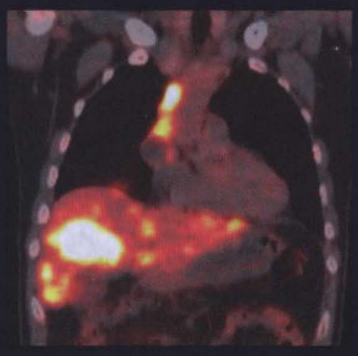
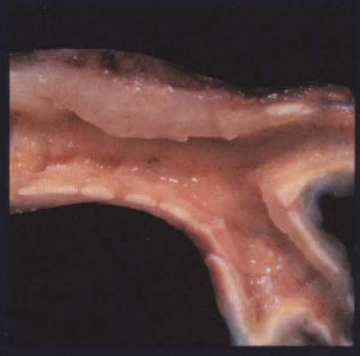
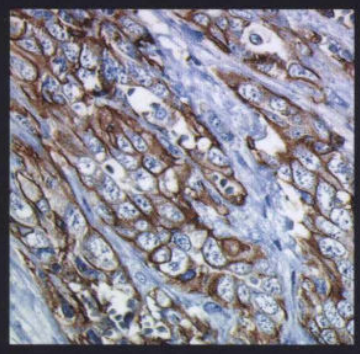
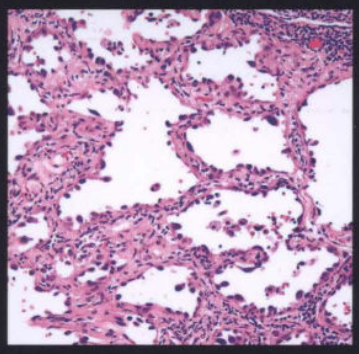
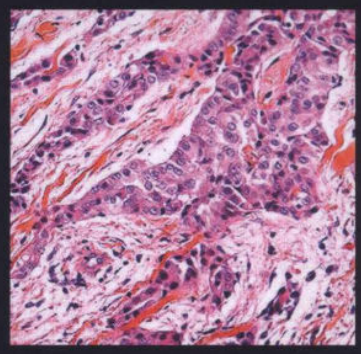
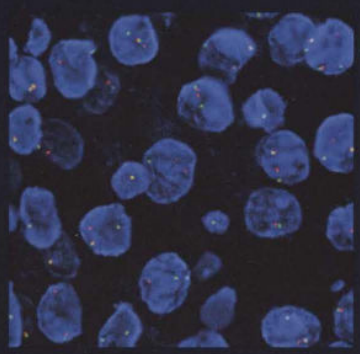
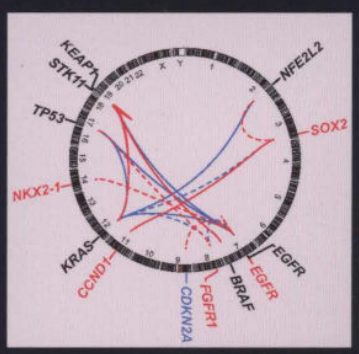
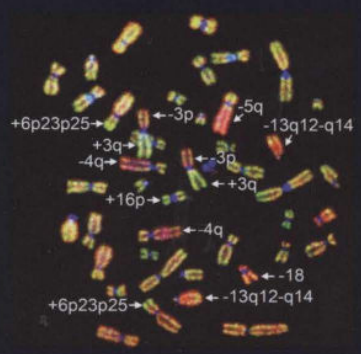
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Edited by
William D. Travis, Elisabeth Brambilla, Allen P. Burke, Alexander Marx, Andrew G. Nicholson



WHO

World Health Organization Classification of Tumours

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ISBN 978 92 832 2415 9

DeLellis R.A., Lloyd R.V., Heitz P.U., Eng C. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Endocrine Organs (3rd edition).
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ISBN 978 92 832 2416 7

Barnes L., Eveson J.W., Reichart P., Sidransky D. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours (3rd edition). IARC Press: Lyon 2005
ISBN 978 92 832 2417 5

LeBoit P.E., Burg G., Weedon D., Sarasin A. (Eds.): World Health Organization Classification of Tumours. Pathology and Genetics of Skin Tumours (3rd edition).
IARC Press: Lyon 2006
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Louis D.N., Ohgaki H., Wiestler O.D., Cavenee W.K. (Eds.): WHO Classification of Tumours of the Central Nervous System (4th edition).
IARC: Lyon 2007
ISBN 978 92 832 2430 2

Swerdlow S.H., Campo S., Harris N.L., Jaffe E.S., Pileri S.A., Stein H., Thiele J., Vardiman J.W. (Eds.): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (4th edition).
IARC: Lyon 2008
ISBN 978 92 832 2431 0

Bosman F.T., Carneiro F., Hruban R.H., Theise N.D. (Eds.): WHO Classification of Tumours of the Digestive System (4th edition).
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Lakhani S.R., Ellis I.O., Schnitt S.J., Tan P.H., van de Vijver M.J. (Eds.): WHO Classification of Tumours of the Breast (4th edition).
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World Health Organization Classification of Tumours

WHO  OMS

International Agency for Research on Cancer (IARC)

4th Edition

WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Edited by

William D. Travis
Elisabeth Brambilla
Allen P. Burke
Alexander Marx
Andrew G. Nicholson

International Agency for Research on Cancer
Lyon, 2015

This volume was produced in collaboration with the

International Association for the Study of Lung Cancer (IASLC)

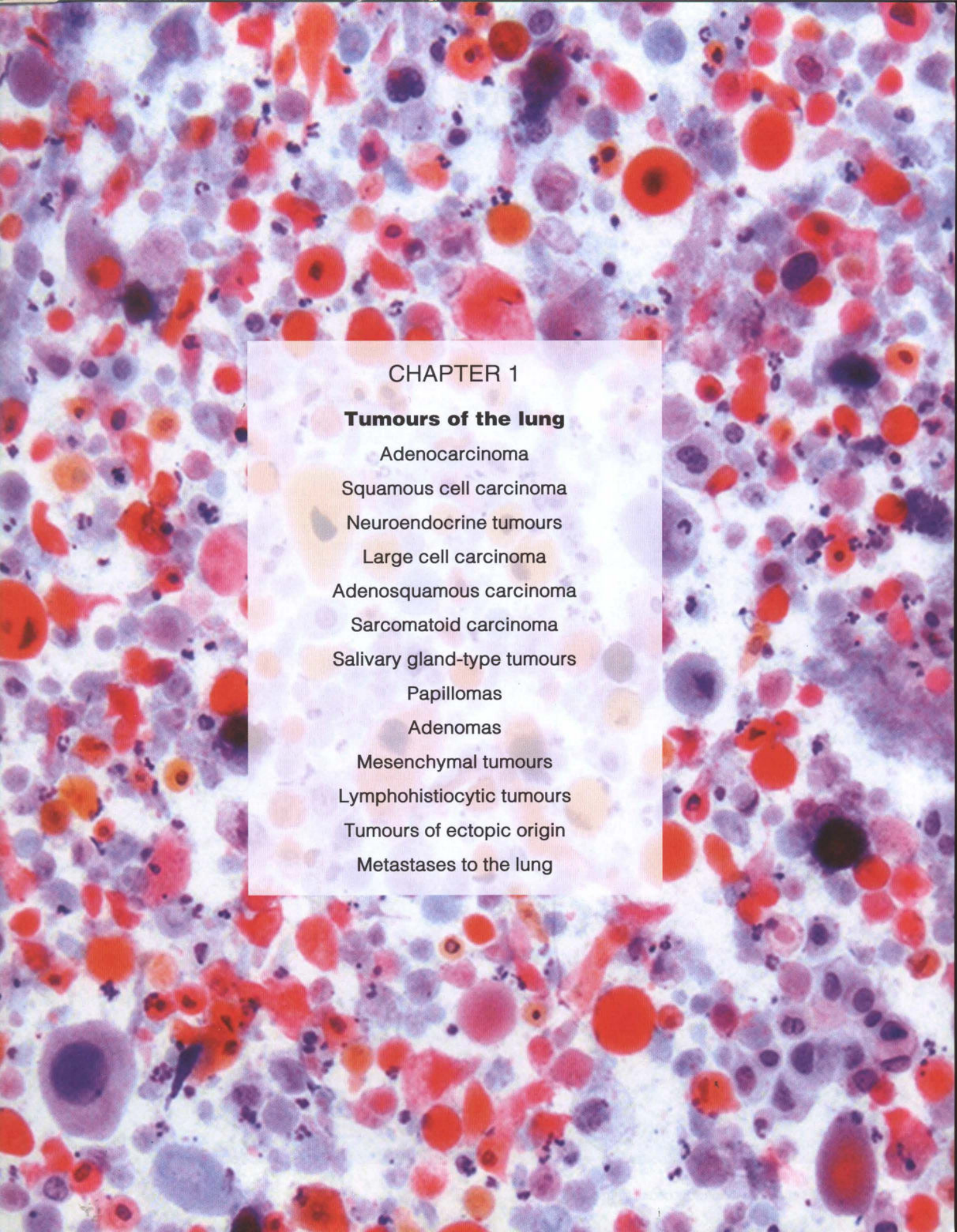
International Thymic Malignancy Interest Group (ITMIG)

International Mesothelioma Panel

The WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart presented in this book reflects the views of a Working Group that convened for a Consensus and Editorial Meeting at the International Agency for Research on Cancer, Lyon
24–26 April, 2014.

Members of the Working Group are indicated
in the List of Contributors on pages 349–358

Contents



CHAPTER 1

Tumours of the lung

Adenocarcinoma

Squamous cell carcinoma

Neuroendocrine tumours

Large cell carcinoma

Adenosquamous carcinoma

Sarcomatoid carcinoma

Salivary gland-type tumours

Papillomas

Adenomas

Mesenchymal tumours

Lymphohistiocytic tumours

Tumours of ectopic origin

Metastases to the lung

WHO classification of tumours of the lung[a,b]

Epithelial tumours	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma	8250/3*
Acinar adenocarcinoma	8551/3*
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma	8253/3*
Mixed invasive mucinous and non-mucinous adenocarcinoma	8254/3*
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Enteric adenocarcinoma	8144/3
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Non-mucinous	8256/3*
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Adenocarcinoma in situ	8140/2
Non-mucinous	8250/2*
Mucinous	8253/2*
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Keratinizing squamous cell carcinoma	8071/3
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Basaloid squamous cell carcinoma	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumours	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
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Atypical carcinoid	8249/3
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Adenoid cystic carcinoma	8200/3
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Pleomorphic adenoma	8940/0
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Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous cell and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumours	
Pulmonary hamartoma	8992/0*
Chondroma	9220/0
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Lymphangioleiomyomatosis	9174/1
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Clear cell tumour	8005/0
PEComa, malignant	8714/3
Congenital peribronchial myofibroblastic tumour	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumour	8825/1
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Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large B-cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
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Germ cell tumours	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8720/3
Meningioma, NOS	9530/0
Metastatic tumours	

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {763}. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. [b] The classification is modified from the previous WHO classification {2672}, taking into account changes in our understanding of these lesions. * These new codes were approved by the IARC/WHO Committee for ICD-O.

TNM classification of carcinomas of the lung

T – Primary Tumour

TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus, i.e. not in the main bronchus[a]
T1a	Tumour ≤ 2 cm in greatest dimension
T1b	Tumour > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumour > 3 cm but ≤ 7 cm or tumour with any of the following features (T2 tumours with these features are classified T2a if ≤ 5 cm or if size cannot be determined and T2b if > 5 cm but ≤ 7 cm.): • Involves main bronchus, ≥ 2 cm distal to the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumour > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumour > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus < 2 cm distal to the carina[a] but without involvement of the carina[a]; or associated atelectasis or obstructive pneumonitis of the entire lung; or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion[b]
M1b	Distant metastasis

Notes:

a) The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is classified as T1a.

b) Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathological examinations of the pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

Stage Grouping

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Compiled from references {2420,652A}

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Lymph node stations

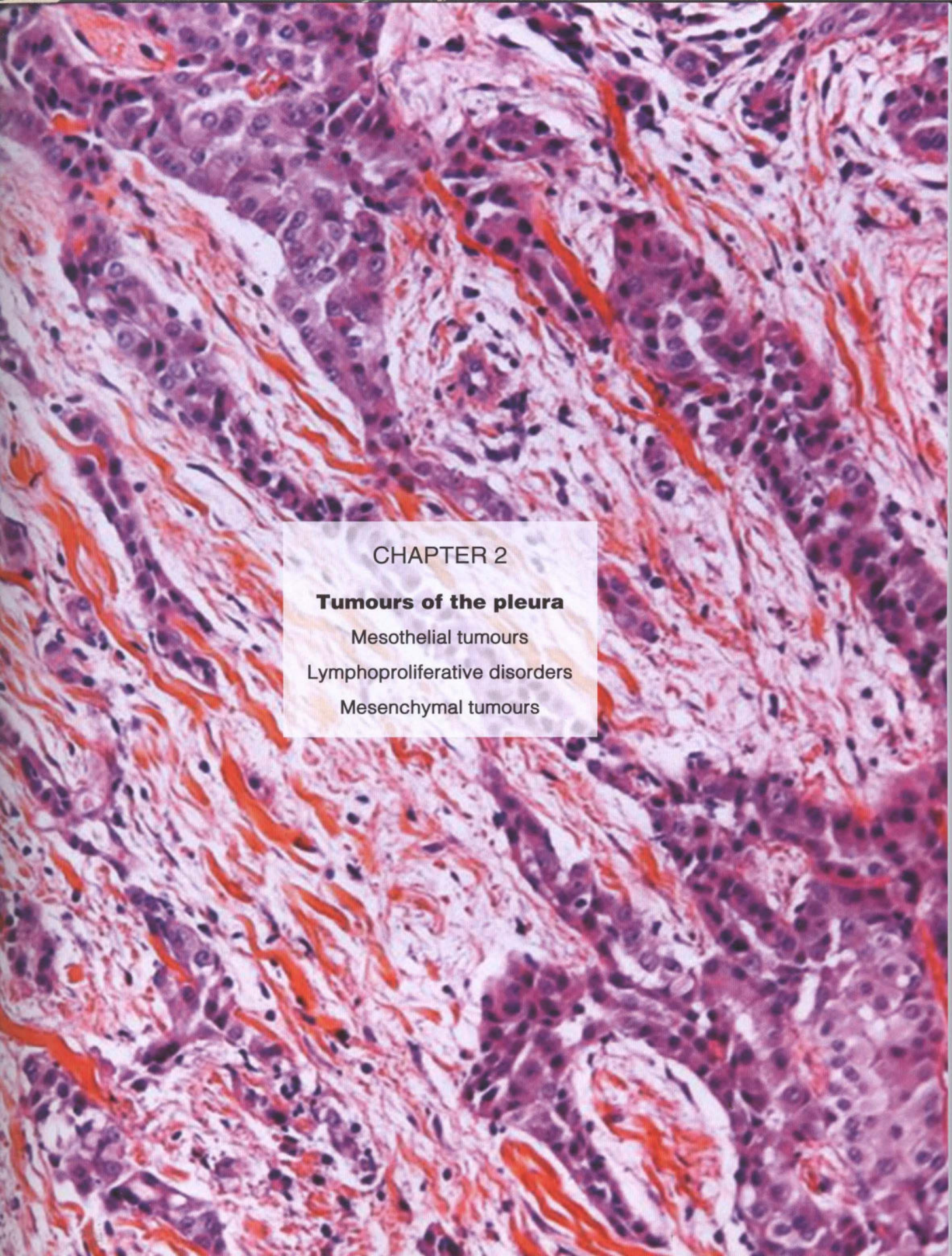
Table 1.01 Anatomical definitions of each lymph node station and station grouping by nodal zones in the map proposed by the International Association for the Study of Lung Cancer (IASLC). Reprinted and adapted from Rusch VW et al. {2225}

Lymph node station number and name	Anatomical limits
Supraclavicular zone	
1. Low cervical, supraclavicular, and sternal notch nodes	• Upper border: the lower margin of cricoid cartilage • Lower border: the clavicles bilaterally, and in the midline, the upper border of the manubrium • Border between 1R and 1L: the midline of the trachea 1R designates right-sided nodes and 1L designates left-sided nodes.
Upper zone	
2. Upper paratracheal nodes	2R • Upper border: the apex of the right lung and pleural space, and in the midline, the upper border of the manubrium • Lower border: the intersection of the caudal margin of the innominate vein with the trachea 2L • Upper border: the apex of the lung and pleural space, and in the midline, the upper border of the manubrium • Lower border: the superior border of the aortic arch Like lymph node station 4R, 2R includes nodes extending to the left lateral border of the trachea.
3. Prevascular and retrotracheal nodes	3a: prevascular • Upper border: the apex of the chest • Lower border: the level of the carina • Anterior border: the posterior aspect of the sternum • Posterior border: the anterior border of the superior vena cava on the right, and the left carotid artery on the left 3p: retrotracheal • Upper border: the apex of the chest • Lower border: the carina
4. Lower paratracheal nodes	4R – includes right paratracheal nodes and pretracheal nodes extending to the left lateral border of the trachea • Upper border: the intersection of the caudal margin of the innominate vein with the trachea • Lower border: the lower border of the azygos vein 4L – includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum • Upper border: the upper margin of the aortic arch • Lower border: the upper rim of the left main pulmonary artery
Aortopulmonary zone	
5. Subaortic nodes (aortopulmonary window)	Subaortic lymph nodes lateral to the ligamentum arteriosum • Upper border: the lower border of the aortic arch • Lower border: the upper rim of the left main pulmonary artery
6. Para-aortic nodes (ascending aorta or phrenic)	Lymph nodes anterior and lateral to the ascending aorta and aortic arch • Upper border: a line tangential to the upper border of the aortic arch • Lower border: the lower border of the aortic arch
Subcarinal zone	
7. Subcarinal nodes	• Upper border: the carina of the trachea • Lower border: the upper border of the lower lobe bronchus on the left, and the lower border of the bronchus intermedius on the right
Lower zone	
8. Paraoesophageal nodes (below carina)	Nodes lying adjacent to the wall of the oesophagus and to the right or left of the midline, excluding subcarinal nodes • Upper border: the upper border of the lower lobe bronchus on the left, and the lower border of the bronchus intermedius on the right • Lower border: the diaphragm
9. Pulmonary ligament nodes	Nodes lying within the pulmonary ligament • Upper border: the inferior pulmonary vein • Lower border: the diaphragm

Lymph node station number and name	Anatomical limits
Hilar/interlobar zone	
10. Hilar nodes	Includes nodes immediately adjacent to the mainstem bronchus and hilar vessels, including the proximal portions of the pulmonary veins and main pulmonary artery • Upper border: the lower rim of the azygos vein on the right, and the upper rim of the pulmonary artery on the left • Lower border: the interlobar region bilaterally
11. Interlobar nodes	Between the origin of the lobar bronchi 11s[a]: between the upper lobe bronchus and the bronchus intermedius on the right 11i[a]: between the middle and lower bronchi on the right
Peripheral zone	
12. Lobar nodes	Adjacent to the lobar bronchi
13. Segmental nodes	Adjacent to the segmental bronchi
14. Subsegmental nodes	Adjacent to the subsegmental bronchi
[a] Optional notations for subcategories of station.	

Table 1.02 Lymph node coding of isolated tumour cells (ITCs) or clusters of tumour cells.
Reprinted from Sobin LH et al. {2420}

Code	Type of involvement, and method of identification
pN0	No regional lymph node metastasis histologically, no examination for ITCs
pN0(i−)	No regional lymph node metastasis histologically, negative morphological findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphological findings for ITCs
pN0(mol−)	No regional lymph node metastasis histologically, negative non-morphological findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive non-morphological findings for ITCs
pN0(i−)(sn)	No sentinel lymph node metastasis histologically, negative morphological findings for ITCs
pN0(i+)(sn)	No sentinel lymph node metastasis histologically, positive morphological findings for ITCs
pN0(mol−)(sn)	No sentinel lymph node metastasis histologically, negative non-morphological findings for ITCs
pN0(mol+)(sn)	No sentinel lymph node metastasis histologically, positive non-morphological findings for ITCs
Note: The same coding applies for distant metastasis, in which case pN is replaced by M, e.g. M0(i+).	



CHAPTER 2

Tumours of the pleura

Mesothelial tumours

Lymphoproliferative disorders

Mesenchymal tumours

WHO classification of tumours of the pleura[a,b]

Mesothelial tumours	
Diffuse malignant mesothelioma	
Epithelioid mesothelioma	9052/3
Sarcomatoid mesothelioma	9051/3
Desmoplastic mesothelioma	9051/3
Biphasic mesothelioma	9053/3
Localized malignant mesothelioma	
Epithelioid mesothelioma	9052/3
Sarcomatoid mesothelioma	9051/3
Biphasic mesothelioma	9053/3
Well-differentiated papillary mesothelioma	9052/1*
Adenomatoid tumour	9054/0
Lymphoproliferative disorders	
Primary effusion lymphoma	9678/3
Diffuse large B-cell lymphoma associated with chronic inflammation	9680/3
Mesenchymal tumours	
Epithelioid hemangioendothelioma	9133/3
Angiosarcoma	9120/3
Synovial sarcoma	9040/3
Solitary fibrous tumour	8815/1
Malignant solitary fibrous tumour	8815/3
Desmoid-type fibromatosis	8821/1
Calcifying fibrous tumour	8817/0
Desmoplastic round cell tumour	8806/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) [763]. Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours. [b] The classification is modified from the previous WHO classification [2672], taking into account changes in our understanding of these lesions. * This new code was approved by the IARC/WHO Committee for ICD-O.

TNM classification of pleural mesothelioma

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

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

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

Compiled from references [2420,652A]

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Mesothelial tumours
Diffuse malignant mesothelioma
Epithelioid mesothelioma

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J. van Meerbeeck

Definition

Diffuse epithelioid malignant mesothelioma of the pleura is a malignant tumour originating from mesothelial cells and showing epithelioid morphology and a diffuse pattern of growth over the pleural surfaces. Diffuse malignant mesotheliomas must be differentiated from localized malignant mesotheliomas, which have different clinical behaviours.

ICD-O code

9052/3

Synonyms

Epithelioid malignant mesothelioma; epithelial-type mesothelioma (not recommended)

Epidemiology

Malignant mesotheliomas occur over a very wide age range. They occasionally occur in children, but the vast majority of tumours are seen in patients aged ≥ 60 years. Patients with the pleomorphic variant tend to be older. The male-to-female ratio is on average 4:1, but varies by geographical location based on the proportion of cases attributable to occupational asbestos exposure {746,1426}.

In North America, the rate in men increased steadily from the 1970s to the early 1990s, peaking at about 23 cases per million per year. Subsequently, there has been a slow but steady decline. In 2009, the rate was about 17 per million men per year. In women, the rate over this same time period remained essentially constant at 2–3 cases per million per year. Mathematical projections suggest that steady decline in the number of cases in males will lead to the convergence of the male and female incidence rates at some time between 2040 and 2050, reflecting the disease's long latency period (about 30 years) and the increased restrictions on the use of asbestos in the 1970s {1426,2085}. In countries that used large amounts of amosite or crocidolite (such as Australia), the incidence rates are considerably higher, but are also starting to show a similar decrease {1020,1710,2042}.

Approximately 60–80% of malignant mesotheliomas are of the epithelioid type.

Etiology

The most common cause of mesothelioma is asbestos exposure. Other established causes include therapeutic radiation for other malignant neoplasms and (in a localized area of Turkey) the mineral fibre erionite. Some mesotheliomas do not have an identifiable cause.

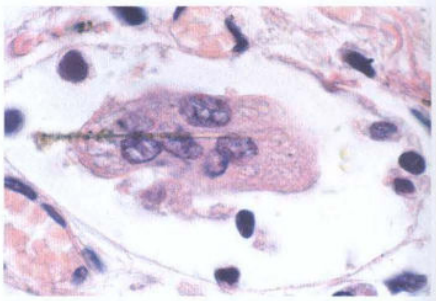

Fig. 2.02 Asbestos body. Ingestion of an asbestos fibre by a multinucliated macrophage. Note the iron-rich deposits on the surface of the fibre.

Asbestos

The relationship between asbestos exposure and mesothelioma is complex, and highly dependent on fibre type and dose. In North America and France, up to 80–90% of mesotheliomas in men are related to asbestos exposure, but only about 20% of cases in women {862,2447}. In western Europe and Australia, a higher proportion of cases in women are asbestos-induced, but the attributable asbestos fraction is < 50% {312}. The latency (time from first exposure to disease) is long, averaging 30–40 years, and few (if any) mesotheliomas are seen with latencies < 15 years {1397}.

Mathematical modelling suggests that mesothelioma incidence is a linear function of amphibole asbestos dose, and a power function of time since first exposure {188,1019,2043}. There are marked differences in the potency of different fibre types in inducing mesothelioma: commercial amphibole asbestos (amosite and crocidolite) is 2–3 orders of magnitude more carcinogenic than chrysotile {188,1019}. Some argue that the mesothelial carcinogenicity of chrysotile depends on the level of contamination by the amphibole fibre tremolite, and that pure chrysotile may not be mesotheliogenic in humans {188,832,1626,1628}.

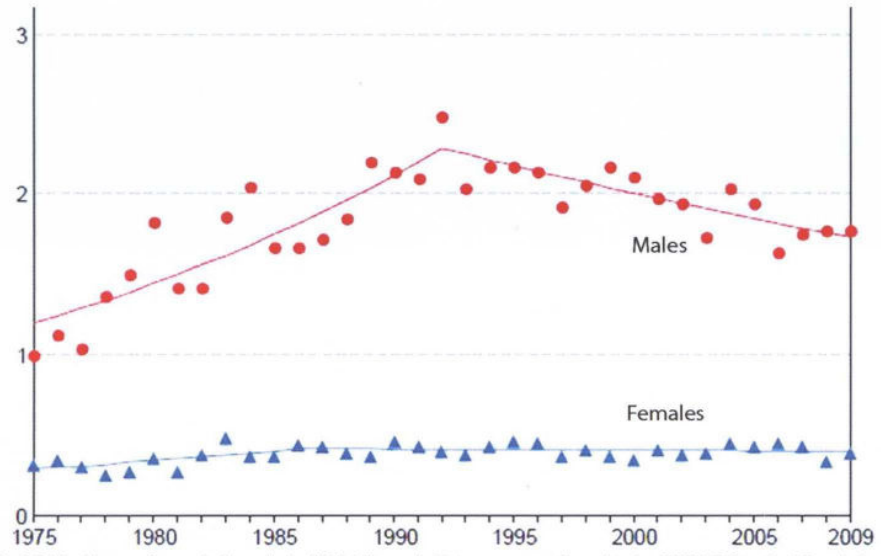

Fig. 2.01 Incidence of mesothelioma in the USA (all races). Rates are age-adjusted to the 2000 US Standard Population. Source: SEER 9 areas. United States National Cancer Institute.

However, in sufficiently high doses, chrysotile appears to cause lung cancer, and at very high doses causes mesotheliomas in experimental animals. There are a few places in the world where other forms of amphibole fibres with dimensions similar to amosite or crocidolite are found, and a high mesothelioma incidence is seen in these locations. An example is Libby, Montana, USA, where the fibre winchite is present in mined vermiculite deposits {832,1627,2862}. There have also been reports that pleural plaques may be an independent risk factor for pleural mesothelioma. In a follow-up study of 5287 male subjects, pleural plaques confirmed on CT were significantly associated with a high risk of mesothelioma, after adjustment for time since first asbestos exposure and cumulative asbestos exposure {1959}.

Erionite

In the Cappadocia region of Turkey, there are outcrops of rock containing erionite fibres of the same size and durability of commercial amphibole asbestos. The incidence of mesothelioma in this region is extraordinarily high {140,602,1134}. Similar fibres have been found in other regions, such as North Dakota, USA (in road surfacing material) {329} and Mexico {1287}.

Therapeutic radiation

There is an increased incidence of pleural mesothelioma after therapeutic radiation for breast cancer, Hodgkin lymphoma, and testicular cancer {430,539,589,2668}. The mesotheliomas typically develop years after the radiation {2625,2896}.

Inherited predisposition

Germline mutations in *BAP1* define a new familial cancer syndrome, which includes malignant mesothelioma, uveal melanoma, clear cell renal cell carcinoma, intrahepatic cholangiocarcinoma, atypical cutaneous melanocytic lesions, and possibly other cancers {700,2053,2074,2624}. More studies are needed to define the lifetime risk of mesothelioma in carriers of germline mutations, but awareness of this syndrome is necessary to ensure that patients with other cancers in the syndrome (especially ocular melanoma) are screened for mesothelioma. Although the interaction with other risk factors such as asbestos exposure remains unclear, some patients with pleural malignant mesothelioma with germline mutation do not have a clear history of asbestos exposure {420,2624,2875}.

Other putative etiological agents

Simian virus 40 (SV40) causes malignancies, including mesothelioma, in experimental animals, in part by inactivating the *TP53* and *RB* genes {2337}. However, neither epidemiological nor molecular data support a role for SV40 in human pleural malignant mesothelioma {811,1513,1562,2337}.

Clinical features

Signs and symptoms

Patients with pleural mesothelioma typically present with insidious onset of chest pain and/or dyspnoea {666,997,2294}. The chest pain is usually dull, unilateral, and non-pleuritic. It sometimes has neuropathic components because of the entrapment of intercostal, autonomic, or brachial plexus nerves. In the early stages, dyspnoea is usually caused by a pleural effusion, but later may occur due to the restrictive effects of pleural thickening. A chest wall mass, weight loss, abdominal pain, and ascites (due to peritoneal involvement) are less common presentations. Cervical adenopathy, haemoptysis, paraneoplastic syndromes, and symptoms due to distant metastases are unusual. Irregular episodes of low-grade fever, profuse sweating, weight loss, and declining performance status are common presenting complaints, although these tend to indicate more advanced disease or the pleomorphic variant of mesothelioma {1178}. Some patients present with acute pleuritic chest pain and a small effusion, but initial investigations may fail to provide a diagnosis. The patient may then remain symptom-free for many months until recurrence of the fluid or development of chest pain leads to further investigation. Other uncommon presentations include pneumothorax, mass lesions, segmental or lobar pulmonary collapse, mediastinal invasion with laryngeal nerve palsy, and superior vena caval obstruction {1407}.

Imaging

Imaging findings in patients with mesothelioma exhibit a wide range of abnormalities. Most classical is the finding of a diffuse circumferential rind of nodular pleura, usually associated with ipsilateral volume loss and an effusion. Less commonly, malignant mesothelioma appears as a pleural effusion without obvious pleural nodularity, which may be associated with acute pleuritic chest pain. Rarely, tumours appear as an isolated nodular pleural density, with or without an accompanying effusion. The presence of pleural plaques, especially when calcified, is suggestive of asbestos exposure; however, they are often absent. The involved haemithorax is sometimes reduced in size, and there may be retraction of the intercostal spaces. CT and MRI are important for evaluation of

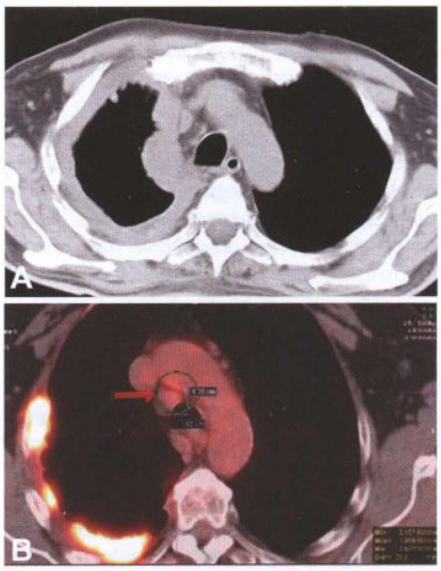

Fig. 2.03 Diffuse malignant mesothelioma. **A** CT shows diffuse right unilateral pleural thickening, with no intraparenchymal lung mass. **B** PET shows increased avidity in the tumour, which is causing right pleural nodularity and thickening.

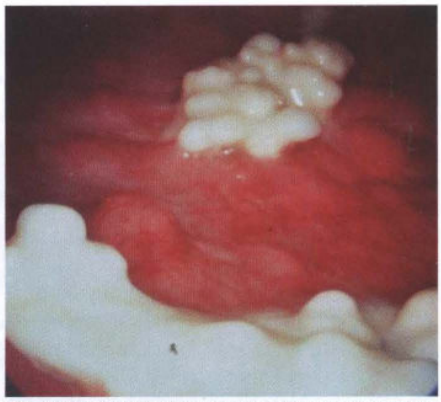

Fig. 2.04 Diffuse malignant mesothelioma. The surface of the pleura is covered by white fibrous plaques and small tumour nodules with a pink surface.

tumour volume and invasion of contiguous anatomical structures (e.g. mediastinal and pericardial involvement).

Tumour spread

Disease progression is variable. Some patients have periods of apparent stability, while others have relentless, rapid deterioration. The disease is more likely to progress by local extension in chest wall and lung than by haematogenous spread. Direct involvement of mediastinal structures is common. Lymphangitic involvement of the lung parenchyma is more common in epithelioid type, and particularly in the predominant micropapillary subtype {1178}. Lymphatic spread gives rise to ipsilateral or contralateral mediastinal lymph node involvement. Ascites may develop at any time during the disease course due to abdominal spread with peritoneal involvement. Distant metastases are common; their presence is reported in more than half of all cases, although usually late in the clinical course or at autopsy {2953}. None of the clinical symptoms or imaging findings described above is specific for pleural mesothelioma; they may be representative of other pleural tumours, or metastasis to the pleura as well.

Staging

The current staging system for malignant pleural mesothelioma is based on the classification proposed in 1995 by the International Mesothelioma Interest Group and adopted by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) {2223}. The system applies to both clinical and pathological staging. Clinical staging is inaccurate for early stages, due to the low accuracy of CT and MRI {622}. Integrated FDG PET-CT is expected to improve the accuracy {2064}. In clinical series, patients most commonly presented with disease that was locally advanced (stage III, 40%), followed by advanced (stage IV, 35%) and local (stage I–II, 25%). A modified TNM-based classification is currently under revision, based on the retrospective analysis of a large series of incident cases accumulated by the International Association for the Study of Lung Cancer (IASLC) {2227}. A prospective database has been created by the IASLC to obtain more meaningful long-term data.

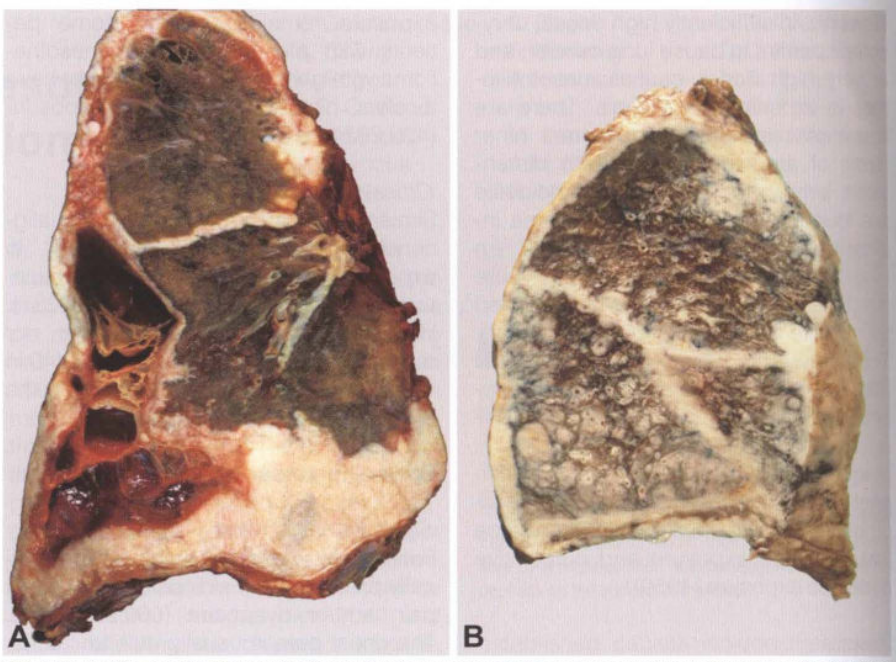

Fig. 2.05 **A** Diffuse malignant mesothelioma. The tumour encases the lung as a rind and grows along the interlobar septa, compressing the lung parenchyma. Reprinted from Galateau-Salle F {785}. **B** Pseudomesotheliomatous adenocarcinoma. The tumour encases the lung, mimicking a malignant mesothelioma. Unlike malignant mesothelioma, the adenocarcinoma shows multiple nodules that infiltrate the lung parenchyma.

The current T descriptors are only qualitative, and best applicable for invasive staging procedures, as is the case for T1a and T1b, which require thoracoscopic assessment of the pleural cavity. They account insufficiently for invasion, extent, thickness, and volume of the circumferential pleural rind. The regional lymph node map and nomenclature are the same as those used for lung cancer, with the addition of lymph nodes in the anterior peridiaphragmatic region and around the internal mammary artery as N2 nodes. This empirical assumption discounts the possible prognostic role of lymph nodes in the extrapleural space and pericardial fat, and associates a better prognosis with intrapulmonary nodes. It may not be possible to perform a thorough N classification, particularly in unresectable tumours. With regard to stage definition, the absence of significant survival differences between stages I and II reflects the above-mentioned inaccuracy of staging, while stages III and IV define broad categories of disease, including locally advanced tumours (T3 and T4), regionally advanced disease (N1 and N2), and metastatic disease (M1). It is expected that substages will be defined in the new classification {653,2418}.

Localization

There is no significant difference in location between the different histological types of mesothelioma. Right-sided involvement is more common than left-sided involvement by a ratio of 3:2. Bilateral involvement at diagnosis is unusual {2953}. Spread occurs along the interlobar fissures and into the underlying lung, and can extend through the diaphragm and into the chest wall. Mediastinal involvement, with direct invasion of the pericardium and other mediastinal structures, is common. The unusual occurence of direct extension into the peritoneum is more common with the epithelioid type.

Macroscopy

The gross findings depend on when mesothelioma is observed during its natural history. Early mesothelioma presents as small nodules distributed on the parietal and (less commonly) on the visceral pleura. As mesothelioma progresses, the nodules coalesce to form a rind of tumour encasing the lung. They typically grow along the interlobular fissures. In late stages, the pleura may be several centimetres thick. The tumour is grey-white and soft. There may be cystic areas containing mucoid-like material.

Cytology

In industrialized countries, about 1% of malignant pleural effusions are caused by diffuse malignant mesothelioma. Malignant mesothelial cells in effusions are nearly always epithelioid morphologically, since sarcomatoid mesotheliomas seldom shed cells into the fluid {1941}.

Mesothelioma cells in effusions may be arranged in sheets, clusters, morules, or papillae. Psammoma bodies may be present. These cells show a range of cytological appearances, from bland to pleomorphic, but often lack the degree of atypia associated with carcinoma. In contrast, benign mesothelial cells may exhibit features most often associated with malignancy, such as increased cellularity, nuclear pleomorphism, and mitotic activity. Therefore, differentiation of mesothelioma from benign mesothelial reactions may be very difficult or even impossible in cytological specimens. Similarly, tissue invasion (an important histological feature of malignancy) cannot be evaluated in effusion specimens. Overall, the accuracy of purely cytological diagnoses of malignant mesothelioma is fairly low compared to that of tissue diagnoses {1056}.

Histopathology

Most epithelioid mesotheliomas are cytologically bland, but more anaplastic forms may be observed {457}. Epithelioid mesotheliomas show a wide range of histological patterns. Several different patterns are often observed in the same tumour, although one pattern may predominate. In most tumours, the cells have eosinophilic cytoplasm with bland vesicular chromatin. Mitoses

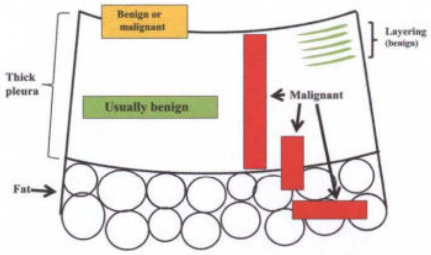

Fig. 2.06 Schematic diagram showing benign versus malignant processes as a function of the distribution of mesothelial cells in a thickened pleura. Reprinted from Churg A et al. {459}.

are infrequent. In the more poorly differentiated forms, the nuclei tend to have coarse chromatin with prominent nucleoli and frequent mitoses; however, these tumours are uncommon, and may be difficult to distinguish from carcinomas {1056}.

The most commonly encountered patterns are solid, tubulopapillary, and trabecular. Less common patterns include micropapillary, adenomatoid (microcystic), clear cell, transitional, deciduoid, and small cell. The tubulopapillary form exhibits varying combinations of tubules and papillae, with connective tissue cores and clefts. The morphology of the cells lining the tubules and papillae ranges from low cuboidal and relatively bland to larger and more atypical. The trabecular pattern consists of relatively small, uniform cells arranged in thin cords, sometimes with a single-file appearance. Psammoma bodies may be observed. The micropapillary pattern consists of papillary structures lacking fibrovascular cores. The adenomatoid form shows microcystic structures, with lace-like or signet ring appearances. Sheets and nests of cells are often seen in association with other patterns. Solid, monotonous, relatively non-cohesive sheets of polygonal cells uncommonly occur, simulating large cell carcinoma or lymphoma. Tumours with anaplastic or prominent giant cells, often multinucleated, are designated pleomorphic {1178,1923}.

Malignant mesothelioma with a heavy lymphoid infiltrate obscuring the polygonal neoplastic cells can mimic malignant lymphoma or lymphoepithelioma-like carcinoma, and these tumours are called lymphohistiocytoid mesothelioma {786}. When there are prominent large cells with clear cytoplasm, these mesotheliomas must be distinguished from renal cell carcinoma and other metastatic clear cell carcinomas. Small foci of cells with abundant eosinophilic cytoplasm resembling the deciduoid cells of pregnancy can be observed in epithelioid mesothelioma, but it is very uncommon in the pleura for this to be a predominant feature (so-called deciduoid mesothelioma) {1921,2342}. A pattern with small cell tumour cells mimicking small cell carcinoma is seen in some cases, but usually lacks the karyorrhexis and haematoxyphylic staining of blood vessels typical of small cell carcinoma. The term small cell mesothelioma is discouraged in diagnostic reports, to avoid confusion with small cell carcinoma {1617,1922}. The term transitional pattern has been used to describe tumours with a sheet-like growth pattern in which the cells are cohesive but have elongated morphology.

The fibrous stroma of epithelioid mesotheliomas can vary from scant to prominent, and can show varying degrees

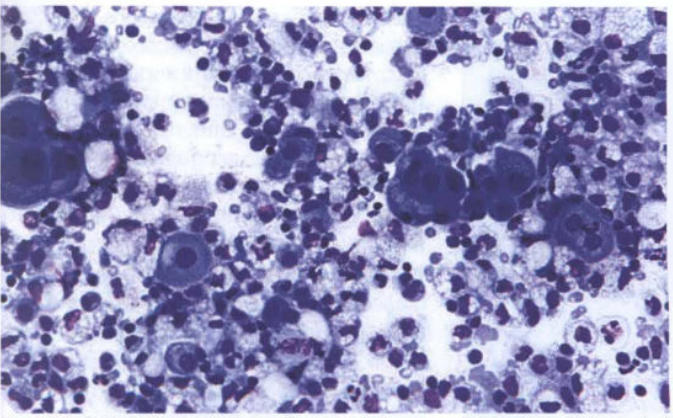

Fig. 2.07 Epithelioid mesothelioma. The sample is very cellular, with multiple atypical mesothelial cells arranged in three-dimensional structures with morulae.

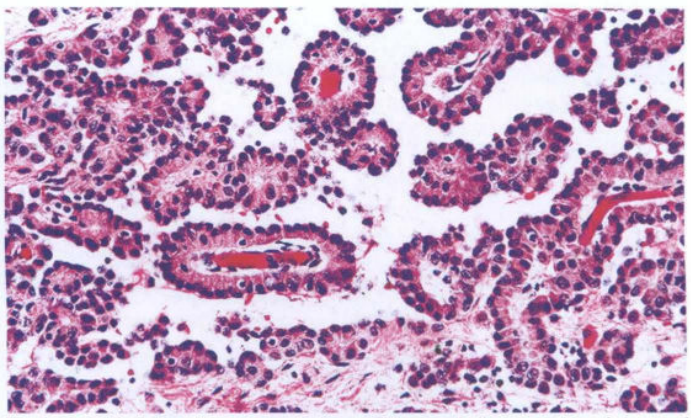

Fig. 2.08 Epithelioid malignant mesothelioma. This mesothelioma consists of sheets of epithelioid tumour cells with a moderate amount of eosinophilic cytoplasm and uniform nuclei with conspicuous nucleoli. Reprinted from Travis WD et al. {2678}.

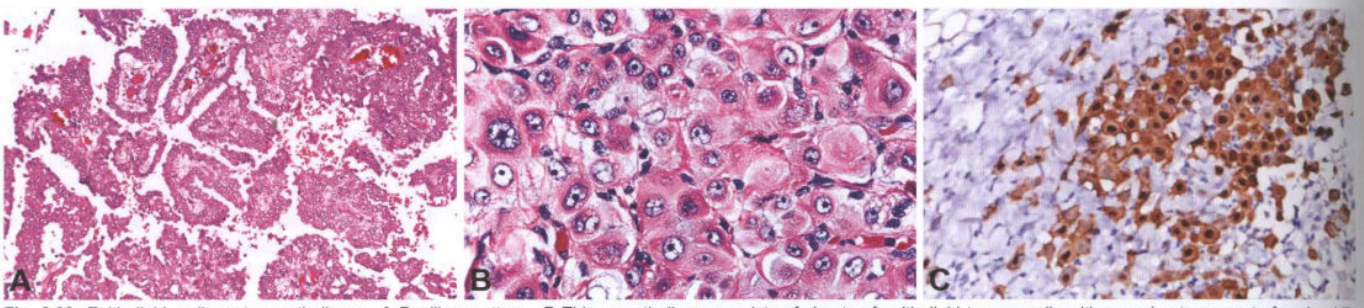

Fig. 2.09 Epithelioid malignant mesothelioma. **A** Papillary pattern. **B** This mesothelioma consists of sheets of epithelioid tumour cells with a moderate amount of eosinophilic cytoplasm and uniform nuclei with conspicuous nucleoli. Reprinted from Travis WD et al. {2678}. **C** Immunohistochemistry shows a diffuse, strong nuclear and weak cytoplasmic staining for calretinin.

of cellularity (from hyalinized acellular to highly cellular), which may make it difficult to distinguish from a true sarcomatoid component. Such tumours may be easily confused with biphasic mesothelioma. Myxoid change may be conspicuous in 5–10% of cases, with nests of cytologically bland, often vacuolated epithelioid cells floating in the matrix. The matrix in such tumours is typically hyaluronate, showing hyaluronidase-sensitive staining with Alcian blue {2361}. Malignant mesotheliomas are generally negative for neutral mucin (with periodic acid–Schiff with diastase or mucicarmine stains); but exceptions occur, limiting diagnostic utility.

Table 2.01 Immunohistochemistry of epithelioid malignant mesothelioma vs. metastatic carcinomas {1925,2569}

Mesothelial markers		
Markers	**Sensitivity**	**Specificity versus lung adenocarcinoma**
Calretinin	> 90%	90–95%
CK5/6	75–100%	80–90%
WT1	70–95%	~100%
D2-40	90–100%	85%
Adenocarcinoma (positive epithelial markers)		
Markers	**Sensitivity**	**Specificity versus malignant mesothelioma**
MOC31	95–100%	85–98%
BerEP4	95–100%	74–87%
BG8 (Lewis Y)	90–100%	93–97%
B72.3	25–85%	> 95%
Monoclonal carcinoembryonic antigen	80–100%	> 95%
Organ specific – lung		
Markers	**Sensitivity**	**Specificity versus malignant mesothelioma**
TTF1 (8G7G3/1)	~80%	High
Napsin A	~80%	High
Organ specific – breast		
Markers	**Sensitivity**	**Specificity versus malignant mesothelioma**
Estrogen receptor α	NA (not available)	NA
Progesterone receptor	NA	NA
GCDFP15	30–40%	High
Mammaglobin	50–85%	High
Organ specific – renal		
Markers	**Sensitivity**	**Specificity versus malignant mesothelioma**
PAX8	70–100%	Unknown
PAX2	80%	Unknown
RCC	Up to 85%	75–90%
CD15 (LeuM1)	60%[a]	High

[a] Variable by subtype.

Immunohistochemistry

Immunohistochemistry plays an important role in distinguishing epithelioid malignant mesotheliomas from other tumours involving the pleura, particularly lung adenocarcinoma. This distinction can be greatly facilitated by the combined use of a minimum of two mesothelial markers and two carcinoma markers. Based on their specificity and sensitivity, calretinin, CK5/6, WT1, and D2-40 are the best positive markers to support a diagnosis of mesothelioma, and BerEP4 or MOC31, B72.3, carcinoembryonic antigen, and BG8 are the are most commonly used to diagnose carcinoma {1056,1925,1926}. A pancytokeratin such as AE1/AE3 is also useful, as a negative result suggests the possibility of other tumours. Other markers can be helpful in the differential diagnosis between mesothelioma and metastatic carcinoma, and also help determine tumour origin. Examples include markers for lung adenocarcinoma (TTF1 and napsin A), breast carcinoma (ERα, progesterone receptor, GCDFP15, and mammaglobin) {1929}, renal cell carcinoma (PAX8), papillary serous carcinoma (PAX8, PAX2, and estrogen receptor), and adenocarcinomas of the gastrointestinal tract (CDX2) and prostate (prostate-specific antigen) {1056,1925,1927,1928}. GATA3 is expressed in more than half of all mesotheliomas, including both epithelial and sarcomatoid types {1668}.

Additionally, p40 (or p63) is helpful for distinguishing epithelioid mesotheliomas with pseudosquamous morphology from squamous cell carcinomas {1919}. CK5/6 is not helpful in this differential diagnosis, as it stains both tumours. Some non-epithelial tumours that are usually keratin-negative (including epithelioid haemangioendotheliomas and angiosarcomas, melanomas, and large cell lymphomas) can occasionally mimic epithelioid mesothelioma. In such cases, endothelial-associated markers (i.e. CD31, CD34, ERG (v-ets avian erythroblastosis virus E26 oncogene homologue protein, and FLI1), melanoma markers (i.e. HMB45, melan A, and SOX10), and haematopoietic markers (i.e. CD20 and CD45) can be used. All of these markers are negative in mesothelioma. Keratin can occasionally be positive in epithelioid vascular tumours, although it is usually focal. A relatively large number of immunohistochemical markers for distinguishing between malignant mesotheliomas and reactive mesothelial proliferations have been investigated, but the results of these studies remain controversial. No marker or combination of markers has yet been identified that can be used with confidence for routine diagnostic work in this differential diagnosis. As a general recommendation, whenever immunohistochemistry is used in diagnosis, high-quality staining must be ensured, and participation in a quality assurance programme is encouraged.

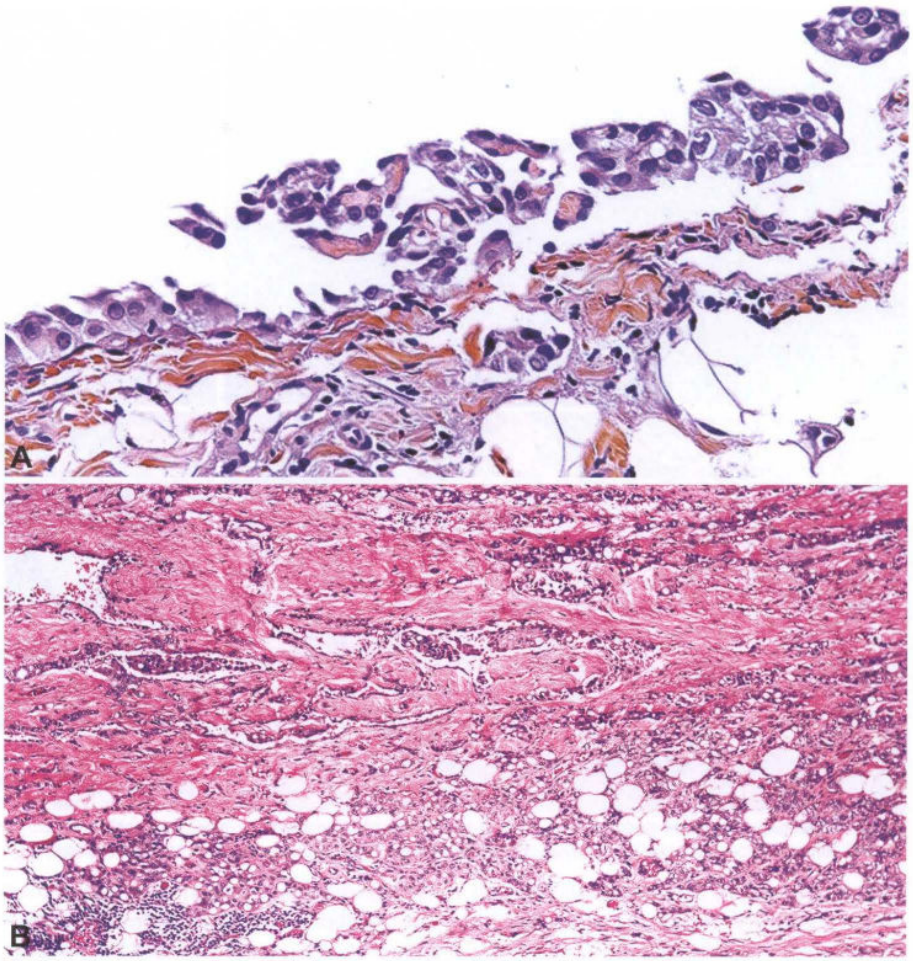

Fig. 2.10 Atypical mesothelial hyperplasia versus invasive epithelioid malignant mesothelioma. **A** Atypical mesothelial hyperplasia of the parietal pleura. The epithelial proliferation on the surface is suspicious for malignancy; however, in the absence of invasion, this is best diagnosed as atypical mesothelial hyperplasia. **B** This proliferation of atypical epithelioid mesothelial cells shows invasion into chest wall fat, supporting the diagnosis of malignant mesothelioma.

Differential diagnosis

The primary differential diagnosis is between epithelioid mesothelioma and metastatic adenocarcinoma. The presence of an intrapulmonary mass favours lung cancer, as the distribution of mesothelioma is typically limited to the pleura. Pseudomesotheliomatous adenocarcinoma with diffuse pleural spread is uncommon, but it can mimic epithelioid mesothelioma clinically, macroscopically, and microscopically. Immunohistochemistry is often helpful in resolving this differential diagnosis. Other epithelioid tumours that can have a pseudomesotheliomatous appearance include epithelioid haemangioendothelioma (see *Epithelioid haemangioendothelioma*, p. 176, and *Angiosarcoma*, p. 177), intrapleural thymoma (see *Thymomas*, p. 187), melanoma, lymphoma, and synovial sarcoma with scant spindle cells (see *Synovial*

Table 2.02 Reactive atypical mesothelial hyperplasia versus malignant mesothelioma {458}

Histological features	Atypical mesothelial hyperplasia	Malignant mesothelioma
Major criteria		
Stromal invasion	Absent	Present (the deeper, the more definitive)
Cellularity	Confined to the pleural surface	Dense, with stromal reaction
Papillae	Simple, lined by single-cell layer	Complex, with cellular stratification
Growth pattern	Surface growth	Expansile nodules, complex and disorganized pattern
Zonation	Process becomes less cellular towards chest wall	No zonation of process, often more cellular away from effusion
Vascularity	Capillaries are perpendicular to the surface	Irregular and haphazard
Minor criteria		
Cytological atypia	Confined to areas of organizing effusion	Present in any area, but many cells are deceptively bland and relatively monotonous
Necrosis	Rare (necrosis may be within pleural exudate)	Necrosis of tumour area is usually a sign of malignancy
Mitoses	Mitoses may be plentiful	Many mesotheliomas show very few mitoses (but atypical mitoses favour malignancy)

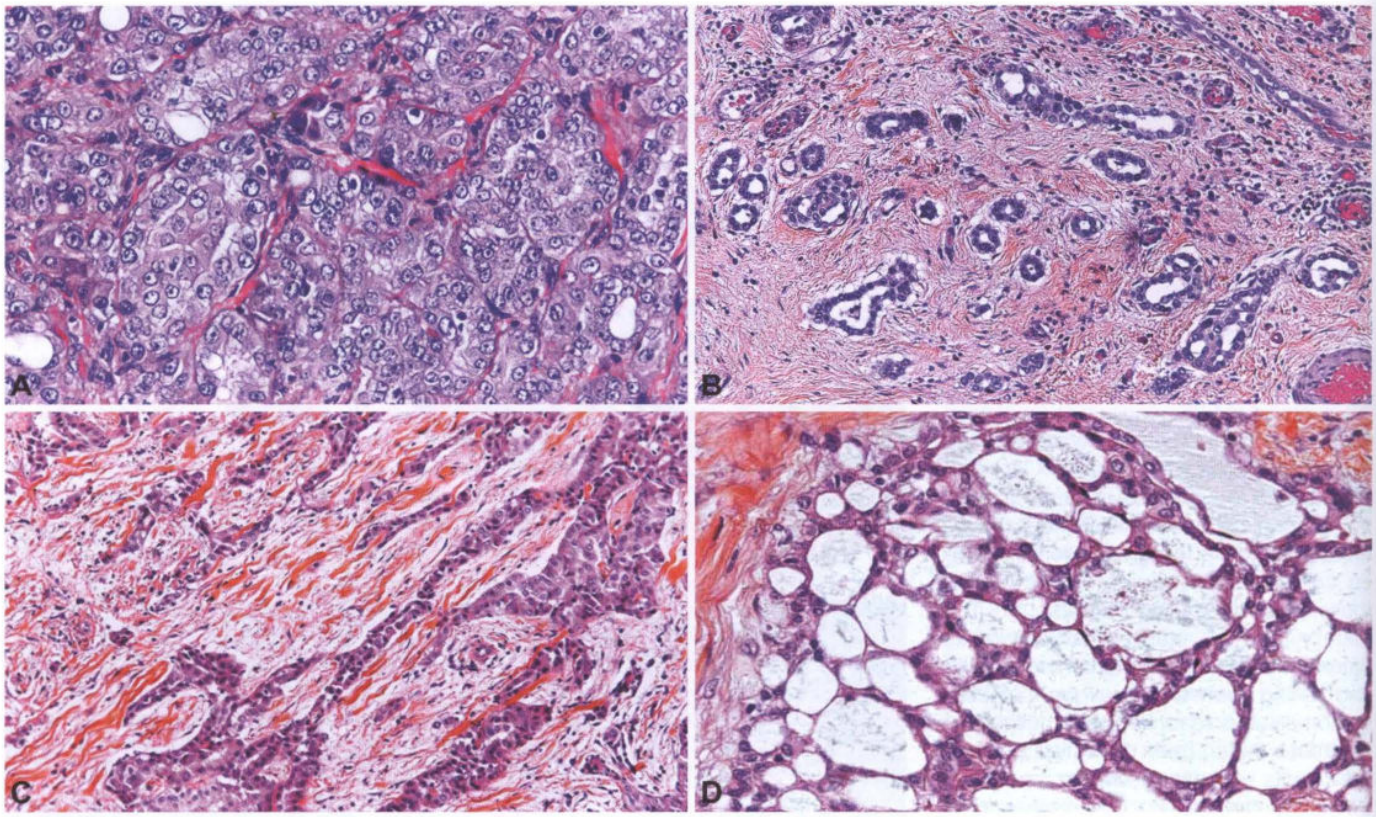

Fig. 2.11 Epithelioid malignant mesothelioma. **A** High-power view showing sheets of large, polygonal epithelioid mesothelial cells with central, round, vesicular nuclei with small nucleoli. Reprinted from Galateau-Salle F {785}. **B** Tubular pattern. **C** Trabecular patterns. **D** Microcystic pattern.

sarcoma, p. 177). Synovial sarcoma can be excluded by negative testing for the translocation t(X;18) {2822}. In the differential diagnosis with synovial sarcoma, TLE1 nuclear immunostaining may not be helpful {1613}. Proximal variant epithelioid sarcoma can involve the pleura and chest wall, mimicking epithelioid mesothelioma {35,966}; however, staining for cytokeratins is typically patchier than would be expected with an epithelioid mesothelioma, and other mesothelial markers (e.g. calretinin, D2-40, and WT1 nuclear staining) are typically negative. In contrast, epithelioid sarcomas stain strongly positive for fascin and vimentin. *SMARCB1* homozygous deletion can be reliably detected by FISH in epithelioid sarcoma.

Reactive mesothelial hyperplasia may be extremely florid, and mimic mesothelioma in the context of a wide variety of diseases, particularly infection. To avoid misdiagnosis on a pleural tissue sample, in the absence of unequivocal malignant tumour fragments, the presence of invasion in the chest wall soft tissue or in the underlying lung parenchyma by the mesothelial cells is the only robust criterion for malignancy. In the case of pleural effusion, the diagnostic utility of FISH for *p16* homozygous deletion for the diagnosis of malignant mesothelioma is promising, but validation studies are needed {1069A,1708}.

In cases with superficial mesothelial proliferation, the diagnostic term mesothelioma in situ should be avoided. In such proliferations, the presence of *p16* deletion in the context of strong clinical and/or radiological evidence of tumour may support a diagnosis of malignant mesothelioma, but this approach needs further validation {1059}.

Florid mesothelial proliferations have also been reported in lymph nodes of patients with recurrent pleuritis without evidence of malignant mesothelioma. They typically involve the subcapsular sinuses without destruction of lymph node architecture {475}.

Genetic profile

Cytogenetic and genomic molecular studies have demonstrated that most malignant pleural mesotheliomas have multiple chromosomal alterations. Chromosomal losses are more common than gains in malignant pleural mesothelioma. The most common losses are on chromosomal arms 1p, 3p, 4q, 6q, 9p, 13q, 14q, and 22q. The most common gains are on chromosomal arms 1q, 5p, 7p, 8q, and 17q {1348,1481,1778}. Several tumour suppressor genes, including *NF2*, *CDKN2A* (*p16INK4a*), *CDKN2B* (*p15INK4b*), and *BAP1*, are frequently altered in malignant pleural mesothelioma.

The *NF2* gene located on 22q12.1 was one of the first tumour suppressor genes shown to be inactivated in malignant mesothelioma {198,2324}. *NF2* is inactivated by some combination of heterozygous deletions, nonsense mutations, and missense mutations in up to two thirds of cases; mutations account for 20% of these alterations {240}. *NF2* inactivation has not been associated with a specific histological subtype of malignant mesothelioma or prognosis. The neurofibromin 2 protein (merlin) is a membrane cytoskeleton-associated protein downstream of integrin-like kinase. It regulates several downstream pathways (including mTOR and the Hippo pathway), and is a key molecule determining invasion, cell growth, and survival of malignant

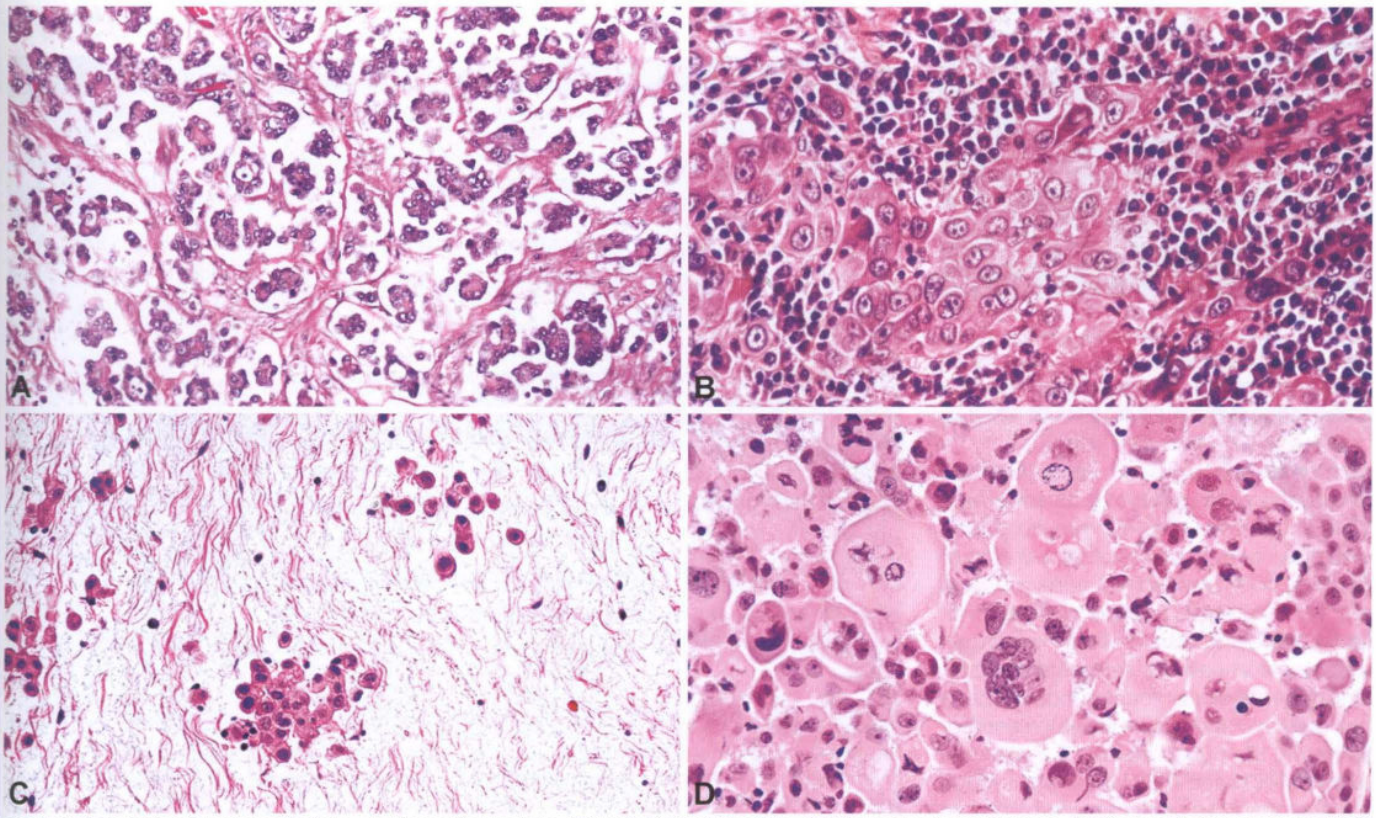

Fig. 2.12 Epithelioid malignant mesothelioma. **A** Micropapillary pattern. **B** Lymphohistiocytoid pattern. **C** With prominent myxoid stroma. **D** This mesothelioma shows deciduoid features and is composed of numerous large tumour cells with abundant eosinophilic cytoplasm. Some tumour cells show multinucleation.

mesothelial cells {934,1382,2640}. *NF2* inactivation is associated with increased mTOR signalling and Hippo pathway activation {1510,2967}. Deletion of the 9p21 locus is the most common genetic abnormality in malignant pleural mesothelioma {1004,1071,1512,2090}, resulting in loss of *CDKN2A* (*p16INK4a*), and p53 regulator *CDKN2A/p14ARF*, as well as the frequent loss of *CDKN2B* (*p15INK4b*) and *MTAP*. *CDKN2A* (*p16INK4a*) and *CDKN2B* (*p15INK4b*) are tumour suppressor genes that encode cyclin-dependent kinase inhibitor proteins that function in the retinoblastoma pathway, regulating the cell cycle during the G1/S phase. The loss of *p14ARF* leads to destabilization of p53. Since *TP53* is rarely mutated in malignant pleural mesothelioma, loss of *p14ARF* is a mechanism for functional loss of p53 in malignant pleural mesothelioma.

Loss of *p16/CDKN2A* in malignant pleural mesothelioma is a result of deletion, promoter hypermethylation, or point mutation, with homozygous deletion being the most common {2322,2909}. Deletion of *p16/CDKN2A* has been reported in 67–83% of malignant pleural mesotheliomas. The reported frequency of deletion varies depending on the histological subtype; rates are highest in sarcomatoid mesothelioma – approaching 100% {240,428,1512,2918}.

Between 42% and 60% of malignant pleural mesotheliomas harbour some form of *BAP1* loss (with a combination of large deletions, point mutations, and insertions). The rate may be higher in epithelioid malignant mesothelioma than other histological subtypes {2981,3009}. The rate of somatic mutations is about 20–30% {2981,3009}. Patients with *BAP1* somatic mutations are more commonly smokers, but no other distinct clinical feature has been reported {3009}. It is estimated that < 5% of patients with a newly diagnosed malignant mesothelioma have *BAP1* germline mutations {240,420,2624,2875}. No association has been found between *BAP1* mutations and the other common alterations in malignant pleural mesothelioma (i.e. *CDKN2A* deletion and *NF2* deletion/mutation) {240}. BAP1 is a nuclear protein that functions as a deubiquitinase that regulates multiple cellular functions, including the activity of specific transcription factors, the presence of specific chromatin modifications, and the activity of double-stranded DNA repair mechanisms {1382}. It is currently unclear which of these functions are important in malignant mesotheliomas.

Other tumour suppressor genes that are occassionally mutated include *LATS1* and *LATS2*.

LATS2 kinase is a key member of the Hippo signalling pathway, which regulates transcriptional targets through YAP1. Approximately 10% of malignant mesotheliomas harbour mutations in *LATS2* and the closely related *LATS1* {240,1772,2323}. There is no clear association with histological subtype or prognosis. Loss of LATS2 results in activation of Hippo signalling through YAP1 {1693,2967}.

Although activating mutations in RTKs have been described as oncogenic drivers in a variety of malignancies, these do not appear to be a common mechanism in pleural malignant mesothelioma. Even in the absence of activating mutations, many studies have confirmed the importance of receptor tyrosine kinase signalling pathways, including

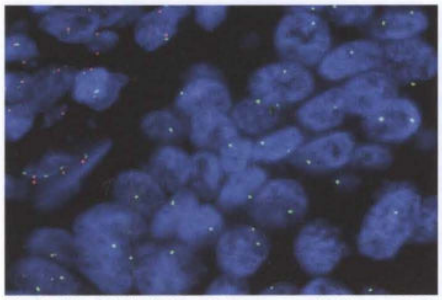

Fig. 2.13 Epithelioid malignant mesothelioma. 9p21 (*p16*) FISH: Malignant mesothelial cells with homozygous deletion of 9p21 show centromere 9p only (green signal) and lack the *p16* gene (red signal). Normal cells (as a positive control) show both red and green signals.

Table 2.03 Genes of potential interest for malignant pleural mesothelioma characterization and predictive prognostic value {1138}

Genes	Significance	Sources
p16/CDKN2A	Gene loss or no protein expression is associated with poor survival	{411,1378A, 520,1345,1512}
KIAA0977/GDIA1, L6/CTHBP, L6/GDIA1	Gene ratios predict outcome	{875}
CD9/KIAA1199, CD9/THBD, DLG5/KIAA1199, DLG5/THBD	Gene ratios predict outcome	{876}
TM4SF1/PKM2, TM4SF1/ARHDDIA, COBLL1/ARHDDIA	Gene ratios discriminate high-risk from low-risk patients	{874}
Gbx2, KI67, CCNB1, BUB1, KNTC2, USP22, HCFC1, RNF2, ANK3, FGFR2, CES1	Expression associated with poor prognosis	{852}
CDH2	Overexpressed in the short-term recurrence group	{1109}
DNAJA1	Underexpressed in the short-term recurrence group	{1109}
AURKA, AURKB	Expression associated with poor outcome	{502}
MELK	Upregulation associated with poor survival	{1512}
BIRC5, KIF4A, SEPT9	Upregulation associated with poor prognosis	{501}
HAPLN1	Expression negatively correlated with survival	{1110}
DNAJA1	Underexpressed in the short-term recurrence group	{1109}
MMP14	High expression associated with poor survival	{501}
LELK1	Upregulation associated with poor survival	{1512}
13 genes involved in extracellular matrix, regulators of extracellular matrix assembly, angiogenesis	High expression associated with poor survival	{2939}

epidermal growth factor receptor, MET (the hepatocyte growth factor receptor), VEGFR, platelet-derived growth factor receptor, and insulin-like growth factor pathways {1138,1944}. Overexpression of VEGF/VEGFR, hepatocyte growth factor/MET, and insulin-like growth factor receptor and ligands suggests the possibility of distinct autocrine loops driving cell growth in malignant pleural mesothelioma {1017,1600,1765,2486}. Activation of p38 MAPK and PI3K/Akt kinase, which are the downstream effectors of receptor tyrosine kinase activation, is well described in pleural malignant mesothelioma {263,1138,1914,1944}.

Gene expression profiling has identified specific gene expression changes in malignant mesothelioma compared with normal mesothelium, effects of fibre/asbestos exposure, and several new candidate oncogenes and tumour suppressor genes {897,1138}. Patient prognosis and response to therapy have been shown to correlate with specific gene expression profiles {1138}. However, published expression microarray studies show only limited overlap in predictive or prognostic expression profiles {1512}. MicroRNA profiling has shown multiple microRNAs to be implicated in the biology, prognosis, and diagnosis of malignant mesothelioma {177,2686}. Gene expression changes due to promoter methylation have been reported, and affect many genes (e.g. *APC*, *p16*, *p14*, *RASSF1*, and *RARB*) {443,730} and pathways, including the Wnt pathway {152,1307,1429,2757}.

Prognosis and predictive factors

The long-term survival rate of patients with malignant mesothelioma is poor {2227,2228,2750}. Younger age, epithelioid type (versus sarcomatoid or biphasic type), and early TNM staging are indicators of longer median survival, and strongly influence the therapeutic strategy {742,2226}. Although the evidence is sparse, multimodality therapy is indicated in patients with a good performance status and early-stage disease {2754}. Additionally, a histological subtype of epithelioid mesothelioma, such as mesothelioma with abundant myxoid changes, is a more favourable prognostic factor {2361}. In contrast, the presence of pleomorphic features strongly predicts poor survival {1178}. A histological grading system has not been established for malignant mesothelioma, but preliminary data suggest that nuclear grade (including nuclear atypia) and mitotic count are independent poor prognostic factors {1176}.

Sarcomatoid, desmoplastic, and biphasic mesothelioma

V. Roggli, A. Churg, L.R. Chirieac, F. Galateau-Salle, A. Borczuk, S. Dacic, S. Hammar, A.N. Husain, K. Inai, M. Ladanyi, A.M. Marchevsky, D. Naidich, N.G. Ordóñez, D.C. Rice, M.T. Sheaff, W.D. Travis, J. van Meerbeeck

Definition

Diffuse sarcomatoid malignant mesothelioma of the pleura is a malignant tumour arising from mesothelial cells and showing a diffuse pattern of growth over the pleural surfaces and a mesenchymal or spindle cell morphological appearance.

Diffuse desmoplastic malignant mesothelioma is characterized by dense collagenized tissue separated by malignant mesothelial cells arranged in a storiform or so-called patternless pattern, which must be present in at least 50% of the tumour.

Diffuse biphasic malignant mesothelioma is a mesothelioma showing at least 10% each of epithelioid and sarcomatoid patterns.

Diffuse malignant mesotheliomas must be differentiated from localized malignant mesotheliomas, which have different clinical behaviours.

ICD-O codes

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

Synonyms

Sarcomatoid mesothelioma: sarcomatous mesothelioma

Biphasic mesothelioma: mixed mesothelioma; mixed epithelioid and sarcomatoid mesothelioma; mixed epithelial and sarcomatous mesothelioma

Epidemiology

Among the mesotheliomas, these tumours are rare. Sarcomatoid type accounts for < 10%, biphasic for 10–15%, and desmoplastic for < 2% of all mesotheliomas. The epidemiology for all histological types of mesothelioma is similar (see *Epithelioid mesothelioma*, p. 156).

Etiology

See *Epithelioid mesothelioma*, p. 156.

Clinical features

The signs, symptoms, and staging of these tumours are similar to those of the epithelioid histological type (see *Epithelioid mesothelioma*, p. 156). Desmoplastic mesothelioma progresses more rapidly than epithelioid mesothelioma, and there is a trend towards older patient age and greater pain, weight loss, and loss of performance status {1278}. Sarcomatoid mesotheliomas are associated with frequent distant metastases and little or no effusion. Desmoplastic mesothelioma can metastasize to bone {1537}.

Localization

See *Epithelioid mesothelioma*, p. 156.

Macroscopy

See *Epithelioid mesothelioma*, p. 156. Sarcomatoid mesothelioma typically presents with diffuse pleural thickening or as a pleural-based mass.

Cytology

For information about effusion cytology, see *Epithelioid mesothelioma*, p. 156. In fine-needle aspiration biopsy specimens, sarcomatoid mesotheliomas may have features similar to those of other soft tissue sarcomas or sarcomatoid carcinoma, with spindle morphology and varying degrees of atypical nuclear features. Biphasic mesotheliomas can also have an epithelial component {457}.

Histopathology

Sarcomatoid mesothelioma

Sarcomatoid mesothelioma is characterized by a proliferation of spindle cells arranged in fascicles or with a haphazard pattern, and involves the adipose tissue of the parietal pleura or the adjacent lung parenchyma. Sarcomatoid mesotheliomas may present a wide range of morphologies – from plump cells to thin, long cells with scant cytoplasm. Nuclear atypia and mitotic activity vary from minimal to moderate or marked. In the latter setting, there is also marked pleomorphism. The presence of necrosis and the degree of atypia and mitoses parallel the aggressiveness of the tumour {457}.

The term mesothelioma with heterologous elements is applied when a mesothelioma shows rhabdomyosarcomatous, osteosarcomatous, or chondrosarcomatous elements {1279}. These elements must be differentiated from osteoid and chondroid metaplasia.

Some sarcomatoid mesotheliomas are characterized by atypical giant cells with large, multilobulated, bizarre, hyperchromatic nuclei with a high mitotic count and atypical mitoses {1178}. These may morphologically mimic undifferentiated high-grade pleomorphic sarcoma.

Table 2.04 Immunochemistry and molecular findings in the differential diagnosis between sarcomatoid malignant mesothelioma and selected other neoplasms {167,957,2025,2670,2973}

Sarcomatoid malignant mesothelioma	Sarcomatoid carcinoma	Monophasic synovial sarcoma	Solitary fibrous tumour	Angiosarcoma
		Immunochemistry		
- Keratin positive - Low expression of mesothelial markers	- Keratin positive - TTF1 or p63/p40 may be positive - Positive carcinoma markers (see Table 2.01)	- Keratin usually weak and/or focal	- CD34 positive - STAT6 positive - Bcl2 positive - Keratin usually negative; rarely focally positive	- Keratin usually negative; can be focal/weak; rarely strong - CD31, CD34 - ERG, FLI1
		Molecular findings		
	- *KRAS* mutation (20–30%) - Rare *EGFR* mutations	- Translocation t(X;18) (p11.2;q11.2) - SYT-SSX fusion protein	- Translocation - *NAB2-STAT6*	

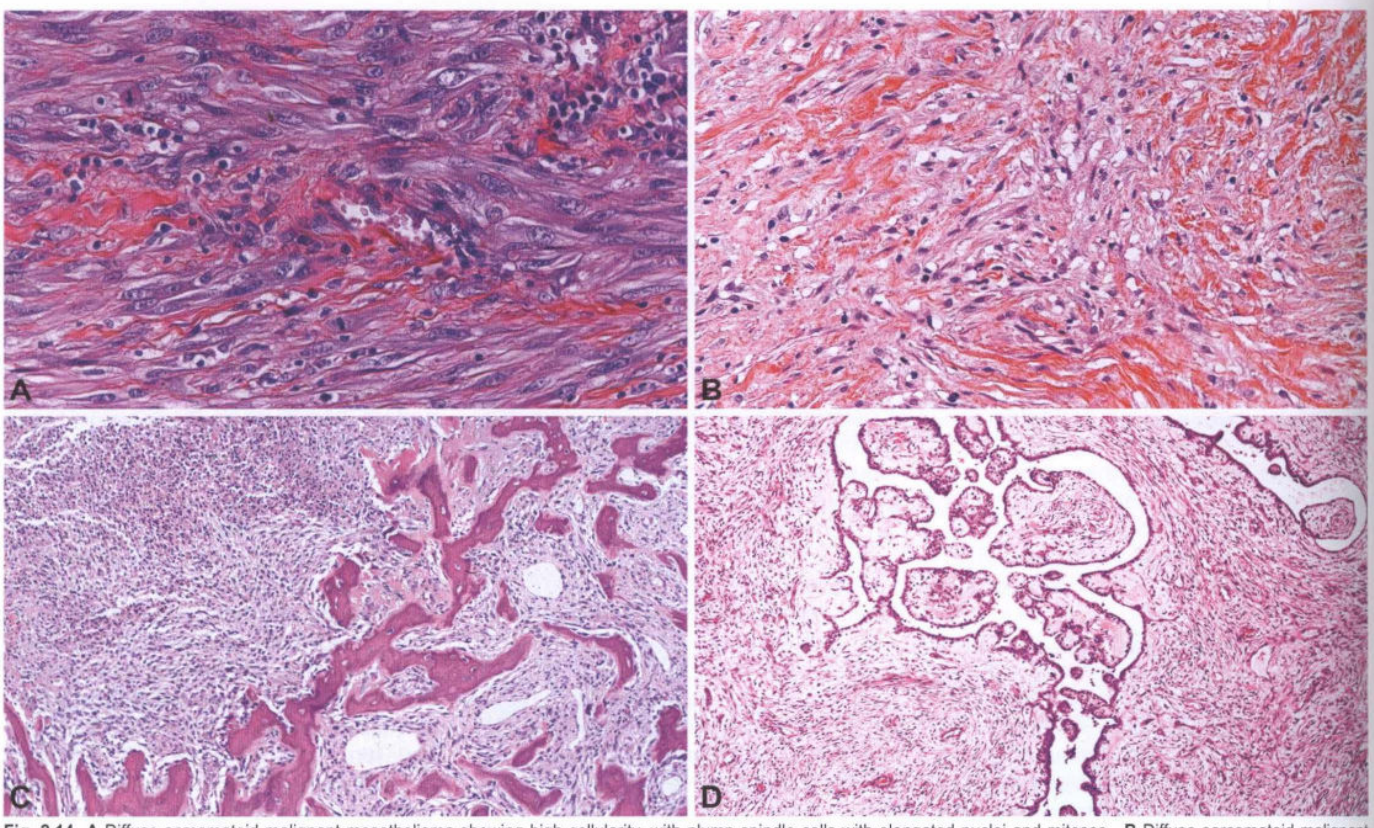

Fig. 2.14 **A** Diffuse sarcomatoid malignant mesothelioma showing high cellularity, with plump spindle cells with elongated nuclei and mitoses. **B** Diffuse sarcomatoid malignant mesothelioma showing low cellularity, with long, thin spindle cells, bland nuclei, and sparse cytoplasm. **C** Diffuse sarcomatoid malignant mesothelioma with a heterologous element (osteosarcoma). Reprinted from Galateau-Salle F {785}. **D** Biphasic malignant mesothelioma. This mesothelioma consists of an epithelial component (which is mostly papillary) and a sarcomatoid component.

Desmoplastic mesothelioma

Desmoplastic mesothelioma is characterized by areas of atypical spindle cells arranged in a so-called patternless pattern {1563} within a dense, hyalinized, fibrous stroma constituting at least 50% of the tumour. Invasion of adipose tissue is the most reliable criterion to distinguish desmoplastic mesothelioma from organizing pleuritis. In small biopsy, the diagnosis of desmoplastic mesothelioma is very difficult. In addition to invasion, other helpful criteria that favour malignancy include the presence of bland necrosis, cellular stromal nodules, and other areas of clear epithelioid or sarcomatoid mesothelioma.

Biphasic mesothelioma

Diffuse biphasic malignant mesothelioma is a mesothelioma showing at least 10% each of epithelioid and sarcomatoid patterns. Reporting the amount of the sarcomatoid component is recommended, because of its potential impact on prognosis and the therapeutic management of the patient.

Immunohistochemistry

Sarcomatoid mesotheliomas almost invariably stain, at least focally, with the AE1/AE3 broad-spectrum antikeratin antibody cocktail and the pancytokeratin antibodies OSCAR and KL1, as well as with the CAM5.2 antibody, which reacts primarily with CK8 {431,1056,2570}. CK18 may be positive in tumours where other keratins are negative. However, keratin negativity may be encountered in 5% of sarcomatoid malignant mesotheliomas, and in 10% of tumours with heterologous elements {1279}. About 30% of these tumours express calretinin {98,998,1278}, and these tumours are more often positive for D2-40 {431,998,1955}. Other mesothelial markers, including CK5/6 and WT1, are relatively insensitive {1056}. Sarcomatoid mesotheliomas are often vimentin-positive and occasionally express actin, desmin, or S100 protein.

Immunohistochemistry must be applied to rule out a sarcomatoid carcinoma; TTF1, napsin A, and p63/p40 expression support a diagnosis of sarcomatoid carcinoma. Myogenin and MyoD1 nuclear staining is useful for recognizing a rhabdomyosarcomatous component in mesothelioma with heterologous elements.

In desmoplastic mesothelioma, keratin immunostaining can be very useful for highlighting the tumour cells and for demonstrating invasion into adjacent soft tissues, particularly adipose tissue.

Differential diagnosis

The major differential diagnoses for sarcomatoid mesothelioma are soft tissue sarcoma metastatic to the pleura and primary chest wall sarcoma that has reached the pleura. Unlike sarcomatoid mesotheliomas, most sarcomas are keratin-negative. However, keratin-positive sarcomas (such as primary angiosarcomas of the pleura and monophasic synovial sarcomas) can present a diagnostic problem. Most sarcomas also show specific lineage markers and characteristic genetic changes {2670,2822}.

Primary pleural tumours causing diffuse pleural thickening with

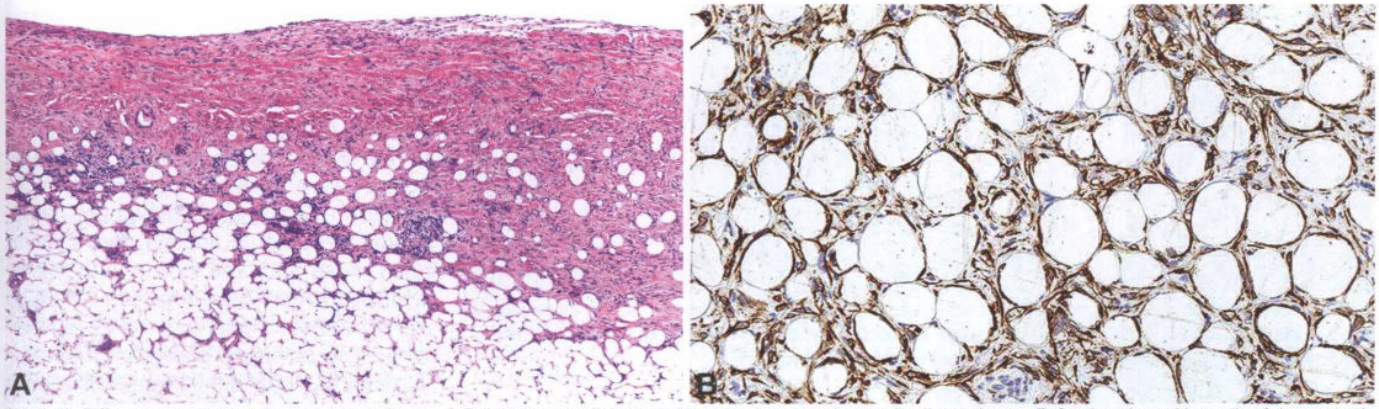

Fig. 2.15 Diffuse sarcomatoid malignant mesothelioma. **A** Full-thickness cellularity and invasion into true chest wall adipose tissue. **B** Cytokeratin-positive cells of desmoplastic mesothelioma in the chest wall fat.

osteosarcomatous or chondrosarcomas differentiation are probably all mesotheliomas. In most cases, pankeratin staining is positive, but keratin expression is sometimes difficult to demonstrate {1279}. Cases have been reported of osteosarcomas and chondrosarcomas growing diffusely in the pleural cavity with a gross distribution mimicking that of malignant mesothelioma {828,1132,1215}. *IDH1/2* mutation can differentiate chondrosarcoma from chondroblastic osteosarcoma or mesothelioma with a heterologous component.

Inflammatory myofibroblastic tumours can involve the pleura, but it is very unusual for these tumours to show diffuse pleural thickening. The myofibroblastic spindle cells with bland nuclei admixed with inflammatory cells and collagen may be difficult to distinguish from cells of mesothelioma with a dense inflammatory component {1279,1499}. The spindle cells may show ALK expression and *ALK* chromosomal rearrangement {303,467,828}.

Finally, there are some chest wall sarcomas, formerly classified as malignant fibrous histiocytomas, that are pleomorphic (undifferentiated), with anaplastic multinucleated giant cells and bizarre mitotic figures {565}. They typically stain positive for vimentin but negative for broad-spectrum cytokeratins and mesothelial markers.

Desmoplastic mesotheliomas must be distinguished from organizing pleuritis {458,1563}. In organizing pleuritis, there is typically zonation, with a more cellular infiltrate immediately under the effusion, and increasing degrees of fibrosis towards the chest wall. Desmoplastic mesotheliomas do not show zonation. In organizing pleuritis, there are often small capillaries perpendicular to the pleural surface, whereas in desmoplastic mesotheliomas, capillaries are generally inconspicuous. Desmoplastic mesotheliomas may also form cellular stromal nodules, which are not seen in organizing pleuritis. Desmoplastic mesotheliomas often invade the chest wall fat, and in such cases keratin-positive cells can be found infiltrating fat. Care should be taken not to confuse so-called fake fat (a traction artefact within markedly thickened and fibrotic pleura) with true invasion of fat in desmoplastic mesotheliomas. In true invasion, spindle cells course at some angle downwards from the pleura, whereas in fake fat, the spindle cells are all parallel to the pleural surface {456}. Organizing pleuritis may extend into the fat, but the cells in the fat are not keratin-positive {458}. The presence of bland tumour necrosis or focal areas of frankly malignant sarcomatoid or epithelioid mesothelioma also favours desmoplastic mesothelioma.

Biphasic mesotheliomas must be distinguished from pleomorphic carcinomas and synovial sarcomas. Pleomorphic carcinomas usually form a localized peripheral lung mass, which can invade

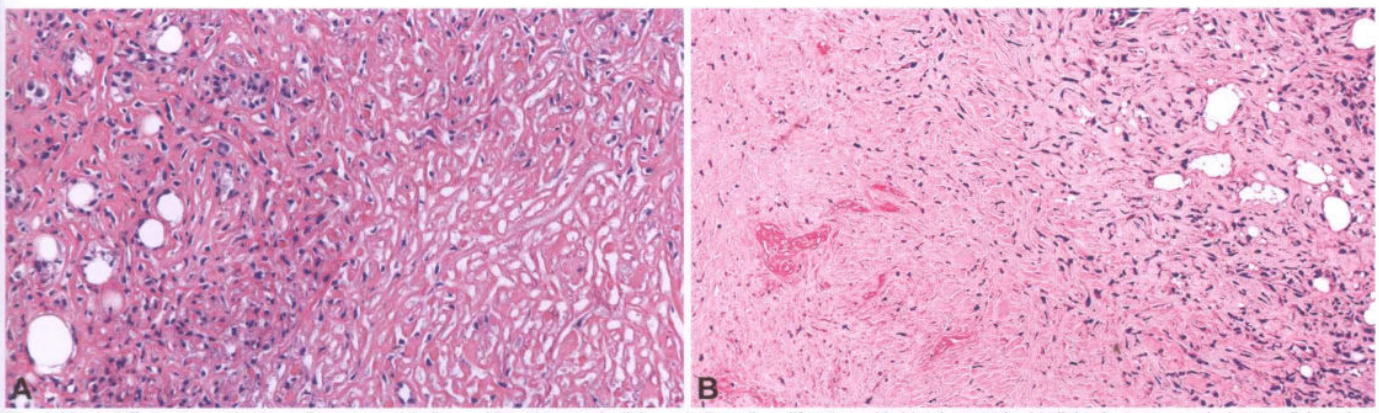

Fig. 2.16 **A** Diffuse desmoplastic malignant mesothelioma. Note the paucicellular spindle cell proliferation with bland necrosis, hyalinized stroma, and chest wall invasion. **B** Desmoplastic malignant mesothelioma. This mesothelioma shows bland necrosis and atypical spindle cells surrounded by a wire-like arrangement of hyaline stroma. The tumour also invades fat.

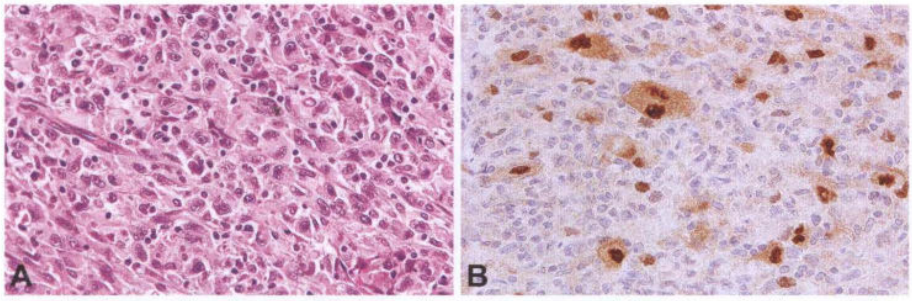

Fig. 2.17 Sarcomatoid malignant mesothelioma with rhabdomyosarcoma differentiation. **A** This mesothelioma shows some pleomorphic tumour cells with abundant eosinophilic cytoplasm, which suggests the possibility of rhabdomyosarcoma. **B** Scattered tumour cells show positive staining for myogenin.

the chest wall, and they frequently show areas of conventional adenocarcinoma or squamous cell carcinoma. They may stain for typical broad-spectrum carcinoma markers such as MOC31/BerEP4 or monoclonal carcinoembryonic antigen; however, these markers may be negative in some tumours, and it may be impossible to morphologically distinguish pleomorphic carcinoma from sarcomatoid mesothelioma. Most synovial sarcomas in the pleura are monophasic, but biphasic tumours also occur {779,2822}. Primary pleural synovial sarcomas can show a mixture of epithelial and spindle cells. Synovial sarcomas show a characteristic t(X;18)(p11.2;q11.2) translocation {1293,2822,2822}.

Genetic profile

The karyotypic and genomic characteristics of sarcomatoid malignant mesothelioma overlap with those of epithelioid malignant mesothelioma (see *Epithelioid mesothelioma,* p. 156). However, there are several differences in the frequency of somatic alterations. For example, homozygous deletion in the region of 9p21 (*p16*) is seen in most sarcomatoid pleural malignant mesotheliomas, approaching 100% of cases in some series {1071,2647,2909,2918}. This higher rate may also be true of biphasic tumours, although reported rates of deletion vary between studies {240,1071}.

In one series, losses at 14q32 and gains in 8q24 were seen at a significantly higher rate in sarcomatoid malignant mesothelioma {2565}. In another series, lower rates of 3p and 17p losses, and higher rates of 15q gain were reported {1348}.

TERT promoter mutations are more common in sarcomatoid malignant mesothelioma (40%) than in the biphasic (19%) or epithelioid (11%) subtypes {2579} (see *Epithelioid mesothelioma,* p. 156).

Prognosis and predictive factors

In most series, sarcomatoid and desmoplastic variants have poorer prognoses than epithelioid mesothelioma {2224,2227}. Biphasic tumours have an intermediate survival. Desmoplastic mesothelioma has a dismal prognosis; most patients die within 6 months after diagnosis. No patient with sarcomatoid mesothelioma has been known to survive for 5 years. TNM staging is a significant predictor of prognosis.

Localized malignant mesothelioma

A. Churg
V. Roggli
L.R. Chirieac
F. Galateau-Salle
A. Borczuk
S. Dacic
A. Gibbs
S. Hammar
A.N. Husain
K. Inai
A.M. Marchevsky
D. Naidich
N.G. Ordóñez
D.C. Rice
M.T. Sheaff
W.D. Travis
J. van Meerbeeck

Definition

Localized malignant mesothelioma is a rare tumour that grossly appears as a distinctly localized nodular lesion. It shows no gross or microscopic evidence of diffuse pleural spread, but has the microscopic, immunohistochemical, and ultrastructural features of diffuse malignant mesothelioma.

ICD-O codes

Localized malignant mesothelioma should be coded according to the histological type of analogous mesothelioma.

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

Synonyms

Localized mesothelioma; solitary malignant mesothelioma

Epidemiology

This tumour is very rare; fewer than 50 cases have been reported. There is a slight male predisposition, and the mean age is between 60 and 65 years {52,1803}.

Etiology

The etiological role of asbestos exposure in localized malignant mesothelioma is unclear.

Clinical features

Localized mesothelioma can be an incidental finding. Patients may present with chest pain, dyspnoea, malaise, fever, or night sweats.

Localization

Localized malignant mesotheliomas usually grow into the chest wall or the adjacent lung parenchyma.

Macroscopy

Localized mesothelioma is a solitary, circumscribed, pleural-based mass attached to the visceral or parietal pleura. The tumours can be pedunculated or sessile.

Cytology

Pleural effusions are uncommon, so cytological examination of these tumours is mostly conducted on fine-needle aspirates. The cytological features resemble those of diffuse malignant mesothelioma (see *Epithelioid mesothelioma*, p. 156, and *Sarcomatoid, desmoplastic, and biphasic mesothelioma*, p. 165).

Histopathology

Localized malignant mesotheliomas have morphological, immunohistochemical, and ultrastructural features indistinguishable from those of diffuse malignant mesotheliomas. The tumours can show epithelioid, sarcomatoid, or biphasic morphologies {52,507} (see *Epithelioid mesothelioma*, p. 156, and *Sarcomatoid, desmoplastic, and biphasic mesothelioma*, p. 165).

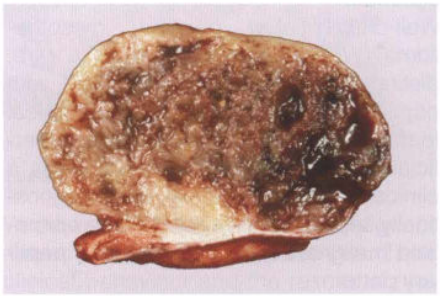

Fig. 2.18 Localized malignant mesothelioma. This mesothelioma consists of a circumscribed pleural-based mass. The cut surface is tan-brown, with focal haemorrhage and cystic changes.

The differential diagnoses include solitary fibrous tumour (see *Solitary fibrous tumour*, p. 178), carcinoma (see *Epithelioid mesothelioma*, p. 156 and *Sarcomatoid, desmoplastic, and biphasic mesothelioma*, p. 165), and synovial sarcoma (see *Synovial sarcoma*, p. 177).

Prognosis and predictive factors

Localized mesotheliomas have a better prognosis than diffuse mesotheliomas, and may be cured by surgical excision {52}.

Well-differentiated papillary mesothelioma

V. Roggli
A. Borczuk
L.R. Chirieac
A. Churg
S. Dacic
F. Galateau-Salle
A. Gibbs
S. Hammar
A.N. Husain
K. Inai
D. Naidich
N.G. Ordóñez
D.C. Rice
M.T. Sheaff
W.D. Travis
J. van Meerbeeck

Definition

Well-differentiated papillary mesothelioma (WDPM) of the pleura is a rare, distinct tumour of mesothelial origin, with papillary architecture, bland cytological features, and a tendency towards superficial spread without invasion. This is a clinically, morphologically, and prognostically separate entity from diffuse epithelioid malignant mesothelioma with papillary pattern.

ICD-O code

9052/1

Epidemiology

This tumour is much rarer in the pleura than in the peritoneum, with fewer than 50 cases reported {302,787}. It has occurred over a wide age range, with a mean of about 60 years. There is no sex predominance.

Etiology

The histogenesis of WDPM remains poorly understood. When it occurs in the peritoneum of women, it appears to be unrelated to asbestos exposure. The reports of pleural cases have suggested a link with asbestos exposure, but this has not been established in a formal epidemiological study.

Clinical features

Most patients present with a history of dyspnoea and recurrent pleural effusion without chest pain. Chest radiography and CT show unilateral pleural effusions, without nodularity.

Localization

These mesothelial lesions may be localized or multifocal.

Macroscopy

WDPM may present with a granular pleural surface or as multiple millimeter sized nodules on the parietal and/or visceral pleura, resulting in a velvety appearance {787}.

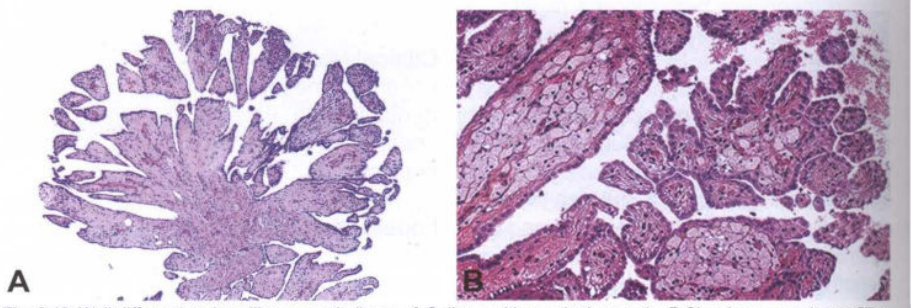

Fig. 2.19 Well-differentiated papillary mesothelioma. **A** Solitary, with exophytic growth. **B** Showing macrophages filling the papillae.

Cytology

In cytological specimens, WDPM demonstrates stout papillary cores lined by a single layer of flattened to cuboidal mesothelial cells. These cells have bland nuclear features and inconspicuous nucleoli. Mitotic figures are typically absent. The finding of significant nuclear atypia, architectural complexity, or solid areas tends to suggest malignant epithelioid mesothelioma with papillary pattern. Since cytological specimens may fail to reveal an invasive component, cytological diagnosis of WDPM is not recommended.

Histopathology

Histologically, the proliferation arises from the mesothelial surface of the pleura, and is characterized by a prominent papillary architecture composed of papillae with more-or-less myxoid cores covered by a single layer of flattened or cuboidal bland epithelioid cells. Macrophages may be present in the cores of the papillae. The nuclei are round, small, and devoid of atypia and mitoses. Invasion is generally not seen. Rare cases with superficial invasion should be called WDPM with invasive foci {455}.

The immunohistochemical pattern of WDPM is that of mesothelial origin {787} (see *Diffuse malignant mesothelioma*, p. 156).

The most important differential diagnosis is epithelioid diffuse malignant mesothelioma with a papillary pattern. Such foci may be extremely difficult to distinguish

Table 2.05 Differential diagnosis between epithelioid malignant mesothelioma with papillary pattern and well-differentiated papillary mesothelioma

Characteristic	Epithelioid malignant mesothelioma with papillary pattrn	Well-differentiated papillary mesothelioma
Growth feature - bulk of disease	Diffuse or multinodular, grossly apparent	Often incidental, solitary, focal area of velvety appearance
Morphology of papillae	Fibrous cores, lined by cells with stratification	Fibrous and stout cores, single-cell layer
Cytology	Cuboidal cells with nucleoli and variable anisocytosis	Flat cuboidal, no anisocytosis
Mitoses	Low	Low
Other growth patterns	Tubular, solid, cribriform, complex papillae	Absent
Stromal invasion	Present	Predominantly exophytic growth, usually absent; when present, only very focal and superficial
Prognosis	Poor	Good, with local recurrence

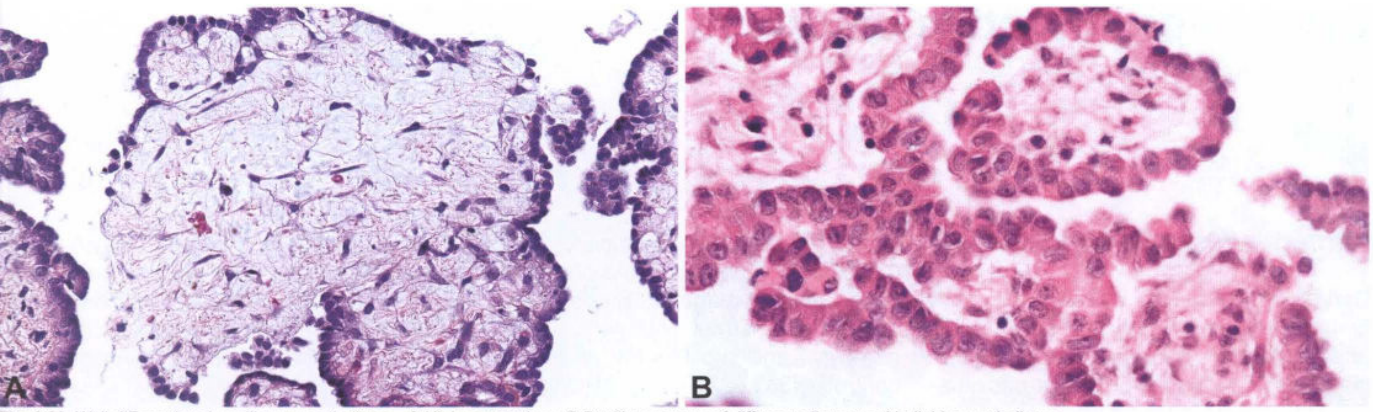

Fig. 2.20 Well-differentiated papillary mesothelioma. **A** High-power view. **B** Papillary pattern of diffuse malignant epithelioid mesothelioma.

morphologically from a WDPM in a small biopsy. Areas of solid tumour favour a diagnosis of malignant mesothelioma. Reference to the operative or radiological findings can be extremely helpful. WDPM should appear as small translucent nodules, whereas diffuse malignant mesothelioma typically looks like diffuse carcinomatosis or a rind of tumour.

Genetic profile

The molecular pathogenesis of WDPM is largely unstudied, so its relation to diffuse malignant epithelioid mesothelioma is unknown. A single pleural WDPM was reported to have a germline *BAP1* mutation {2149}. Single cases of peritoneal WDPM with *NF2* heterozygous deletion {1826} and *E2F1* point mutation {2999} have also been reported.

Prognosis and predictive factors

WDPMs of the pleura are indolent tumours (and in most cases probably clinically benign if completely resected), and are associated with a very long survival. Whether WDPMs give rise to malignant mesotheliomas remains uncertain. Their clinical behaviour and the results of molecular analyses are suggestive of a neoplastic process {302,787} Follow-up of patients presenting with WDPM with focal invasion is recommended on the basis of possible recurrence {455}.

Adenomatoid tumour

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Definition

Pleural adenomatoid tumour is a mesothelial tumour histologically identical to adenomatoid tumours in other locations (especially the female genital tract), but located in the visceral or parietal pleura {1681}. Very few examples of pleural adenomatoid tumours have been reported.

ICD-O code

9054/0

Clinical features

The tumour is found incidentally on gross examination of the pleura {196,1208}.

Localization

Adenomatoid tumours can occur on the visceral or parietal pleura {196,1208}.

Macroscopy

The tumours are solitary, whitish, firm nodules measuring 0.5–2.5 cm.

Histopathology

Irregularly shaped, gland-like spaces are composed of flattened or cuboidal cells, and associated with a fibrous stroma {196,1208}. The tumour cells have a bland nucleus and scant eosinophilic cytoplasm. Intracytoplasmic vacuoles can sometimes be seen, and the spaces may contain basophilic material.

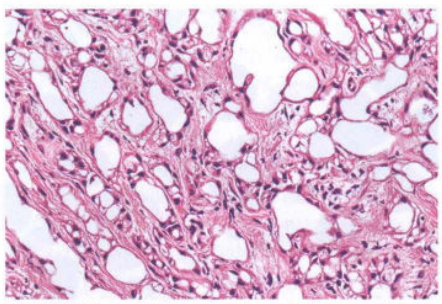
Fig. 2.21 Adenomatoid tumour. Irregularly shaped tubular and microcystic spaces lined by flattened endothelial-like cells within a fibrous stroma.

Immunohistochemically, the tumour cells stain identically to those of epithelioid malignant mesothelioma (see *Diffuse malignant mesothelioma*, p. 156).

The crucial distinction is from epithelial malignant mesotheliomas that have adenomatoid-appearing areas. Epithelial malignant mesotheliomas always show diffuse spread along the pleura and invasion of the underlying stroma, whereas adenomatoid tumours (by definition) are solitary localized lesions. Similar to adenomatoid tumours in the genitourinary tract, they only show localized infiltration of tissue adjacent to the tumour.

Prognosis and predictive factors

Like adenomatoid tumours in other locations, this tumour is benign. Complete removal should be curative.