Postgraduate Course ERS Glasgow 2004
Large cell carcinoma

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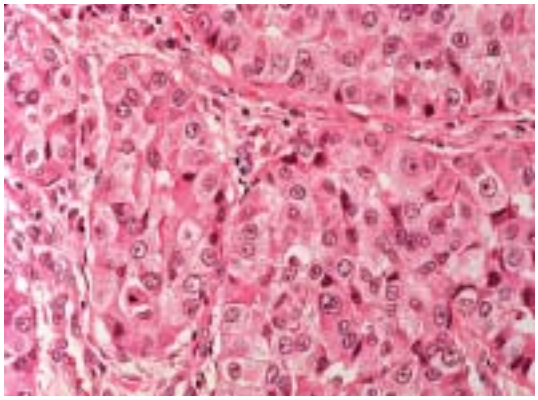
Educational aims

- To explain the importance of discriminating between different histological types of NSCLC.
- To explain the differences between large cell carcinoma (NOS) and their variants.
- To link precise histopathological class with prognosis.

Summary

The histopathological classification of lung cancer was revised in 1999, and, in addition, descriptions of their phenotypic and genetic abnormalities were reported in 2004. Several changes have occurred that increased the clinical significance of lung cancer histopathological classification. These include the subclassification of large cell carcinoma, which was defined on a negative basis (on exclusion criteria), into variants which are defined on objective histopathological positive criteria that endowed them with a strong clinical significance.



Large cell neuroendocrine carcinoma: large tumour cells with low nuclear-to-cytoplasmic ratio forming tumour cell sheets lacking architectural pattern.

In the past, large cell carcinoma have essentially been defined by negative criteria, since their definition rested on lack of squamous, glandular or small-cell features of differentiation. They have thus been previously called large cell anaplastic carcinoma and large cell undifferentiated carcinoma, indicating that they have been essentially defined by their differences from other subtypes of lung cancer, on the basis of what they were not, instead of what they were. Consequently, their clinical features were undefined, and there was no specific biological pattern associated with this uncircumscribed entity. They have been included in the category of non-small cell lung carcinoma (NSCLC) for therapeutic purposes in clinical trials comparing the effect of chemo- or radiotherapeutic approaches. This subgroup was always small and no specific response to therapy had been associated with it. In addition, as another consequence of their blurred contours, evaluation of their incidence has been very variable in different series over the last 10 years (ranging from 2 to 20%).

The aim of the last World Health Organization (WHO) classification in 1999 [1], which has been further refined with associated molecular and genetic alterations [2], was to break up this entity in describing two variants of large cell carcinoma, setting aside the not otherwise specified (NOS): the large cell neuroendocrine carcinoma (LCNEC), described in 1991 by TRAVIS *et al.* [3]; and the basaloid carcinoma, described in 1992 [4]. Both variants

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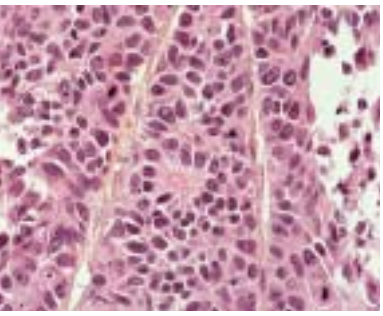
were recognised as distinct clinico-pathological entities with a dismal prognosis by the WHO classification in 1999 [1]. Since each of these two variants each represent 3–5% of lung cancer, the aim of this review is to delineate more precisely their morphological and phenotypical appearance, as well as their prognosis. Another variant with a better prognosis has also been added, the lymphoepithelioma-like carcinoma. For histological recognition as primary lung cancer, the clear cell carcinoma variant and the large cell carcinoma with rhabdoid phenotype were also identified with no specific prognosis.

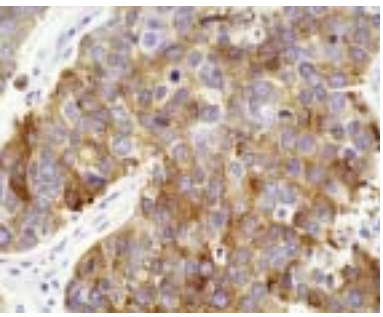
Epidemiology and clinical features

Large cell carcinoma accounts for ~9% of all lung cancers, while both LCNEC and basaloid carcinoma account for ~5%. All types predominate in smokers, except lymphoepithelioma-like carcinoma, a very rare tumour accounting for 1% of lung tumours in China and less than that in Europe, with no relationship with smoking. For the reasons already discussed, the symptoms and clinical behaviour of large cell carcinoma are not well known; however, they have many in common with non-small cell carcinoma. In contrast to their frequency in other neuroendocrine tumours, ectopic hormone production is rare in LCNEC [5]. Large cell carcinoma occur preferentially in the lung periphery and are accessible by transthoracic fine-needle aspiration biopsy and bronchoscopy biopsy, although basaloid carcinomas are more often proximal and accessible by bronchoscopy.

There are no specific cytological features associated with large cell carcinoma, although LCNEC can be distinguished on a cytological basis from small cell carcinoma by the presence of prominent nucleoli and nuclei larger than three times the diameter of a small resting lymphocyte [6, 7]. Cytologically, well-developed nuclear palisading and cohesive aggregates of rather uniform small cells are characteristic of basaloid carcinoma. Lymphoepithelioma-like carcinoma show cohesive flat syncytia [8].



Large cell neuroendocrine carcinoma: tumour cells form palisades and rosettes typical of neuroendocrine features. Note the high mitotic rate.



Chromogranin expression in a large cell neuroendocrine carcinoma.

Macroscopy

Large cell carcinoma typically present with large peripheral masses, which may also involve bronchi, invading visceral pleura, chest wall or adjacent structures. In contrast, basaloid carcinomas are more proximal, often showing exophytic bronchial growth [4].

The pattern of tumour spread is not distinguishable from that of non-small cell carcinoma.

Histopathology

Large cell carcinoma

Large cell carcinoma (NOS) are, by definition, poorly differentiated tumours, and a diagnosis by exclusion is made after ruling out squamous cell carcinoma, adenocarcinoma or small cell carcinoma. The recognition of a component of at least 10% of squamous cell carcinoma or adenocarcinoma is sufficient to these diagnostic terms instead of large cell carcinoma. All together the diagnosis of LC should not exceed 10% on surgical samples. They consist of sheets or nests of large polygonal cells with vesicular nucleoli, prominent nucleoli, a moderate amount of cytoplasm and minimal ultrastructural features of squamous or glandular differentiation.

Variants

1. Large cell neuroendocrine carcinoma

LCNEC are defined on the basis of histological features suggesting neuroendocrine differentiation [1, 3], including organoid nesting, trabecular growth, rosettes and perilobular palisading pattern. Mitotic counts are typically ≥11 per 2 mm^2 (average 75; 10 high-power fields), and large areas of necrosis are common. Neuroendocrine differentiation is confirmed by the demonstration of immunohistochemically positive neuro-endocrine markers (chromogranin, synaptophysin and NCAM CD56) [9]. One positive marker is sufficient if the immunoreactivity is diffuse and clear cut. In addition, 42% of LCNEC express thyroid transcription factor (TTF)-1, which allows assessment of their lung primary origin [10–12]; however, expression of cytokeratins 1, 5, 10 and 14 (34βE12) is absent [11, 13].

LCNEC can be combined and diagnosed as **combined large cell neuroendocrine carcinoma**. Twenty-five per cent of LCNEC are histologically heterogeneous: combined LCNEC is defined as a combination of LCNEC with components of adenocarcinoma, squamous cell carcinoma, giant cell carcinoma and/or spindle cell carcinoma. In view of shared clinical, epidemiological, survival and neuroendocrine properties between LCNEC and small cell carcinoma, these heterogeneous tumours are classified as combined large cell neuroendocrine carcinoma in order to pinpoint their essential component, which is the LCNEC. It should be noted that combinations with small cell carcinoma are frequent (~15% of

small cell carcinoma are combined with LCNEC), although they are then classified as small cell carcinoma combined.

The major **differential diagnosis** for LCNEC is atypical carcinoid and basaloid carcinoma. LCNEC is distinguished from atypical carcinoid primarily by a higher mitotic index (≥11 per 2 mm^2) and extensive necrosis. Differential diagnosis between LCNEC and basaloid carcinoma is more difficult, as both tumours disclose palisading and may show rosettes. However, basaloid carcinoma are usually negative for neuroendocrine markers, and cytokeratin 1, 5, 10 and 14 are expressed in basaloid carcinoma, whereas they are typically negative in LCNEC [11, 13].

The **prognosis** of LCNEC depends on the presentation stage, which is often III–IV at diagnosis. Clinical prognostic criteria do not differ from other NSCLC, except that tumour spread is relatively more extensive in LCNEC. There is a significantly shorter survival for stage I LCNEC when compared with stage I NSCLC [14] and stage I large cell carcinoma [15]. Although there has been no significant difference in some series in the prognosis between LCNEC and small cell lung cancer (SCLC) after stratification by stage [3], the outcome of carefully staged LCNEC may be better than previous studies have indicated [16]. There is ongoing debate concerning whether the presence of neuroendocrine differentiation, which is associated with a rather poor prognosis in LCNEC, has any prognostic significance in other NSCLC (also called NSCLC with neuroendocrine differentiation). Some studies indicate a worse prognosis [15, 17, 18], although others do not [19–23]. No difference in response to chemotherapy between NSCLC with or without neuroendocrine carcinoma differentiation has been detected.

The LCNEC has specific **molecular genetic characters** similar to SCLC, such as allelic losses at 3p21, fragile histidine triad gene, 3p22.24, 5q21, 9p21, and the Rb gene. All of these markers correlate with poor prognosis in these tumours, as well as point mutation of P53 [24]. LCNEC may carry very similar chromosomal imbalances to SCLC [25–27]. LCNEC have P53/Rb mutational patterns that are also shared with SCLC [28–31], such as a high frequency of P53 mutation, blc2 overexpression and lack of bax expression [30], high telomerase activity [32] but lower frequency of Rb, $P14^{ARF}$ loss of protein and E2F1 overexpression [33, 34]. They lack MEN1 mutation and corresponding 11q13 allelic deletion. As SCLC, they display a low frequency of P16 loss cyclin D1 and E overexpression [35]. Fas is downregulated, but its ligand FasL is strongly upregulated [36].

2. Basaloid carcinoma

Basaloid carcinoma is the second variant of large cell carcinoma, showing a solid nodular or trabecular growth pattern with peripheral cell palisading. Tumour cells are monomorphic, rather small and cuboidal to fusiform with highly granular chromatin. Cytoplasm is scant and mitotic rate is high (15–50 per 2 mm^2). Squamous differentiation is absent, in contrast with the basaloid variant of squamous cell carcinoma, which is a mixture of a basaloid component and squamous differentiation. Comedo-type necrosis is frequent and rosettes can be seen in one-third of cases, and, in contrast with LCNEC, neuroendocrine markers are generally negative. The basal cell markers, cytokeratins 1, 5, 10 and 14, recognised by the 34βE12 antibody, are positive in all cases of basaloid carcinoma. In addition, basaloid carcinoma do not express TTF-1 [11].

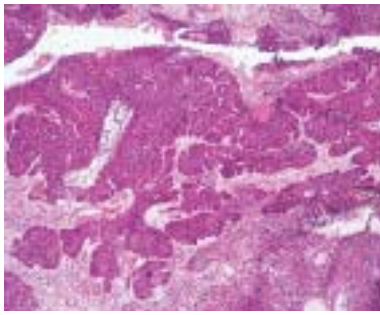
Although most basaloid carcinoma that present at stage I–II are operable tumours, they have a dismal **prognosis**. In contrast with poorly differentiated squamous cell carcinoma [37]; however, another series has challenged this first hypothesis of poorer prognosis [38]. The authors have identified 97 cases over 1,516 surgical resections of NSCLC and found a significant lower rate of 5 years' survival than other NSCLC (p=0.0005) [49].

Although initially described as two forms, one pure and one mixed (basaloid squamous), the latter is now considered as the basaloid variant of squamous cell carcinoma. Small cell carcinoma enters the **differential diagnosis** of basaloid carcinoma due to small cell size and high mitotic rate, but its nuclear-to-cytoplasmic ratio is higher in small cell carcinoma and nuclear chromatin is obviously different.

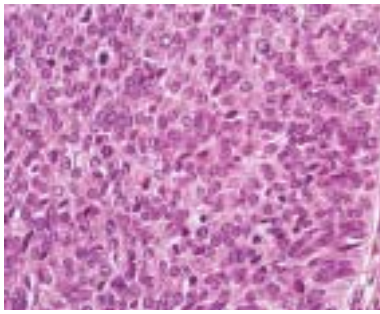
With respect to the **molecular genetics,** P53 mutation and Rb pathway alterations (loss of P16, hyperexpression of cyclin D1 and E) occur with the same frequency in basaloid carcinoma as in other NSCLC. P53 appears to be more frequent, as well as bcl2 over bax hyperexpression.

3. Lymphoepithelioma-like carcinoma

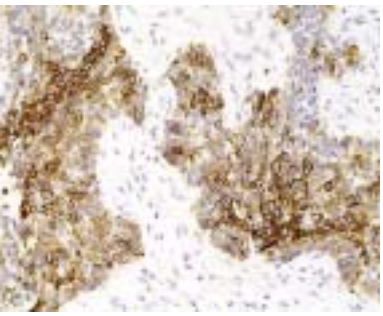
Pulmonary lymphoepithelioma-like carcinoma is characterised by a syncytial growth pattern, large vesicular nuclei with prominent nucleoli and dense lymphocytic infiltration [40–44]. The prominent lymphoid reaction consists of mature lymphocytes mixed with plasma cells and histocytes. The lymphoid component is seen even in



Basaloid carcinoma (low magnification): large implantation of tumour along the bronchial mucosa with infiltrating lobules showing finger-like and petaloid features.



Basaloid carcinoma (high magnification): tumour cells of small cell size are monotonous, with regular nuclei and form peripheral palisading.



Expression of cytokeratin 1, 5, 10 and 14 (antibody CK34bE12) in a basaloid carcinoma.

metastatic sites. EBER-1 RNA is present in the nuclei of the large undifferentiated neoplastic cells. The prominent inflammatory cell infiltrate may lead to consideration of inflammatory pseudotumour malignant lymphoma [45] or primary lymphoid hyperplasia of the lung. Immunohistochemical staining allows recognition of the malignant epithelial cells, characteristically patchy in distribution, and the CD8 expression of the lymphocytic infiltrate. Lymphoepithelioma-like carcinoma is characterised by the presence of Epstein Barr virus viral sequences, reflecting viral (EBER-1)-dependent transformation of lung epithelial cells. This finding is quite common in Chinese cases, but is inconsistent in Europe.

4. Other variants

Clear cell carcinoma and large cell carcinoma with rhabdoid phenotype are described here to demonstrate that they are lung tumours, since clear cell carcinoma, with their large polygonal cells with water-clear or foamy cytoplasm, resemble metastatic clear cell carcinoma arising in organs such as the kidney, thyroid and salivary glands.

In large cell carcinoma with rhabdoid phenotype, at least 10% of the tumour cell population consists of rhabdoid cells. These are characterised by eosinophilic cytoplasmic lobules, consisting of whirls of intermediate filaments immunostained for vimentin, cytokeratin or even desmin antibody. They may display positive neuroendocrine markers. Large cell carcinoma with rhabdoid phenotype has to be clearly distinguished from rhabdomyosarcoma. There are no specific clinical, histopathological or genetic criteria that are predictive of prognosis in these two last variants.

Conclusion

Large cell carcinoma now escape the waste basket of undifferentiated tumours thanks to the new WHO classification (1999 and 2004), at least for their two main variants, specifically in epidemiological, biological and therapeutic trials.

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Educational questions

1. Which of the following two variants of large cell carcinoma is relevant and useful for prognosis and therapeutic response assessment?
   a) LCNEC.
   b) Basaloid carcinoma.
2. Which lung cancer diagnosis is less useful?
   a) Large cell carcinoma.
   b) NOS.
3. What is the consequence of failure to subclassify large cell carcinoma?
   a) Absence of diagnostic consistency.
   b) Lack of epidemiological specificity.
   c) Failure to determine the most effective therapy.
   d) Inability to target therapy.
4. Which of the following diagnoses are useful for preventing a misdiagnosis of metastatic tumour?
   a) Lymphoepithelioma-like carcinoma.
   b) Adenocarcinoma with rhabdoid phenotype.
   c) Clear cell carcinoma.
5. Which of the respective metastatic or other tumours enter the differential diagnosis of the last subclasses, respectively?
   a) Carcinoma of the naso-sinusal tract, inflammatory pseudo-tumour, malignant lymphoma.
   b) Chondrosarcoma, rhabdomyo-sarcoma, glomus tumour.
   c) Carcinomas of the kidney, thyroid and salivary glands.

For answers go to www.breathe-cme.org

Suggested further reading

Travis WD, Brambilla E, Muller-Hemerlink HK, Harris CC, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, IARC Press, 2004.