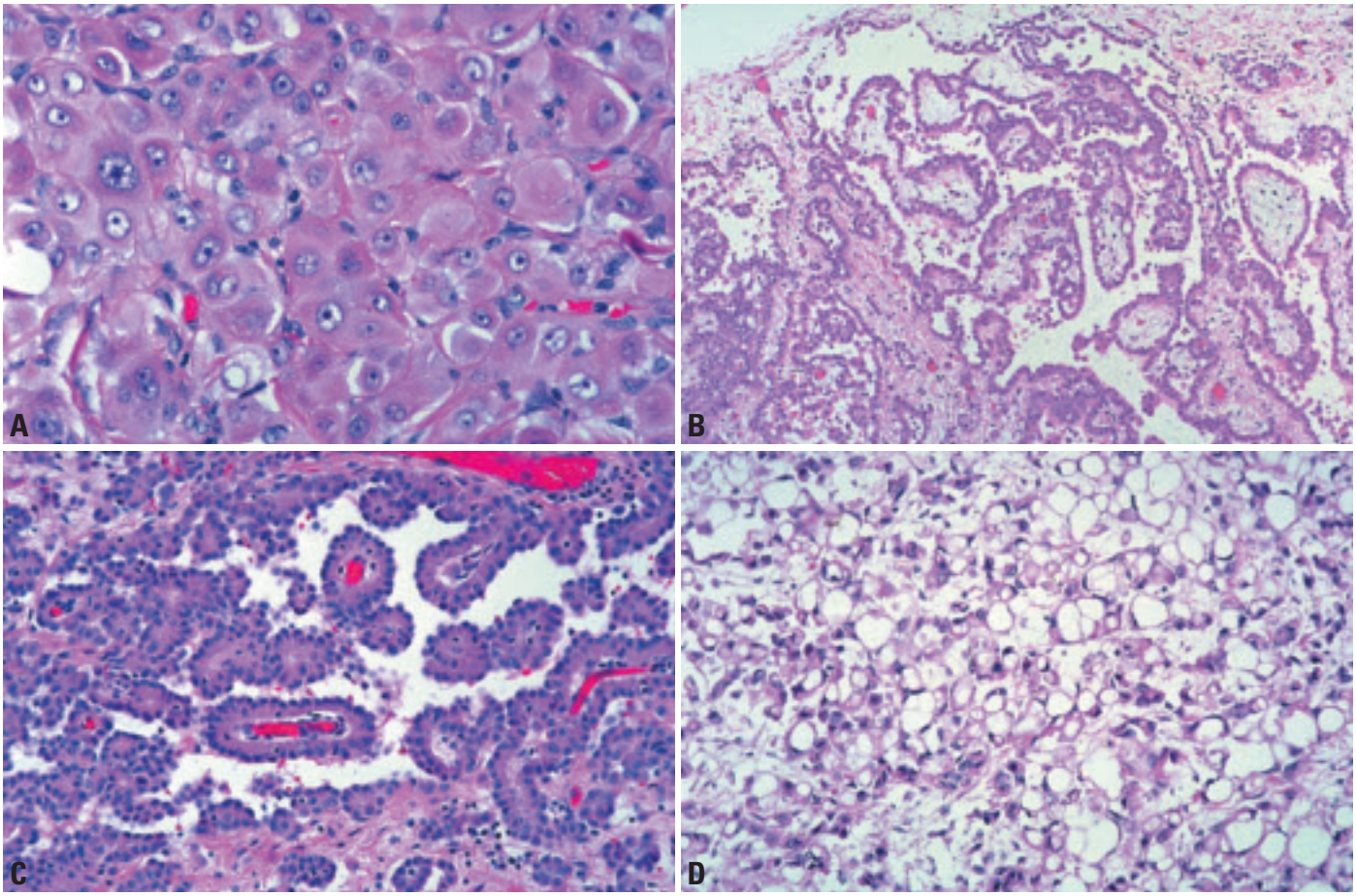


Fig. 2.08 Malignant mesothelioma, epithelioid type. **A** The tumour consists of a sheet of epithelioid cells with abundant eosinophilic cytoplasm and vesicular nuclear chromatin with prominent nucleoli. From Travis et al. {2024}. **B** Papillary proliferation of epithelioid cells. From Travis et al. {2024}. **C** Tubulopapillary pattern. From Travis et al. {2024}. **D** Microcystic (adenomatoid pattern). From Travis et al. {2024}.

ally always of epithelioid type, since cells of the sarcomatoid type are seldom shed into the fluid.

Mesothelioma cells in effusions may be arranged in sheets, clusters, morulae or papillae, sometimes with psammoma bodies. These cells show a range of cytological appearances from pleomorphic to bland, but frequently lack the significant atypia seen in carcinoma. On the other hand, benign mesothelial cells may exhibit features usually associated with malignancy, such as increased cellularity, pleomorphism and mitotic activity. Therefore, differentiation of mesothelioma from benign mesothelial hyperplasia with reactive atypia may be very difficult or impossible in cytologic specimens, since tissue invasion cannot be evaluated. Overall the accuracy of purely cytologic diagnoses, as opposed to tissue diagnoses, of malignant mesothelioma is fairly low. Immunostains of sections from paraffin-embedded cell blocks may help to confirm the lineage of the cells.

Macroscopy and localization

In its early stages, mesothelioma presents as multiple small nodules on the parietal and sometimes visceral pleura. With progression the nodules become confluent with resulting fusion of the visceral and parietal pleurae and encasement and contraction of the lung. The tumour may reach several centimetres in thickness and range from firm to gelatinous in consistency. Loculated collections of fluid may occur within the tumour. Spread frequently occurs along the interlobar fissures, into the underlying lung, through the diaphragm, and into the chest wall. Mediastinal involvement with invasion of the pericardial sac and encirclement of other midline structures is also common, as is extension to the opposite pleural cavity. Mesotheliomas may metastasize to the pulmonary parenchyma and to hilar and mediastinal lymph nodes. This appearance is not pathognomonic for mesothelioma, since a variety of primary and secondary pleural malignancies may spread in a similar fashion leading to the encasement of the lung.

Tumour spread and staging

Patterns of mesothelioma spread

Invasion of chest wall fat and muscle is characteristic, especially along needle tracks or surgical biopsy sites. Substantial displacement of the mediastinum to the contralateral hemithorax may occur. Spread through the diaphragm can result in seeding of the peritoneum and ascites, which is frequently found at autopsy and rarely causes uncertainty regarding the primary site.

Infiltration into alveolar spaces may produce a histologic pattern that resembles organising pneumonia, desquamative

interstitial pneumonia, or bronchioloalveolar carcinoma {1476}. Peribronchial lymphovascular spread can occur, sometimes with miliary spread. Lymph node metastasis rarely is a presenting manifestation of mesothelioma {1906}. At autopsy, haematogenous metastases from pleural mesothelioma may be found in lung, liver, adrenals, bone, brain or kidney {815}. It is rare for mesothelioma to present clinically as metastatic disease {1415}. Staging is performed according to the TNM classification proposed by the International Mesothelioma panel and the UICC {738,2045}.

Histopathology

While the term "desmoplastic mesothelioma" is universally accepted for a particular subtype of highly aggressive sarcomatoid mesothelioma, there is no agreement on the nomenclature of other subtypes, particularly the numerous morphologic variants of epithelioid malignant mesothelioma. Recognition of these variants is important for diagnosis, but because they have no clear prognostic significance, we recommend that most epithelioid and sarcomatoid mesotheliomas be diagnosed with no further subclassifiers beyond those shown at the beginning of this chapter.

Epithelioid mesothelioma

Epithelioid mesothelioma shows epithelioid cytomorphology. Most epithelioid mesotheliomas are remarkably bland, but more anaplastic forms are occasionally seen. Epithelioid mesotheliomas show a wide range of morphologic patterns. Sometimes one pattern predominates but several different patterns are commonly seen in the same tumour. In most tumours the cells have eosinophilic cytoplasm with bland relatively open nuclei. Mitoses are infrequent. In the poorer differentiated forms, the nuclei are coarser with prominent nucleoli, mitoses are frequent, and some multinucleate tumour giant cells occur; however, these tumours are uncommon and often difficult to separate from carcinomas.

The most frequent patterns encountered are tubulopapillary, adenomatoid (microglandular) and sheet-like. Less common patterns include small cell, clear cell and deciduoid. The tubulopapillary form exhibits varying combinations of tubules, papillae with connective tissue cores, clefts and trabeculae. The cells lining the tubules and papillae are flattened to low cuboidal and relatively bland. Psammoma bodies are occasionally observed. The adenomatoid form shows microcystic structures, with lacelike, adenoid cystic or signet ring

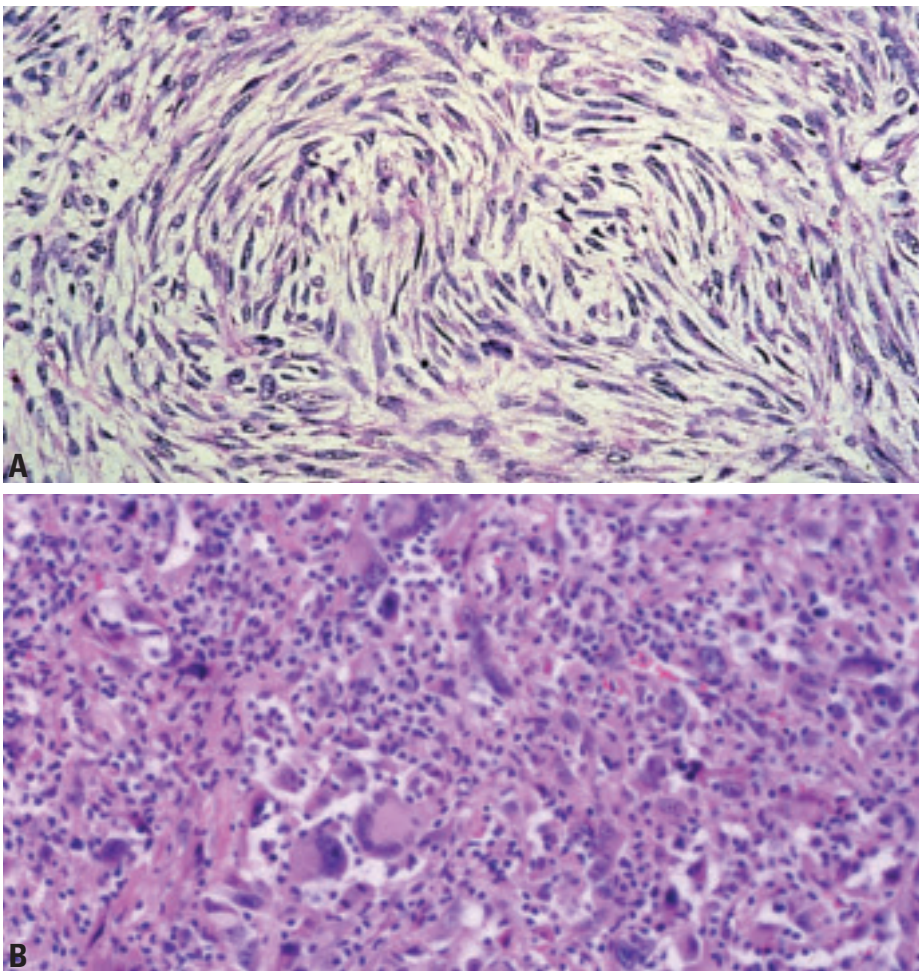


Fig. 2.09 Sarcomatoid mesothelioma. **A** Interlacing fascicles of spindle cells. From Travis et al., {2024}. **B** Sarcomatoid pleural mesothelioma with bizarre anaplastic tumor giant cells. Such an appearance closely mimics that of malignant fibrous histiocytoma.

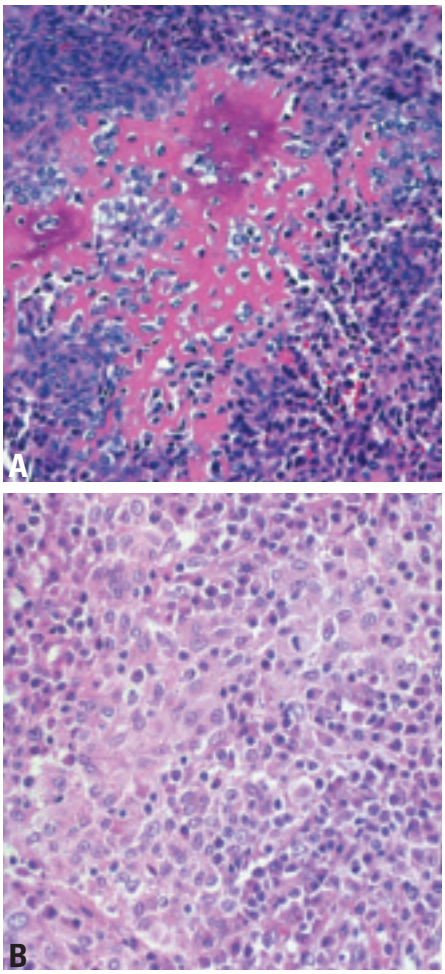


Fig. 2.10 Sarcomatoid mesothelioma with **A** osteosarcomatous differentiation. **B** Inflammatory lymphohistiocytic pattern. From Travis et al. {2024}.

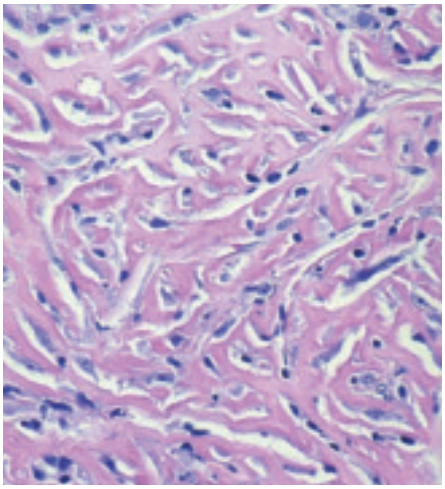


Fig. 2.11 Malignant mesothelioma, desmoplastic type. Haphazard arrangement of slit-like spaces. From Travis et al. {2024}.

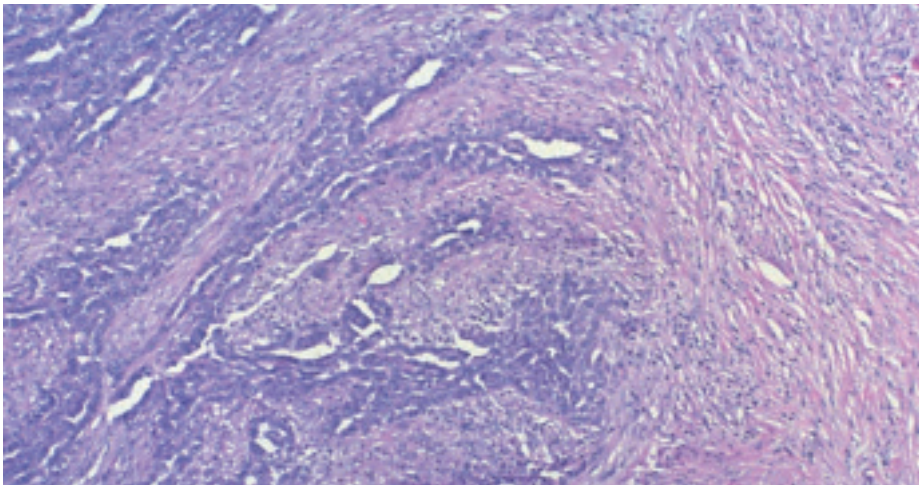


Fig. 2.12 Malignant mesothelioma, biphasic type. A combination of sarcomatoid and epithelioid patterns. From Travis et al. {2024}.

appearances, but does not stain for neutral mucin. Sheets and nests of cells are frequently seen in association with other patterns. Uncommonly, solid, monotonous, relatively non-cohesive sheets of polygonal cells occur, simulating large cell carcinoma or lymphoma. Tumours with anaplastic and/or tumour giant cells may be designated pleomorphic. Mesothelioma can mimic non-Hodgkin lymphoma (so-called lymphohistiocytoid mesothelioma, regarded by some as a form of sarcomatoid mesothelioma) and small cell carcinoma, but usually lacks karyorrhexis and haematoxyphylic staining of blood vessels of the latter tumour. Rarely large cells with clear cytoplasm are prominent, mimicking metastatic renal cell carcinoma. Small foci of cells with plump eosinophilic cytoplasm resembling deciduoid cells of pregnancy are frequently present in epithelioid mesothelioma and uncommonly predominate (so-called deciduoid mesothelioma). The fibrous stroma of epitheloid mesotheliomas can vary from relatively scanty to copious and can show varying degrees of cellularity from hyalinised acellular to highly cellular, merging with sarcomatoid. These tumours may be difficult to distinguish from a biphasic mesothelioma. Myxoid change may be conspicuous, with nests of epithelioid cells "floating" in the matrix; the matrix in such tumours is hyaluronate, and shows hyaluronidase-sensitive staining with Alcian blue.

Immunohistochemistry is an important adjunct to the diagnosis of malignant mesothelioma, particularly in distinguishing it from pulmonary adenocarcinoma. A combination of two or more positive mesothelial with two or more negative epithelial (carcinoma) markers is most useful, their choice to a large extent depending upon the experience of the laboratory. The most useful mesothelial markers appear to be cytokeratin 5/6, calretinin and Wilms tumour gene-1 (WT1). N-cadherin is promising but needs more study. The most useful epithelial markers appear to be CEA (monoclonal), CD15, Ber EP4, B72.3, MOC 31 and thyroid transcription factor 1 (TTF-1). The immunohistochemistry panel will require amendment where the differential diagnosis includes tumours other than pulmonary adenocarcinomas. A broad-spectrum keratin is useful to exclude rare cases of large cell lymphoma, metastatic malignant melanoma and epithelioid haemangioendothelioma. The use of immunohistochemical markers for the diagnosis of malignant versus reactive mesothelial lesions remains controversial.

Sarcomatoid mesothelioma

The sarcomatoid variant of pleural mesothelioma consists of spindle cells arranged in fascicles or having a haphazard distribution. The pattern most often resembles fibrosarcoma, but marked anaplasia and bizarre multinucleate tumour cells may result in a picture closely mimicking that of malignant fibrous histiocytoma. In a small percentage of cases, areas resembling osteosarcoma, chondrosarcoma or other sarcomas may be present.

Sarcomatoid mesotheliomas typically stain positively for cytokeratins when a broadspectrum antibody cocktail is used, although an absence of staining may be seen in occasional cases. Areas with chondrosarcomatous or osteosarcomatous differentiation often stain negatively for cytokeratins {2220}. Sarcomatoid mesotheliomas may stain positively for vimentin, actin, desmin, or S-100. Some cases may also show staining for calretinin {87}.

The differentiation from sarcomatoid (pleomorphic) carcinoma of the lung secondarily invading the pleura or metastatic sarcomatoid renal cell carcinoma can be exceedingly difficult. Immunostains do not reliably differentiate between these possibilities {271}. In such cases, gross and clinical features may be helpful.

Desmoplastic mesothelioma

Desmoplastic mesothelioma is characterized by dense collagenized tissue separated by atypical cells arranged in a storiform or "patternless" pattern, present in at least 50% of the tumour. These tumours can readily be confused with benign organizing pleuritis, especially on small biopsy specimens. Certain diagnostic criteria strongly suggest malignancy. These include frankly sarcomatoid areas, foci of bland collagen necrosis, invasion of adipose tissue, skeletal muscle, or lung, and distant metastases {1229}. Bone metastases from desmo-

Table 2.01
Differential diagnosis of diffuse malignant mesothelioma.

Metastases to the pleura*
- Carcinoma - Sarcoma - Lymphoma - Malignant Melanoma
Primary diffuse pleural sarcoma
- Angiosarcoma - Epithelioid haemangioendothelioma - Synovial sarcoma - Other sarcoma
Thymic tumours, primary or metastatic
Desmoplastic small round cell tumour and Ewing sarcoma family
Localized primary pleural tumours
- Localized malignant mesothelioma - Solitary fibrous tumour (benign and malignant forms) - Sarcomas - Well-differentiated papillary mesothelioma - Adenomatoid tumour - Calcifying fibrous pseudotumour - Nodular pleural plaque

*Metastasis to the pleura or reaching the pleura by direct spread from the lung or chest wall.

plastic mesothelioma {1219} are potentially liable to histological misdiagnosis as a primary benign fibrous tumour of bone.

Cytokeratin staining may be of greatest utility in highlighting invasion by keratin positive spindle cells into adipose tissue, skeletal muscle, or lung. The mere presence of keratin positive staining in the thickened pleura itself is of no particular benefit, since reactive processes often have keratin-positive spindle cells.

Biphasic mesothelioma

Mesotheliomas contain both epithelioid and sarcomatoid patterns in about 30% of cases. Any combination of the patterns noted above may be present. Each component should represent at least 10% of the tumour to warrant the term biphasic. The percentage of cases classified as biphasic will increase with more thorough tumour sampling.

Grading

Malignant mesotheliomas are not ordinarily graded. Epithelioid forms are often deceptively monotonous and can be remarkably bland in appearance. Mitoses are scarce in most epithelioid mesotheliomas. Sarcomatoid forms may be bland or fairly anaplastic. However, beyond the distinction between epithelioid and sarcomatoid forms, these histopathologic features do not correlate well with prognosis.

Differential diagnosis

The differential diagnosis of diffuse malignant mesothelioma is shown in Table 2.01. The most important differential is metastatic or locally invasive (from lung or chest wall) tumour that covers the pleural surface. However, various localized tumours also exist in the pleura and some mimic mesothelioma microscopically. For this reason, knowledge of the gross distribution of tumour, whether obtained from radiographic studies, the operator's description of the findings at thoracotomy or thoracoscopy, or from a resected or autopsy specimen, is crucial to making a proper diagnosis.

Postulated cell of origin

The exact cell of origin of malignant mesothelioma is unclear. Although the common belief is that these tumours arise from surface mesothelial cells, some experimental data suggest that they may arise from submesothelial cells that differentiate in a variety of directions.

Precursor lesions

It is likely that malignant mesothelioma develops through an in-situ stage. There are at present no reliable histologic criteria for separating lesions that might be *in situ* mesothelioma from atypical benign reactions. The use of the term 'atypical mesothelial hyperplasia' is recommended for purely surface mesothelial proliferations that might or might not be malignant.

Somatic genetics

Cytogenetics and CGH

Most studied cases appear to be epithelioid mesotheliomas, although some reports do not distinguish cell type. Karyotypic and comparative genomic hybridisation (CGH) analyses have demonstrated that most mesotheliomas have multiple chromosomal alterations.

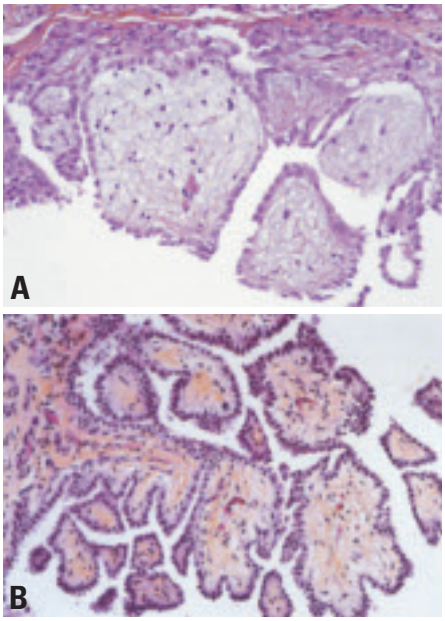


Fig. 2.13 **A** Well differentiated papillary mesothelioma. **B** Solitary papillary WDPM.

Although no single change is diagnostic, several recurrent sites of chromosomal loss have been identified. Deletions of 1p21-22, 3p21, 4q, 6q, 9p21, 13q13-14, and 14q have been repeatedly observed {103,177,178,1075,1942}. Monosomy 22 is the most frequent numerical change. Losses of 4p and proximal 15q have been reported in some CGH studies, and minimally deleted regions at 4p15 {1815} and 15q15 {457} have been documented. Recurrent losses of 17p12-pter, including the p53 locus, have been observed in some investigations {103, 1075}. Loss of heterozygosity (LOH) analysis has confirmed that each of the above sites is frequently deleted in mesothelioma and, for most of the affected chromosomes, has defined a single minimally deleted region (reviewed in {1997}). Allelic loss from chromosome 4 has been reported to occur at multiple locations, with the most frequent site being 4q33-34 {1815}. LOH in 6q occurs at several non-overlapping regions between 6q14 and 6q25 {142}. Similarly, multiple non-overlapping regions of allelic loss have been reported for chromosome 14, with 14q11.2-12 and 14q23-24 each being observed in two independent studies {179,458}. Chromosomal gains are less common than losses in mesothelioma, although recurrent gains of 1q, 5p, 7p, 8q22-24, and 15q22-25 have been described. These abnormalities reflect

similarities and differences with carcinoma of the lung.

Molecular genetic alterations
Inactivation of the *CDKN2A/ARF* locus at 9p21 is a frequent finding in mesothelioma {345,2178}. *CDKN2A/ARF* encodes the tumour suppressor genes $p16^{INK4a}$ and $p14^{ARF}$. Homozygous deletions of this locus are common, especially in cell lines, and inactivation by promoter methylation is also a recurrent finding {1071}. Immunohistochemical analysis suggests that loss of $p16^{INK4a}$ expression is a frequent finding {839}. Deletions of $p14^{ARF}$ are frequently observed. This mechanism of cell cycle control disruption is also common in non-small cell carcinomas. Unlike lung cancers, *TP53* mutations are relatively uncommon {417, 1020,1302}, possibly because SV40 Tag is expressed in some mesotheliomas and retains its ability to bind to and inactivate p53 {284}. Also in contrast to lung cancer, mutations of the *NF2* tumour suppressor gene, located at chromosome 22q12, have been reported frequently in mesothelioma {165,1778}. Biallelic inactivation of *NF2* occurs by combined point mutation and LOH {346}. The previously mentioned monosomy of chromosome 22 may reflect these findings. Another tumour suppressor gene, *GPC3*, is frequently down regulated due to aberrant promoter methylation {1413}.
Recurrent activation of oncogenes by point mutation or amplification has not been documented in mesothelioma {1020,1302}. However, asbestos induces mRNA expression of the c-*fos* and c-*jun* proto-oncogenes in mesothelial cells {810}, and asbestos-induced mesothelial cell transformation is linked to increases in AP-1 DNA binding complexes and the AP-1 component, Fra-1 {810,1639}. Other experimental evidence indicates that when SV40 infects mesothelial cells, it causes activation of the Met and notch-1 proto-oncogene products {185,267}. In contrast to lung cancers, relatively few genes are methylated in mesotheliomas. The gene most frequently methylated is the *RASSF1A* tumour suppressor gene {2018}.

Genetic susceptibility (Familial cancer syndromes)
Multiple cases of pleural mesothelioma have been reported from families with documented exposure to asbestos or other carcinogenic mineral fibres, such as erionite {81,1175,1697}. While investigation of members of one family with familial mesothelioma failed to identify germline mutations, the molecular changes in the tumours were similar to those found in sporadic mesothelioma {80}. One study {960} described an association at population level with HLA antigens B41, B58 and DR16. Specific genetic indicators of susceptibility to mesothelioma development have not yet been identified {1740}: currently available observations may reflect differential levels and duration of exposure to carcinogenic fibres among affected and non-affected members of a family, random sequences of events, or genuine variations in individual susceptibility.

Prognosis and predictive factors
Clinical criteria
Chest pain, dyspnoea and weight loss as presenting symptoms may be associated with a poorer prognosis {822,1708}. There was a trend towards pain being related to sarcomatoid differentiation {1711}. Good prognostic indicators are a young age at presentation, epithelioid subtype, stage of disease {1711} good performance status, lack of chest pain and female sex below the age of 50 years {1861}.

Histopathological criteria
Most series show that patients whose tumours have a purely epithelioid histology have the longest survival, those with a purely sarcomatoid histology the worst, and those with mixed patterns an intermediate survival. The differences in median survivals as a function of histologic subtype are only however, a matter of a few months. In the future, therapy may be influenced by histologic subtype, since no patient with a sarcomatoid pattern treated with trimodality therapy survived for 5 years {2235}.

Genetic predictive factors
While there are many similarities in the frequencies of various genomic imbalances between epithelioid and sarcomatoid mesotheliomas, several chromosomal locations (3p, 7q, 15q, 17p) show significant variations {1075}. For example, deletion at 3p21 is common in epithelioid tumours but rare in sarcomatoid and biphasic tumours. To date, cytogenetic prognostic factors have not been reported. Loss of 7q, which is associated with poor prognosis in other tumour types, was observed in ~20% of sarcomatoid tumours but was not observed in epithelioid cases {1075}. Moreover, the incidence of amplicons was 4-5-fold higher in sarcomatoid than in epithelioid tumours. Gene expression profiles in a small number of cases has been reported to predict outcome independent of histologic subtype {714}

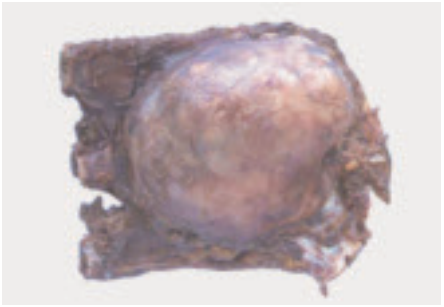


Fig. 2.14 Localized malignant pleural mesothelioma.

Well differentiated papillary mesothelioma

Definition
Well differentiated papillary mesothelioma (WDPM) of the pleura represents a distinct tumour with a papillary architecture, bland cytologic features and a tendency toward superficial spread without invasion.

ICD-O code 9052/1

Epidemiology
WDPM is a rare pleural tumour, with fewer than 50 cases reported in the world literature {261,864,2204}. These tumours are considerably more common in the peritoneum, where they predominantly occur in women {444}. This sex predominance is not obvious in the pleural cases. The reported age range in pleural lesions is 31-79 with a median of 63 for both sexes {261,864,2204}.

Etiology
Asbestos exposure has been reported in some cases {261,656}, but this has not been established in epidemiologic studies.

Localization
These lesions may be localized or multifocal and widespread.

Clinical features
Patients present with dyspnoea and recurrent pleural effusion or as an incidental finding. They rarely present with pneumothorax or chest pain. Unilateral free-flowing pleural effusions may be seen, with or without nodular pleural thickening or fibrous hyaline plaques.

Macroscopy
These tumours may appear as solitary or multiple localized masses. The visceral or parietal pleura may be involved and may have a velvety appearance.

Histopathology
WDPM is characterized by papillae, consisting of predominantly stout myxoid fibrovascular cores covered by a single layer of bland flattened to cuboidal mesothelial cells, exuding from the pleural surface. Basal vacuoles may be present in the lining cells. Nucleoli are inconspicuous and mitotic figures absent. The surface cells stain positively for mesothelial markers.
In the strictest definition, invasion is not present in WDPM. However, some cases of otherwise typical WDPM may show limited invasion. Nevertheless, diffuse malignant mesotheliomas may have areas with a WDPM-like pattern and should not be designated as WDPM. Consequently, great caution should be employed in diagnosing WDPM in small biopsies.

Prognosis and predictive factors
These tumours are often indolent with prolonged survival. The development of invasion may herald a more aggressive clinical course. The occurrence of rapidly progressive disease suggests that the underlying disease is a diffuse malignant mesothelioma, a problem that may reflect sampling inadequacy.

Localized malignant mesothelioma

Definition
A rare tumour that grossly appears as a distinctly localized nodular lesion without gross or microscopic evidence of diffuse pleural spread, but with the microscopic, histochemical, immunohistochemical and ultrastructural features of diffuse malignant mesothelioma.

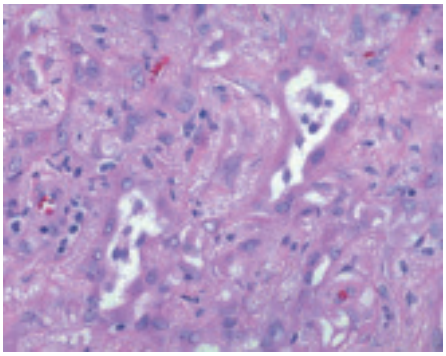


Fig. 2.15 Adenomatoid tumour. Irregularly shaped gland-like spaces are present within a fibrous stroma. From Travis et al. {2024}.

ICD-O code: code according to the histologic subtype of mesothelioma.

Clinical features
Most reported cases have been incidental findings on chest x-ray or CT scan. Occasionally they present with pleural effusions.

Macroscopy
Localized malignant mesotheliomas are circumscribed nodular tumours that measure up to 10cm in diameter. They may be attached to the visceral or parietal pleura, are pedunculated or sessile, and can extend into the subjacent lung.

Histopathology
These tumours are histologically identical to diffuse malignant mesotheliomas and may be epithelioid, sarcomatoid, or biphasic (mixed). They show a pattern of immunohistochemical staining identical to diffuse malignant mesothelioma {425}.

Prognosis
Some localized malignant mesotheliomas are cured by surgical excision {425}. Recurrent tumours may metastasize like sarcomas and usually do not spread along the pleural surface.

Adenomatoid tumour

Definition
A rare solitary small pleural tumour with histological features identical to those seen in adenomatoid tumours in other locations.

ICD-O code 9054/0

Clinical features
The few reported cases have been incidental findings at gross examination of the pleura.

Macroscopy
The tumours appear as solitary distinctly nodular lesions.

Histopathology
The tumour cells are flattened to cuboidal and usually eosinophilic; they form glands and tubules, often with marked cytoplasmic vacuolisation {958}. They show a pattern of staining identical to that seen in diffuse malignant mesothelioma. Adenomatoid tumour must be separated from some diffuse epithelial mesotheliomas that may, in individual microscopic fields, show a similar pattern.

Prognosis and predictive factors
These neoplasms are identical to adenomatoid tumours in other locations and are benign.

Lymphomas

P.M. Banks
N.L. Harris
R.A. Warnke
Ph. Gaulard

Primary effusion lymphoma

Definition
A neoplasm of large B-cells presenting as serous effusions, usually without detectable tumour masses, universally associated with human herpes virus 8 (HHV8)/Kaposi sarcoma herpes virus (KSHV), and usually occurring in the setting of immunodeficiency.

ICD-O code 9678/3

Synonym
Body cavity-based lymphoma.

Epidemiology
The majority of cases arise in the setting of human immunodeficiency virus (HIV) infection {60,311,1421}. Most patients are young to middle aged homosexual males. This neoplasm is rare even in the setting of HIV infection. Cases have been reported in HIV negative allograft recipients, particularly after cardiac transplantation {512,561,937}. The disease has also been reported in the absence of immunodeficiency especially in elderly individuals {282,380,821,1029,1422, 1995}.

Localization
The most common sites of involvement are the pleural, pericardial and peritoneal cavities. Typically only one body cavity is involved. One case has been reported arising in the artificial cavity of a breast implant {1721}. The most common extracavitary site of presentation is the gastrointestinal tract; the GI tract, mediastinal and retroperitoneal soft tissue and other extranodal sites may also be secondarily involved {130,209,415,479,877}.

Clinical features
Patients typically present with effusions in the absence of lymphadenopathy or organomegaly. Some patients, both HIV+ and HIV-, have pre-existent Kaposi sarcoma {60,937,1721}. Rare cases are associated with multicentric Castleman disease {380,1995}.

Etiology
The consistent presence of HHV8 in the neoplastic cells in all cases suggests a pathogenetic role for this virus in the development of the tumour {311}. There is consistent expression of viral IL-6 (vIL-6) in primary effusion lymphomas, suggesting that this and other cytokines may play a role in the pathogenesis of the tumours {62,514}. In one study of an EBV- HIV- case, HHV8 related transcripts including viral G-coupled protein receptor, viral Bcl2, viral cyclin D1, viral IL6 and viral MIP I and II were detected in tissue from a primary effusion lymphoma and an HHV8+ gastric lymphoma but only vIL6 was detected in a multicentric Castleman disease lesion from the same patient {1995}. Oncogenic genes encoding viral cyclin D, bcl2, G-protein coupled receptor IL-6, Flice inhibitory protein and others were also shown to be expressed in another EBV- PEL {379}. NF kappa-B is constitutively activated on HHV8+ PEL cell lines, and its inactivation leads to apoptosis, suggesting that, similarly to EBV, HHV8 may promote cell survival through this pathway {989}.
Although multicentric Castleman disease and primary effusion lymphoma may coexist in some patients, a clonal relationship between them has not been established {82}.
Most but not all cases are coinfected with EBV, but do not express the transforming proteins EBNA-2 and LMP1 and 2. Each case contains a single strain of clonal EBV, but there is considerable heterogeneity among cases; thus no specific role for EBV in the pathogenesis has been found {561,868}.

Histopathology
With Wright or May Grunwald Giemsa staining performed on cytocentrifuge preparations, the cells exhibit a range of appearances, from large immunoblastic or plasmablastic cells to cells with more anaplastic morphology. Nuclei are large, round or irregular in shape, with prominent nucleoli. The cytoplasm is typically very abundant and is deeply basophilic,

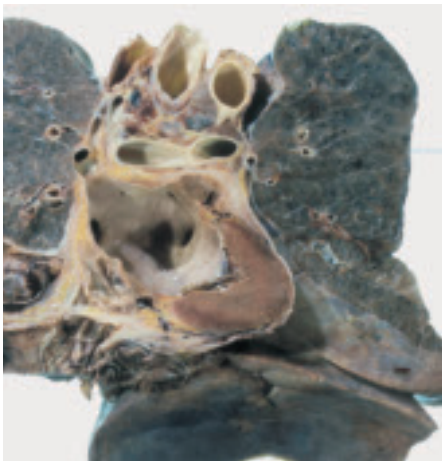


Fig. 2.16 Diffuse lymphoma of the pleura in a patient with AIDS.

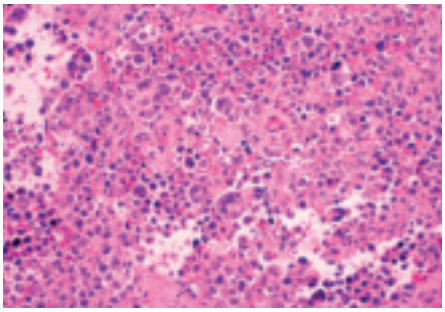


Fig. 2.17 Primary effusion lyphoma of pleura. Discohesive atypical lymphoid tumour cells with a few pleomorphic cells.

and vacuoles may be present in occasional cells. A paranuclear hole suggesting plasmacytoid differentiation may be seen. Binucleated or multinucleated cells may be present that can resemble Reed-Sternberg cells.
The cells often appear more uniform in histological sections than in cytospin preparations. They are large, with some pleomorphism, ranging from large cells with round or ovoid nuclei to very large cells with irregular nuclei and abundant cytoplasm; multinucleation can occur {60,311,1421}. Pleural biopsies show tumour cells adherent to the pleural surface, often embedded in fibrin and occasionally invading the pleura.
This disease should be distinguished from pyothorax-associated diffuse large

B-cell lymphoma, which usually presents with a pleural mass lesion. The cells of pyothorax-associated diffuse large B-cell lymphoma have the appearance of immunoblasts, and are EBV positive and HHV8 negative {1972}.

Immunoprofile

The neoplastic cells typically express leukocyte common antigen (CD45) but are usually negative for the pan-B-cell markers CD19, CD20 and CD79a {60, 1421}. Surface and cytoplasmic expression of immunoglobulin is likewise often absent. The B-cell specific transcriptional activator programme appears to be disrupted in primary effusion lymphoma, with decreased or absent expression of PU.1, Oct 2 and BOB.1, possibly accounting for the failure to produce immunoglobulin {72}. CD30 is typically positive. The cells lack germinal centre-associated markers CD10 and Bcl-6 and express MUM1/IRF4, associated with late germinal centre and post-germinal centre B cells {281}. Plasma cell-related markers such as CD38, and CD138 are typically expressed {650}. Aberrant cytoplasmic CD3 expression has been reported {130}, as well as CD7 and CD56 {1608}. Because of the markedly aberrant phenotype, it may be difficult to assign a lineage with immunophenotyping. Rare cases of HHV8+ primary effusion lymphoma that express only T-cell-associated antigens have been reported {1146,1720}.

The nuclei of the neoplastic cells are positive by immunohistochemistry for the HHV8/KSHV-associated latent protein {522,1555}, and this staining can be useful in confirming the diagnosis. EBV-positive cases have a Type I latency phenotype, expressing only EBNA-1; EBNA-2 and LMP-1 and 2 are not expressed at levels detectable by immunohistochemistry {278}.

Cell lines from primary effusion lymphomas have been shown to express both the Met tyrosine kinase receptor and its ligand, hepatocyte growth factor, similarly to myeloma cell lines {278}.

Histogenesis

Post-germinal center B-cell with differentiation towards plasma cells.

Somatic genetics

Immunoglobulin genes are rearranged and are mutated consistent with a post-germinal center B cell {1258}. The BCL6 gene is somatically mutated in most cases, consistent with a post-germinal center B cell {649}. Some cases also have rearrangement of T-cell receptor genes {865}. Most cases have multiple but non-recurring cytogenetic abnormalities {512}. Comparative genomic analysis has revealed gains in sequence of chromosomes 12 and X {1401}. HHV8 viral genomes are present in all cases. EBV is detected in most but not all cases by EBER *in-situ* hybridisation {60,209, 561,1421}. Cases in HIV- non-immunosuppressed patients appear to be more often EBV- {512}. Two cases with only T-cell antigen expression and rearrangement of the T-cell receptor gene have been reported {1146,1720}. The relationship of these cases to the more common B-cell neoplasm is unclear.

Gene expression analysis by DNA microarray technology has shown a distinctive profile for the cells of primary effusion lymphoma, including genes indicating differentiation towards plasma cells and a set of genes unique to this type of lymphoma {1027}.

Prognosis and predictive factors

The clinical behaviour is extremely aggressive, with most reported patients dead in less than one year. Recently a few cases have been reported to respond to antiviral therapy or combination chemotherapy or both with prolonged survival {209,1029}.

Pyothorax-associated lymphoma

Definition

Pyothorax-associated lymphoma (PAL) is a neoplasm of large B cells, typically with immunoblastic morphology, usually presenting as a pleural mass. It is strongly associated with Epstein-Barr virus (EBV). This rare type of primary pleural B-cell lymphoma occurs in patients with a clinical history of longstanding pyothorax resulting from pulmonary tuberculosis or tuberculous pleuritis.

Synonyms and historical annotation

Since its first recognition in 1987, it has been established that PAL belongs to the diffuse large B-cell lymphoma (DLBCL) category {915}. Although the recent WHO classification of Tumours of Haematopoietic and Lymphoid Tissues describes different clinical subtypes among DLBCL (i.e. mediastinal, intravascular, and primary effusion lymphoma) {919}, PAL has not been included as a distinct clinico-pathologic entity in this recent classification, probably in view of its rarity in most western countries. We include it in this classification of pleural tumours since it specifically occurs in this location.

Epidemiology

Pyothorax-associated lymphoma (PAL) occurs in adults, usually in the 5-8th decades with a median age around 65-70 years. It seems to affect males more often than females {1437,1586}. PAL develops in patients without overt systemic immunosuppression, but consistently after a history of pyothorax resulting from artificial pneumothorax for treatment of pulmonary tuberculosis or, more rarely, tuberculous pleuritis. The interval between the onset of pleuritis and initial symptoms of lymphoma ranges from 20—67 -years, with a 37-48 years median interval {1437,1586}. Most PALs have been reported in Japan, apart from several cases in France and Italy {63,79, 1250,1339,1437,1503,1586}.

Etiology

Strong association with Epstein-Barr virus (EBV) has been demonstrated {631, 1503,1743}. Depending on the series, EBV DNA or EBV-encoded RNA (EBERs) are demonstrated in lymphoma cells of 70-100% of cases. They also express latent infection genes, including EBV nuclear antigen 2 (EBNA-2) and latent membrane protein 1 (LMP-I), resulting in a latency III pattern of EBV expression, similar to that observed in lymphoproliferative disorders occurring in immunocompromised patients. Although the pathogenesis is not clearly understood, previous findings {954} suggest a role for chronic inflammation at the local site in the proliferation of EBV-transformed B-cells by enabling them to escape the host immune-surveillance system and/or by providing local production of cytokines such as IL-6 and IL-10 {955, 956}.

There is no association with HIV, HTLV, or HHV8 infections.

Sites of involvement

In contrast to primary effusion lymphoma (PEL), PAL typically presents as a tumour

mass that involves the pleural cavity and shows direct invasion to adjacent structures such as the chest wall, lung and diaphragm in most cases, whereas pleural effusion is rarely observed. Extrathoracic/metastatic dissemination (bone marrow, liver, abdominal lymph nodes, etc) is only rarely observed at presentation {1437,1586}.

Clinical features

Patients typically present with symptoms related to a pleural tumour mass, with pains in the chest and/or back, or respiratory symptoms such as productive cough, often with haemoptysis or dyspnoea. Other common symptoms are fever and weight loss. A tumour swelling in the chest wall is present in 40% of the patients. Chest radiography and computed tomography reveals a tumour mass in most patients, which is located in the pleura (80%), pleura and lung (10%) and lung near pleura (7%) with a tendency to invade adjacent structures, mainly the chest wall, and is larger than 10 cm in about half of the patients {1437}. These features often suggest a diagnosis of lung cancer or pleural mesothelioma. About 70% of the patients have a Ann Arbor stage I-II localized disease. The serum lactate dehydrogenase (LDH) level is elevated in most patients {1437, 1586}. Due to the presence of several clinical prognostic factors (low performance status, age, elevated LDH level), the majority of patients belong to the intermediate group of the International Prognostic Index (IPI) score {2}.

Morphology

In tissue sections, there is a diffuse destructive proliferation of large cells. Despite a range of appearances, most cases show a predominant population of immunoblasts with round nuclei showing large single or multiple nucleoli. They may have features of plasmacytoid differentiation. Some cases are consistent with a centroblastic lymphoma and a few have been reported to have anaplastic features. PAL is characterized by a high proliferative rate with numerous mitotic figures and prominent apoptosis. Areas of necrosis and angiocentric or angioinvasive features have been reported, thus resembling features of lymphoproliferative disorders occurring in immunocompromised patients. The disease should be distinguished from primary effusion lymphoma (PEL), which commonly presents as serous effusions without detectable tumour masses in patients with a setting of immunodeficiency, is characterized by a proliferation of large B-cells which are CD30, CD38 and CD138 positive but lack CD20 and CD79a B cell markers, and is constantly associated with HHV8 infection.

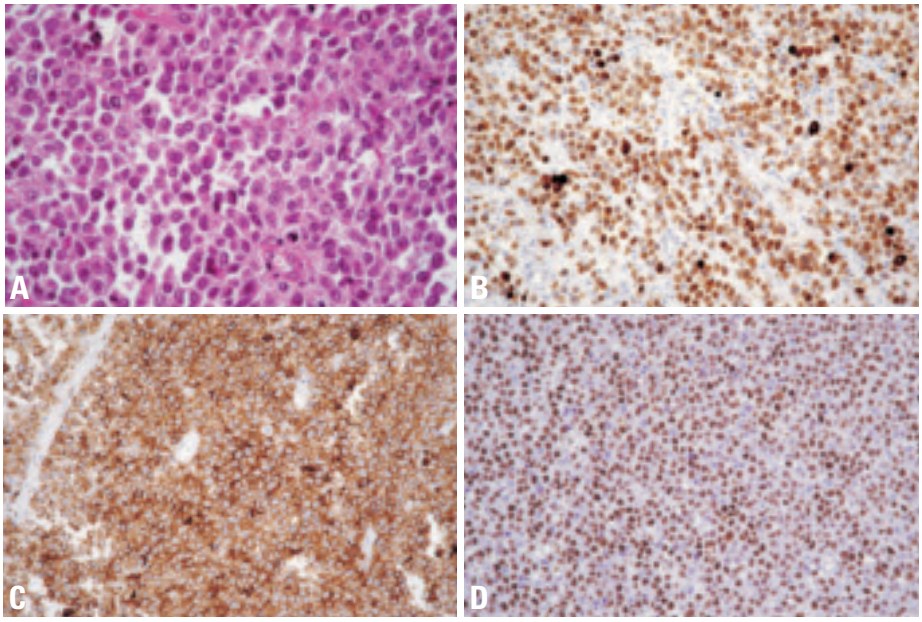


Fig. 2.18 Pyothorax associated lymphoma. **A** At a higher magnification, the infiltrate consists of large neoplastic cells, with immunoblasts and many cells showing a plasmacytoid differentiation with eccentric nuclei and abundant cytoplasm. **B** The neoplastic cells are strongly positive for CD79a. **C** However, in this case, they also show aberrant strong expression for CD2. **D** Immunostaining with the EBNA-2 antibody shows that virtually all neoplasic cells disclosed strong nuclear staining for EBNA-2.

Immunophenotype

Typically, lymphoma cells are positive for CD79a and CD20 B-cell antigens. Cases with plasmacytoid differentiation, however, have been reported to lack CD20 or even CD79a. They may show weak heterogeneous expression of plasma cell related markers such as CD138. Cytoplasmic expression of immunoglobulins can be detected. CD30 activation marker can be expressed. Surprisingly, a number of cases may express at least one T-cell marker (CD2, CD3, CD4, and/or CD7), most frequently with a dual B/T phenotype {1380,1433,1437,1586, 2010}. A similar observation has been made in PAL cell lines {36,433}. Thus, in some PALs, because of a markedly aberrant phenotype – i.e., null-cell phenotype or expression of some T-cell markers – it is difficult to assign a lineage.

Based on CD20 negativity and expression of T-cell antigens, rare cases of pyothorax-associated T-cell lymphoma have even been reported. However, one of these cases, investigated for genotypic studies, was demonstrated to contain a B-cell clone without clonal rearrangement of the T-cell receptor genes, thus indicating that such cases correspond to B-cell lymphomas with aberrant T-cell phenotype {2010}. Although the reason for such an aberrant phenotype in PAL is unknown, it is noteworthy that it has also been described in B-cell lines infected by EBV as well as in some EBV transformed B-cell lymphomas arising in immunosuppressed patients, and it has been suggested that EBV might promote this dual phenotype.

Recently, it has been shown that lymphoma cells in PAL express a uniform $CD10^{-}$, BCL-6^{-}, $MUM1/IRF\text{-}4^{+}$ phenotype, in agreement with derivation from a late germinal centre/post-germinal centre B-cell {1586}.

Lymphoma cells are positive by immunohistochemistry for EBV in most cases, showing an $EBNA\text{-}2^{+}/LMP\text{-}1^{-/+}$ phenotype consistent with a type III latency. EBNA-2 is usually highly expressed in the nuclei of most tumour cells, whereas LMP-1 is found in a few neoplastic cells {1339,1586}. Demonstration of EBV is very useful in establishing a diagnosis.

Genetic features
Immunoglobulin genes are rearranged and are mutated {1333}. No characteristic chromosomal alterations have been identified. A high frequency of p53 mutations and of c-myc amplifications have been described {867,2191}. As seen above, EBV genomes are detected in virtually all cases by in situ hybridization with EBERs probes and lymphoma cells also express EBNA-2 and LMP-I viral proteins. By Southern blot, they carry monoclonal EBV genome {433,631} and chromosomal integration of EBV has been recently demonstrated in one cell line {433}. A small percentage of PAL are reported to be EBV-negative. However, EBV genomes have been found by using sensitive PCR techniques in at least a few cases that were scored as EBV-negative on the results of in situ hybridization and immunohistochemical studies {1503, 1586}. In contrast to PEL, HHV8 sequences and expression of HHV8 /ORF73 antigens are absent in PAL {1496,1586}.

Postulated normal counterpart
EBV-transformed late germinal centre/ post-germinal centre B-cell.

Prognostic features
Most series report a very poor prognosis with a median survival of less than one year. However, in a recent series, more than half of the patients showed a responsiveness to chemotherapy and/or radiotherapy and the patients who achieved complete remission after therapy had a 50% 5-year survival rate {1437}.

Mesenchymal tumours

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Epithelioid haemangioendothelioma / angiosarcoma

Definition
Pleural epithelioid haemangioendothelioma (PEH) is a low to intermediate grade vascular tumour composed of short cords and nests of epithelioid endothelial cells embedded in a myxohyaline matrix. The tumours are distinctive for their epithelioid character, sharply defined cytoplasmic vacuoles, intraalveolar and intravascular growth and central hyaline necrosis. High-grade epithelioid vascular tumours are called epithelioid angiosarcomas.

ICD-O code
Epithelioid haemangioendothelioma 9133/1
Angiosarcoma 9120/3

Epidemiology
Most patients with PEH are Caucasian, 65-85% are men and the mean age is 52 years with a range of 34-85 years {424, 435,533,1184,2120}.

Clinical features
Patients usually present with diffuse pleural thickening, pleural effusion, and/or pleuritic chest pain. Some patients have both pulmonary as well as pleural involvement. {424,1184,510,536,1184, 1227,1453}.

Imaging
CT scans or chest x-rays characteristically demonstrate pleural thickening and pleural effusions may represent the primary manifestation {424,1184}, sometimes accompanied by pulmonary nodules.

Macroscopy and localization
Epithelioid haemangioendotheliomas may involve the pleura diffusely and mimic the gross appearance of diffuse malignant mesothelioma {424,1184, 2222,2239}.

Histopathology
The tumours often show a biphasic pattern with nests of epithelioid cells within a spindle cell stroma. The stroma is usually reactive, but may be neoplastic. It often shows a myxoid or chondroid appearance. A tubulopapillary pattern may be seen in about one third of cases. The epithelioid tumour cells show large round to oval nuclei with a vesicular chromatin pattern. Epithelioid angiosarcomas are high grade and typically show large nucleoli more frequent mitoses than the low to intermediate grade epithelioid haemangioendotheliomas. Intracytoplasmic vacuoles are common.

Immunohistochemistry
Most tumours stain with one or more endothelial markers including CD31, CD34, Fli1, and factor VIII (von Willebrand factor) {599,828,1184}. Cytokeratin is expressed in up to 50% of cases, causing some difficulty in differentiating it from carcinoma {424,1184, 1308}. However, the staining is usually weak to moderate and weaker than vimentin staining {424,1184}.

Electron microscopy
Electron microscopy reveals abundant intermediate filaments, micropinocytosis and Weibel- Palade bodies. An interrupted basal lamina surrounding the tumour cells is present and cytoplasmic lumina may be seen {1184}.

Differential diagnosis
The differential diagnosis includes chronic fibrous pleuritis, malignant mesothelioma, metastatic carcinoma and melanoma. Key to recognition of this tumour in the pleura is awareness of its morphologic and immunohistochemical characteristics, particularly that it may show a biphasic and papillary appearance. If keratin staining in an epithelioid tumour in the pleura is weak or negative, an epithelioid vascular tumour should be considered and immunohistochemistry for vascular markers should be performed.

Histogenesis
Epithelioid haemangioendotheliomas are derived from endothelial cells.

Prognostic factors
Epithelioid vascular tumours that present in the pleura have an aggressive clinical course. There is no known effective therapy for these patients.

Synovial sarcoma (SS)

Definition
Synovial sarcoma (SS) is a biphasic mesenchymal neoplasm with epithelial and spindle-cell components, or a monophasic tumour which consists purely of a spindle cell component. Both biphasic and monophasic types can occur in the pleura and they can be easily confused with malignant mesothelioma or pulmonary sarcomatoid carcinoma.

ICD-O codes
Synovial sarcoma 9040/3
Synovial sarcoma, spindle cell 9041/3
Synovial sarcoma, biphasic 9043/3

Synonyms
Synovial cell sarcoma, malignant synovioma, synovioblastic sarcoma

Etiology
There are no known etiological factors.

Clinical features
Patients with biphasic tumors may present at a younger age (mean 25 years, range 9-50 years) {644} than those with monophasic tumours (mean of 47 years (range 33-69 years) {89}. SS shows no gender predilection {89,644,1463}. chest pain is the most common presenting manifestation but pleural effusions, dyspnea, dysphagia or pneumothorax can occur {89,644}. Pleural SS can be aggressive with almost half of patients dead of disease (with a mean of 18 months).

Macroscopy and localisation
Pleural SS are usually localized, solid tumours, but they can present with diffuse pleural thickening like mesothelioma

{89,394,644,1463}. Some tumors have a pseudocapsule, causing them to be well demarcated from the surrounding tissues. The tumors may grow on a pedicle. They are usually large tumours with a mean size of 13 cm (range 4-21 cm). Cut surface of the tumour can show cystic degenerative changes and necrosis.

Tumour spread and staging
Pleural SS typically recurs within the pleural cavity and may invade theinvolving chest wall as well as adjacent structures including the pericardium, and diaphragm.

Histopathology
Histologic features of pleural SS are exactly the same as for those described in the lung (see lung chapter). While the monophasic type is most common within the lung, a high percentage of pleural tumors are biphasic {89,394,644,1463}. Mucin can be demonstrated in some biphasic tumors.
Immunohistochemistry of pleural SS typically shows focal positive staining for keratin and/or EMA with positive bcl-2, CD99 and vimentin. The glandular component of biphasic tumors may express BER-EP4 and CEA. Calretinin and S-100 may be focally positive, but desmin, smooth muscle actin and CD34 are usually negative.

Differential diagnosis
In the pleura, the most important differential diagnosis is malignant mesothelioma, followed by sarcomatoid carcinoma, solitary fibrous tumour and metastatic synovial sarcoma {89,394,644,1463}. Compared to mesothelioma, pleural SS occur more often in younger patients, they are more likely to be localized, and tend to grow more rapidly. A pseudocapsule may be present in pleural SS, but this is typically absent in mesothelioma {644}. The spindle cells of SS tend to grow in long interweaving fascicles while in mesothelioma the cells grow in blunt short fascicles. Haemangioperi-cytomatous growth and hyaline fibrosis are common in SS and uncommon in mesothelioma. The presence of mucin in glands and expression of CEA and/or BER-EP4 favors biphasic SS, although BER-EP4 can be seen in some series in a high percentage of mesotheliomasup to 20% of mesotheliomas. Demonstration of the X:18 translocation is very helpful in confirming the diagnosis of SS.

Histogenesis
Remains unknown. It is thought to be a totipotential mesenchymal cell and it has not been proven to arise or differentiate from synovium.

Somatic genetics
Synovial sarcoma has the distinctive translocation t (X; 18)(p11; q11) that is not seen in the other tumors mentioned above in the differential diagnosis, most importantly mesothelioma and sarcomatoid carcinoma {89,694,850,957,1310, 1992}. Fortunately this can readily be demonstrated in formalin-fixed paraffin-embedded tissue. Other details about this translocation are summarized in the lung chapter.

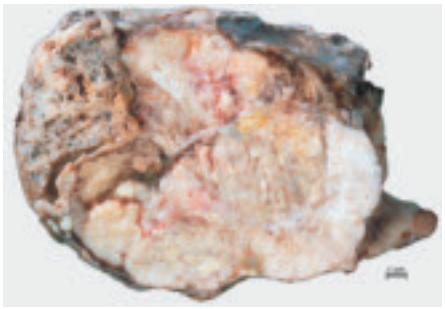

Fig. 2.19 Malignant fibrous tumour of the pleura.

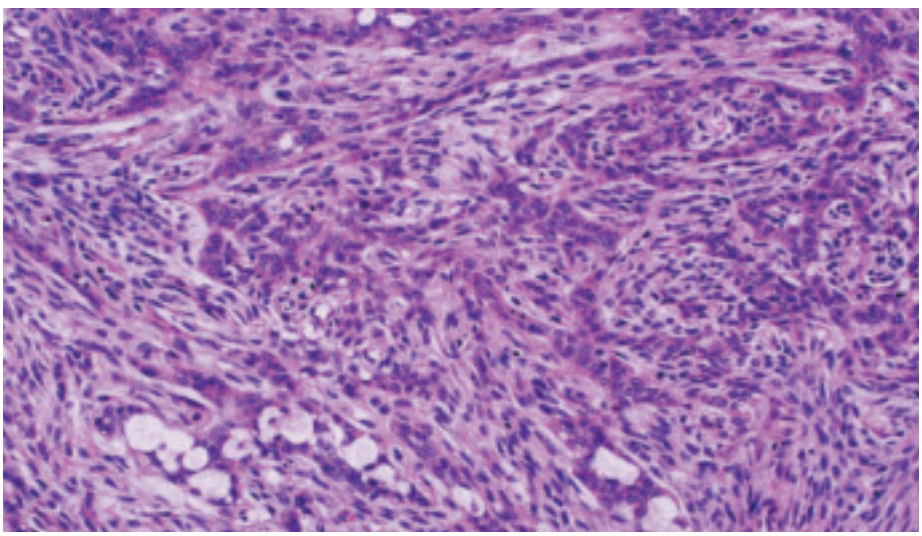

Fig. 2.20 Pleural synovial sarcoma. This biphasic tumour consists of glandular and spindle cells.

Solitary fibrous tumour (SFT)

Definition
An uncommon spindle-cell mesenchymal tumour of probable fibroblastic derivation that often presents a prominent haemangiopericytoma-like vascular pattern, but may exhibit other histologic patterns. A morphologically identical tumour occurs in numerous other extrathoracic sites.

ICD-O code 8815/0

Synonyms
Also known as localized fibrous tumour, this lesion was once variously designated benign mesothelioma, localized fibrous mesothelioma, and submesothelial fibroma. The use of names that include 'mesothelioma' for this tumour is discouraged because of potential confusion with diffuse malignant mesothelioma.

Etiology
No etiologic agent has been identified; in particular there is no link with asbestos exposure.

Clinical features
Signs and symptoms
The most common symptoms at presentation are cough, chest pain, and dyspnoea. Some patients may present with hypertrophic osteoarthropathy and, on rare occasions, symptomatic hypoglycemia as a result of the production of an insulin-like growth factor {629}. Some tumours are incidental findings.

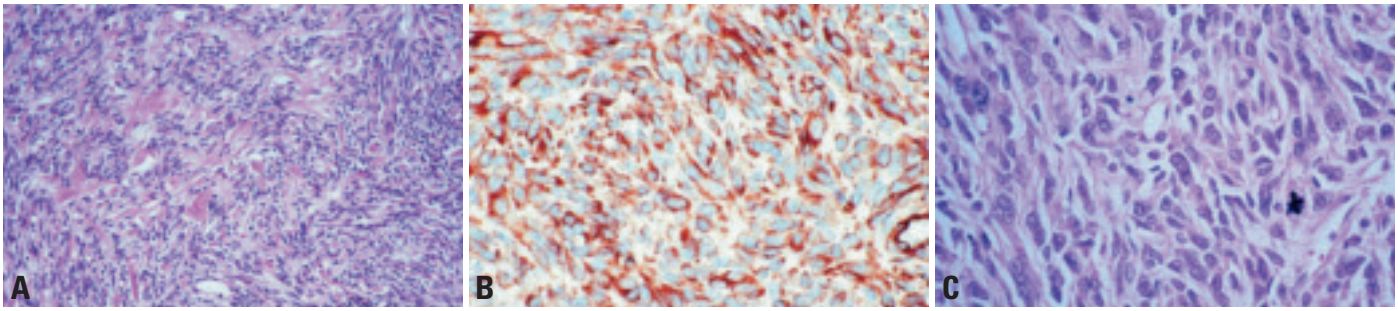

Fig. 2.21 Solitary fibrous tumour. **A** Spindle cells with ropy collagen stroma. **B** Diffuse strong positivity for CD34. **C** Malignant SFT showing hypercellularity, marked cellular atypia and high mitotic activity.

Imaging

Solitary fibrous tumours of the pleura present on chest radiographs as pleural-based soft tissue masses. The margins are well defined and there is no associated rib destruction or chest wall abnormality. A pleural effusion may be present. Tumours can vary in size from small lesions to very large masses that occupy most of the hemithorax. When large, they require CT or MR scanning to differentiate them from lung masses. The margin at which the lesion meets the chest wall is smooth. On CT scanning, they show a pattern of heterogeneous contrast enhancement and compress but do not invade the contiguous lung. Rarely, their attachment to the chest wall by a pedicle can be seen.

Macroscopy

Most tumours arise in the visceral pleura, but they may also originate in the lung parenchyma and mediastinum. They are well circumscribed and often pedunculated {544}. Rarely they may be multiple. The cut surface is usually firm and whitish, often with a whorled appearance. Myxoid change, haemorrhage, and necrosis may occasionally be seen and suggest that the tumour is malignant; large size also suggests malignancy. These features mandate extensive sampling.

Histopathology

SFT typically exhibits a patternless architecture characterized by the coexistence of hypo- and hypercellular areas separated by fibrous stroma having haemangiopericytoma-like branching blood vessels. The hypercellular areas are composed of bland spindle cells arranged in short intersecting fascicles, creating herringbone or storiform arrays. The hypocellular areas may be highly collagenized or, less frequently, present myxoid changes. Malignant SFTs (ICD-O 8815/3) are characterized by greater cellularity with an infiltrative growth pattern, moderate to marked cellular atypia and high mitotic activity (> 4 mitoses per 10 high-power fields) {544}.

Immunohistochemical studies are helpful in confirming the diagnosis of SFT. In contrast with sarcomatoid mesothelioma, these lesions tend to be positive for CD34, and bcl-2, and are always negative for cytokeratin {1519}. However, malignant SFT may not always express CD34 and bcl-2. The differential diagnosis of SFT in the pleura includes sarcomatoid mesothelioma, and a variety of benign and malignant soft tissue tumours, such as haemangiopericytoma, malignant fibrous histiocytoma, monophasic synovial sarcoma, thymoma, and peripheral nerve sheath tumours.

Somatic genetics

Only a few studies have reported cytogenetic findings in SFT. Reported abnormalities include: t(4;15)(q13;q26){436}; 46,XY,t(6;17) (p11.2;q23), ins (9;12) (q22;q15q24.1), inv (16) (p13.1q24) {508}. In the latter case the rearrangement of 12q13-15 is similar to that described in a subset of haemangiopericytomas of soft tissue and meninges {508}.

In one malignant SFT of the pleura successful karyotyping was obtained from the primary and recurrent tumours. The initial karyotype showed two abnormal clones: 48, XY; +8; +8; del(9)(q22; q32) [19] and 46, XY, t(1;16)(q25;p12) [7]. Culture of the recurrent tumour yielded one clone identical to the dominant clone of the initial karyotype {447}.

Comparative genomic hybridisation (CGH) of 12 SFT of pleura showed no chromosomal imbalances in 58 percent of cases. Losses on chromosome arms 13q (33%), 4q and 21q (17% each) were the most frequent abnormality. Significant gains were seen at chromosome 8 and at 15q in two cases each. There was no correlation between tumour size and molecular pathology findings {1073}. Another CGH study of one SFT revealed losses of 1p33—>pter, 17pter q21, entire copies of chromosomes 19 and 22, and gains of 1p21-p22, 2q23-q32.3, 3pl2-q13.2, 4p14-q28, 6p12-q21, 9p21—>pter and 13q21-q31. Further-more, there was loss of 20q, as was previously reported elsewhere in a case of benign and a case of malignant SFT {48}.

Calcifying tumour of the pleura

Definition

A rare slow growing plaque-like lesion occurring in the visceral pleura, composed of nearly acellular fibrous tissue, and associated with extensive dystrophic calcification (which may be psammomatous).

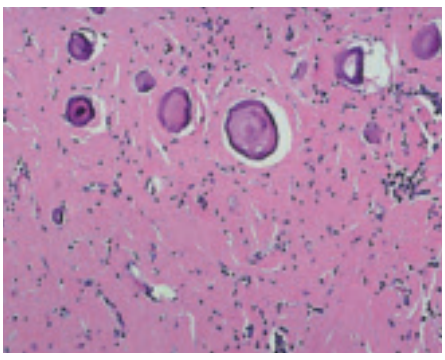

Fig. 2.22 Calcifying tumour. Psammoma-like calcifications within a dense fibrous stroma. From {2024}.

Synonyms and historical annotation
Calcifying fibrous pseudotumour, childhood fibrous tumour with psammoma bodies

Clinical features
Signs and symptoms
Rare examples of calcifying tumour of the pleura (CTP) are reported in the pleura {1599}, or mediastinum {929}, but these tumours more often occur in the soft tissues of the extremities, trunk, scrotum, groin, neck, or axilla {575}. Most cases occur in children and young adults with no sex predilection. Patients may present with chest pain or they may be asymptomatic.

Imaging
Chest radiographs or CT scans show a single pleural mass or multiple pleural-based nodular masses with central areas of increased attenuation due to calcification, which may be extensive.

Macroscopy and histopathology
The lesions consist of circumscribed, but unencapsulated masses of hyalinized collagenous fibrotic tissue interspersed with lymphoplasmacytic infiltrates and calcifications, often with psammomatous features The lesions are limited to the pleura and typically do not involve the underlying lung parenchyma. Multiple lesions may be seen {758}. The fibrous cells may be positive for vimentin and Factor XIIIa and CD68 {830}, but negative for actin, desmin, S100 protein, CD31, and usually, CD34 {2128}.

Differential diagnosis
The differential diagnosis includes other pleural lesions such as solitary fibrous tumour of pleura, calcified granulomas, calcified pleural plaques, and chronic fibrous pleuritis as well as intrapulmonary lesions such as hyalinizing granuloma, inflammatory pseudotumour, and amyloid.

Prognosis and predictive factors
As in the soft tissues, local excision appears adequate therapy for CFT of the pleura. If these lesions behave in a similar fashion to CFT of soft tissues, one might expect a low frequency of local recurrence.

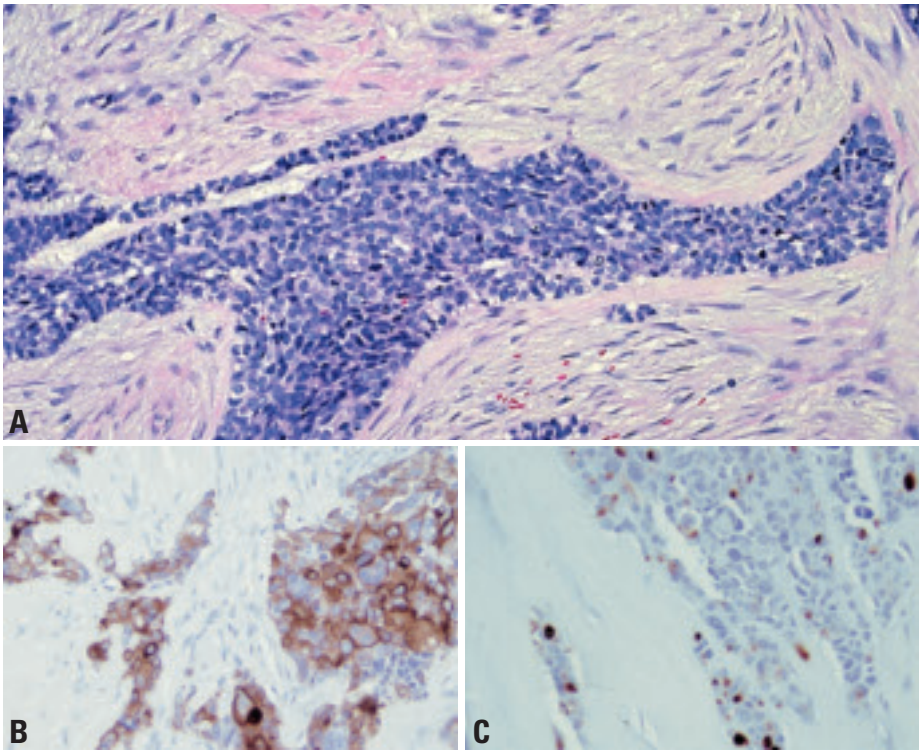

Fig. 2.23 Desmoplastic round cell tumour. **A** Cellular round cell component within a dense fibrous stroma From {2024}. The tumour cells stain positively for **B** keratin and, for **C** desmin with a dot-like pattern.

Desmoplastic small round cell tumour of the pleura

Definition
DRCT is a primitive polyphenotypic neoplasm typically occurring on the serous surfaces in the abdominal cavity and rarely in the pleura of young adult males. It possibly represents a primitive mesothelial-related lesion.

ICD-O code 8806/3

Clinical features
The reported six cases involving pleura {164,1524,1551,1739,1936} occurred in 4 men and 2 women aged 17-29 years (median age 23 years) and usually presented with chest pain and pleural effusion. Although this pleural tumour usually is fatal within 2 years, one patient lived over 5 years {1524}. DRCT can also present with an intrapulmonary mass {1936}.

Histopathology
Grossly the tumour typically forms multiple pleural-based nodular masses and can produce pulmonary encasement resembling that of malignant mesothelioma. Mediastinal involvement is typical of pleural-based tumours; bilateral pleural involvement and pulmonary parenchymal metastases may also occur. Histologically the tumour is composed of irregularly shaped islands or larger sheets of small round tumour cells in cellular desmoplastic stroma. Focal nuclear atypia can occur in the tumour cells, and the stroma may contain vascular proliferation.

Immunohistochemical profile
The typical features include expression of keratins, EMA, desmin (often in a perinuclear dot-like pattern), vimentin and Wilms tumour protein WT1 {677}. Since translocation splits the latter gene, antibodies to WT1 should be used that recognize the preserved carboxyterminus of the protein. NSE-positivity and expression of CD15 are also common.

Genetics
The presence of WT1-EWS gene fusion with the t(11;22) translocation are the key diagnostic features of this tumour {677}.