

## Current problem areas in the classification of lung tumours

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This talk concentrates on diagnosis of 'rare' lung cancers, using cases referred to our institution for specialist opinion in the past five years to explore controversies over proposed new entities, and what is and what is not neoplastic. Auditing of such referrals reveals fairly consistent numbers in the UK where both specialist and general pathologists have the greatest difficulty. Problem areas can be divided into (a) diagnosing adenocarcinoma on small biopsies, (b) the differential diagnosis of mesothelioma, (c) putative rare lung tumours (the subject of this talk), (d) interstitial pneumonias and other diffuse lung diseases and (e) rare non-neoplastic diseases including vascular and systemic disorders.<sup>1</sup>

In the group of rare lung tumours, problems not infrequently arise when putative tumour has a prominent lymphoid component. This not only relates to diagnosing lymphoproliferative disease but also distinguishing other tumours or mimics of tumours that are rich in lymphocytes. Whilst primary pulmonary lymphomas comprised a significant number of such referrals in the 1990s, pathologists are now comfortable diagnosing the vast majority of primary pulmonary marginal zone lymphomas and diffuse large B-cell lymphomas, with referral limited to those with atypical presentation. There are however a few cases each year that fail to show light chain restriction or clonality, where the infiltrate is particularly well organised and these should be accepted as nodular lymphoid hyperplasia.<sup>2</sup> Cases of lymphomatoid granulomatosis (LYG) continued to be referred, and it remains important for the pulmonary pathologist to co-report such cases with experts in lymphoma pathology in order to ensure the best chance of a correct diagnosis. Cases of LYG can show classic morphology without evidence of EBV and/or clonality.

In this area, a new potential entity to consider in addition is hyper IgG4 disease. This term relates to many lymphoproliferative lesions throughout the body, these including idiopathic retroperitoneal fibrosis and sclerosing pancreatitis.<sup>3</sup> It manifests as lymphoplasmacytic inflammation with abundant IgG4-positive cells and sometimes exuberant fibrosis which leaves dense fibrosis on resolution. Its relationship to pulmonary hyalinising granuloma therefore requires investigation and such cases need to be distinguished from inflammatory myofibroblastic tumours<sup>4</sup> and teased from the spectrum of inflammatory pseudotumors,<sup>5</sup> as during the acute phase, there is usually a good response to steroid therapy.

The group of miscellaneous tumours in the 2004 classification system also remain a source of referral material, although the purist would argue that most cases in this subgroup should now be moved to other categories in order to maintain histogenetic accuracy. Sclerosing haemangiomas (pneumocytomas) were initially thought to be endothelial in origin,<sup>6</sup> but there is now a consensus that they are predominantly benign epithelial tumors<sup>7;8</sup> Although most cases are readily diagnosable on biopsy, and criteria are also given for frozen section and cytological diagnosis, rare cases remain where diagnosis is problematic. Such problems tend to arise when presentation is atypical (sites other than the lung and parenchyma such as endobronchial,

mediastinal, nodal metastases, liver metastases) or the tumour itself is atypical (marked pleomorphism, cystic degeneration, 'giant'). Furthermore patients with multiple small bilateral sclerosing hemangiomas combined with tumourlets have been identified, such cases being a recent focus of referral. Follow-up suggests that patients remain stable over years without need for treatment.

Hamartomas should also no longer be considered a miscellaneous tumour, rather classified as a mesenchymal neoplasm on the basis that they show gene mutations similar to those pure mesenchymal tumours, such as lipomas, these relating to the high-mobility group (HMG) proteins.<sup>9</sup> As for sclerosing haemangiomas, most cases are readily diagnosable on histology, cytology and frozen section, with rare difficulties only occurring when presentation is grossly atypical. Malignant change, although exceptional, can occur. Furthermore, recent publications have described combination of hamartomas with salivary gland-type lung tumours showing myoepithelial differentiation<sup>10</sup> and pulmonary pathologists should be aware of this and other morphological variations in hamartoma. Likewise, clear cell tumors or 'sugar tumors' represent a tumour from the family of PEComas, neoplasms originating from the perivascular epithelioid cells (PEC)<sup>11</sup>, and should be grouped with other mesenchymal tumours, and thymomas when primary in the lung should be classified as epithelial, thus leaving only melanoma and teratoma in the miscellaneous category.

Unusual variants of salivary gland-type tumours also appear sporadically, especially in the light of recent publications describing new entities such as pulmonary microcystic fibromyxoma.<sup>12</sup> Such tumours may represent monophasic growth of the stromal component of mixed tumours.<sup>13</sup> Indeed, when confronted with a myxoid/spindle cell endobronchial lesions, one should always consider equally inflammatory polyps or primary/metastatic mesenchymal tumours.

Another area where there have been questions over lung disease being neoplastic is mucinous proliferation in type 1 congenital cystic adenomatoid malformations (CCAM). Mucinous cell hyperplasia without evidence of malignant transformation is reported in about one third of cases, and some have viewed such proliferations as reactive. However, cases with co-existent atypical adenomatous hyperplasia are now described and both intracystic and intra-alveolar areas of mucinous proliferation have been shown to contain K-ras mutation and LOH and/or microsatellite instability at the p16 locus, displaying similar molecular abnormalities and differentiation profiles to those in mucinous bronchioloalveolar carcinoma 'de novo'. Gains in chromosomes 2 and 4 have also been reported in areas of intra-alveolar mucinous proliferation and metastatic disease is occasionally seen, indicating classification as adenocarcinoma is justified.<sup>14;15</sup> Neoplasms can also cause cystic change as an integral part of the tumour, for example pleuropulmonary blastoma, another area of controversial overlap between neoplastic and non-neoplastic disease given its histological similarities to type 4 CCAMs.<sup>16;17</sup>

Finally, in relation to carcinoids, the last three years has seen a significant increase in the number of cases presenting with neuroendocrine cell hyperplasia (NEH) and associated neuroendocrine tumours. Whilst the published literature contains only two series of six and five patients, together with scattered case reports, 11 cases have been identified in one department within the past three years. This has come about

primarily through increased accuracy and frequency of screening of patients for metastatic disease identifying small nodules presumed to be metastases. It is now apparent that NEH may also be associated with atypical as well as typical carcinoids, and may be part of the spectrum of Type 1 MEN syndrome.<sup>18</sup> Indeed peripheral carcinoids, which are those typically seen with NEH, may have a differing biology to the more common central tumours, with the peripheral lesions being more commonly spindle in morphology and TTF-1 positive.<sup>19</sup>

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