Pathology of lung and pleural tumours

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Abstract

Lung and pleural malignancy is a major cause of morbidity and mortality. Approaches to diagnosis and management are evolving, based on both technological and scientific advances. A basic understanding of the classification of lung and pleural tumours and approaches to their pathological diagnosis is important for all those involved in managing these patients. To this end, we present an overview of the current classification of lung tumours, briefly discuss their aetiology and pathogenesis, describe pathological aspects of the diagnosis and staging of bronchial carcinoma (including an outline of the developing role of molecular approaches to refining oncological management), and finally review the pathology of mesothelioma and it differential diagnosis.

Keywords Classification; histopathology; lung cancer; molecular diagnostics; multidisciplinary team; staging

Carcinoma of the lung

Introduction

Bronchial carcinoma is the most common cause of cancer-related death in the UK, with an annual incidence of around 42,000 and an over all 5-year survival rate less than 10%. Rates of the disease in women continue to rise in developed countries, and the potential for a lung cancer 'epidemic' in developing countries is acknowledged.[1] Approaches to diagnosis, classification and management are evolving, based on technological and scientific advances. Patient management is determined by the tumour type, extent of disease and associated medical comorbidities. In the UK, management is discussed in the multidisciplinary team meeting (MDTM) setting and the pathologist plays a key role in this. An understanding of the classification of lung tumours and approaches used in their pathological diagnosis is important for all involved in these meetings.

Aetiology

Epidemiological studies demonstrate a causal association between tobacco (particularly cigarette smoking) and the development of bronchial carcinoma. Other risk factors including exposure to radiation, asbestos, and second-hand smoke are also recognized. Although efforts have been made to reduce environmental exposures to various agents, including second-hand smoke, given that lung cancer risk has been shown to reduce on smoking cessation, the most effective preventative measure for an individual smoker is to stop!

Pathological classification of malignant tumours of the lung

Lung tumours are classified according to the World Health Organization (WHO) scheme (2004), with modification of the classification of adenocarcinomas based on a joint IASLC/ATS/ERS consensus paper from 2011.[2,3] The WHO classification is based on the morphological appearances of resected tumour specimens, whereas the consensus paper includes guidance on classification on small biopsy and cytology samples using ancillary techniques such as immunohistochemistry (an established means of identifying characteristics of a cell using antibodies directed against a target of interest).

Broadly speaking, bronchial carcinomas can be divided into two groups, a heterogeneous group of 'non-small cell carcinomas' accounting for about 80% of cases and small cell carcinoma making up the remainder. Accurate subclassification is essential to guide oncology practice and appropriate molecular pathology testing.

Non-small cell carcinoma

Squamous cell carcinoma (Figure 1)**:** these are typically large, centrally placed tumours arising in male patients with a long smoking history. The tumours may be necrotic and show extensive cavitation. The presence of keratinization and/or intercellular bridge formation (prickles), indicate the squamous nature of the tumour histologically. Papillary, small cell, basaloid and clear cell morphological variants are recognized, but are of no clinical significance.

Adenocarcinoma (Figure 2)**:** this is now the most common subtype of lung cancer, with an as yet unexplained rise in the relative incidence of this tumour in men. Morphologically, glandular or papillary differentiation and/or mucin production are required for diagnosis. Lepidic, acinar, papillary, micropapillary, and solid with mucin production subtypes are described. The significance of detailed subtyping is a matter of debate, although there is evidence that pure solid or micropapillary tumours may do worse than pure lepidic types.[3] There is a subgroup of in-situ/minimally invasive adenocarcinoma type lesions that would be expected to have 100% or near 100% 5-year survival following resection. These have traditionally been grouped together using the term bronchioloalveolar carcinoma (BAC). There is a move away from this terminology in favour of more specific entities such as adenocarcinoma in-situ, minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma. It is beyond the scope of this article to discuss the intricacies and merits (or otherwise) of such a revised system, but it is important to be aware of the potentially changing terminology to ensure appropriate clinical management of these patients.

Large cell carcinoma: resected tumours showing no specific features of either squamous or glandular differentiation fall into this category. They are poorly differentiated tumours with a poor prognosis. The most important subtype is large cell neuroendocrine carcinoma (LCNEC), which is a high-grade carcinoma

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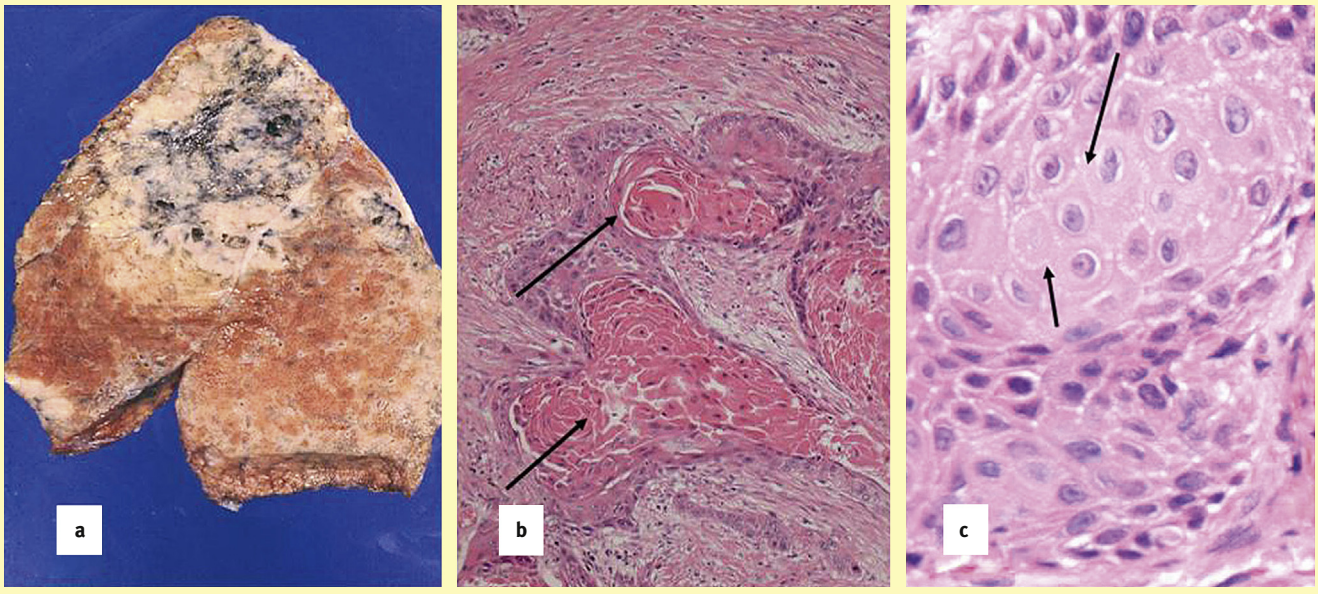

Squamous cell carcinoma. (**a**) Macroscopic appearance of a large squamous carcinoma of the upper lobe. (**b, high power, H&E**) Demonstrating keratin formation within the tumour (arrows). (**c, high power, H&E**) Demonstrating intracellular bridge formation, 'prickles' (arrows).

Figure 1

showing morphological and immunohistochemical evidence of neuroendocrine differentiation.

Sarcomatoid carcinomas: these are poorly differentiated tumours characterized by cells showing either a spindle cell or pleomorphic giant cell morphology, often admixed with more typical areas of squamous/adenocarcinoma. In some cases foci of true malignant mesenchymal differentiation may also been seen. Their prognosis tends to be poor.

Small cell carcinoma (Figure 3)

This is the third most common type of carcinoma accounting for around 20% to 25% of cases. It is a poorly differentiated carcinoma with neuroendocrine features and is often disseminated with extensive nodal disease and/or distant metastases at the time of diagnosis. These tumours are composed of cells with little cytoplasm, easily identified mitotic figures, apoptotic debris and often extensive necrosis.

Carcinoid tumours

These represent neuroendocrine tumours at the low and intermediate end of the malignant spectrum (compared to LCNEC and small cell lung carcinoma [SCLC]). They may present as well-circumscribed peripheral lesions or polypoid endobronchial tumours. They are composed of uniform polygonal cells, which may show a packeted, trabecular, or spindle cell arrangement. Immunohistochemistry shows expression of neuroendocrine markers. A potentially important feature from the unwary clinicians' viewpoint is the high vascularity of the tumour, which may result in haemorrhage on biopsy.

The differentiation between carcinoid and atypical carcinoid usually requires examination of the resected tumour specimen with identification of either focal necrosis or 2–10 mitoses per 2 mm^2 making the 'atypical' diagnosis. Differentiation from SCLC on biopsies can be difficult histologically, although some have advocated the use of Ki-67 immunohistochemistry to assess proliferation, as a discriminator, in problematic cases.

The demonstration of neuroendocrine differentiation, by immunohistochemistry, in tumours which do not fall into the categories described above (SCLC, LCNEC, carcinoid) is reported, but is of no clinical significance.

Other tumours

Other, rare, primary, lung malignancies include: salivary gland type tumours (e.g. adenoid cystic carcinoma), lymphoma, and sarcomas (e.g. synovial sarcoma).

Pathogenesis and natural history of bronchial carcinomas

Our understanding of the development of bronchial carcinoma is incomplete. There is a lack of a well-defined model for the development of the various cancer subtypes and no clear consensus regarding the optimum means of identifying so-called 'premalignant' lesions or how they should be managed. These gaps in knowledge provide challenges to both basic science research and also those wishing to devise screening and treatment strategies for patients at risk of lung cancer.

Squamous carcinoma (Figure 4)**:** this is described as arising in a stepwise fashion with respiratory-type epithelium undergoing metaplasia to squamous epithelium which subsequently becomes dysplastic, and eventually frankly malignant. This hypothesis is supported by experimental work in animals, clinical work in humans, and by the genetic changes identified.

However, epidemiological data challenge this hypothesis, with mild or moderate dysplasia apparently having virtually no