

Pathology of Lung Cancer

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Contents

3.1	Introduction	39
3.2	Preinvasive Lesions	40
3.2.1	Squamous Dysplasia and Carcinoma In Situ	40
3.2.2	Atypical Adenomatous Hyperplasia	41
3.2.3	Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)	41
3.3	Squamous Cell Carcinoma	42
3.4	Adenocarcinoma	42
3.5	Small Cell Carcinoma	45
3.5.1	Combined Small Cell Lung Cancer	46
3.5.2	Differential Diagnosis	46
3.6	Adenosquamous Carcinoma	47
3.6.1	Large Cell Neuroendocrine Carcinoma	48
3.6.1.1	Clinical Features	48
3.6.1.2	Differential Diagnosis	49
3.6.2	Basaloid Carcinoma	49
3.6.2.1	Differential Diagnosis	49
3.7	Large Cell Carcinoma	50
3.8	Carcinomas with Pleomorphic Sarcomatoid, or Sarcomatous Elements	50
3.8.1	Carcinosarcoma and Pulmonary Blastoma	50
3.9	Typical And Atypical Carcinoid	51
3.10	Conclusions	42
	References	42

3.1 Introduction

With 169,500 new cases per year in the United States and 182,000 new cases per year in Europe, lung cancer is the most common worldwide diagnosed cancer and the major cause of mortality (Parkin et al. 1999), with 157,400 cancer deaths in the US (Greenlee et al. 2001) and 190,000 cancer deaths in the European Union in 2001. Although the incidence of cancer has declined among men in the United States since 1980 (Travis et al.

1996), its rate is increasing among women (Greenlee et al. 2001), as a consequence of the increased proportion of women who smoke.

This review focuses primarily on the histology of lung cancer. The histologic evaluation for lung cancer diagnosis is based on several types of biopsy specimens, including bronchoscopy or fine needle biopsies and video-assisted thoracoscopic biopsy, as well as wedge resection and lobectomy (or pneumonectomy). Light microscopy is sufficient for the diagnosis of most lung cancer types and subtypes, reducing the need for histochemical stains or immunohistochemistry to a few histologic types. The international standard for histologic classification of lung tumors is that proposed by the World Health Organization (WHO) and the International Association for the Study of Lung Cancer (IASLC; Table 3.1) (Travis et al. 1999). The four major histologic types of lung cancer are squamous cell carcinoma, adenocarcinoma – the incidence of which is increasing at the expense of squamous cell carcinoma – small cell carcinoma (SCLC) and large cell carcinoma. These major types have been classified into subtypes, the clinical significance of which might be extremely important – for example, bronchioloalveolar carcinoma (BAC) as a variant of adenocarcinoma (Travis et al. 1999).

Although lung cancer can be divided into many subtypes, the most important distinction is between SCLC and non-small cell lung carcinoma (NSCLC). However, this is an extremely simplistic distinction between these subtypes and its use is not recommended because it may obscure the clinical significance of specific subtypes such as BAC. Nevertheless, importance has been given to this distinction because of the major clinical differences in presentation, metastatic spread and response to therapy of SCLC. Histologic heterogeneity is an important feature of the pathology of lung cancer, which consists of a variety of histological types that derive from a pluripotent stem cell (Churg 1978; Horie and Ohta 1981; McDowell and Trump 1981; Auerbach et al. 1982; Roggli et al. 1985; Mooi et al. 1990). This histologic heterogeneity is apparent on light microscopic

Table 3.1. WHO/IASLC Histologic Classification, 3rd edn, 1999 (Travis et al. 1999)

Preinvasive Lesions
Squamous Dysplasia/Carcinoma in situ
Atypical adenomatous hyperplasia
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Squamous cell carcinoma
Variants
Papillary
Clear cell
Small cell
Basaloid
Small cell carcinoma
Combined small cell carcinoma
Adenocarcinoma
Acinar
Papillary
Bronchioloalveolar carcinoma
Non-mucinous
Mucinous
Mixed mucinous and non-mucinous or indeterminate
Solid adenocarcinoma with mucin
Adenocarcinoma with mixed subtypes
Variants:
Well-differentiated fetal adenocarcinoma
Mucinous ("colloid") adenocarcinoma
Mucinous cystadenocarcinoma
Signet ring adenocarcinoma
Clear cell adenocarcinoma
Large cell carcinoma
Variants
Large cell neuroendocrine carcinoma
Combined large cell neuroendocrine carcinoma
Basaloid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Large cell carcinoma with rhabdoid phenotype
Adenosquamous carcinoma
Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements
Carcinomas with spindle and/or giant cells
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Other
Carcinoid tumor
Typical carcinoid
Atypical carcinoid
Carcinomas of salivary gland type
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Others
Unclassified carcinoma

WHO = World Health Organization; IASLC = International Association for the Study of Lung Cancer

examination in at least 30% of lung cancers, and it is even more frequently seen using electron microscopy. For these reasons, it is appropriate to use the term *non-small cell lung carcinoma* in small tissue specimens when it is impossible to ascertain a histologic subtype.

3.2 Preinvasive Lesions

The concept of the preinvasive lesion has evolved, as evidenced by the fact that the topic was not even mentioned in the 1967 WHO classification (Travis 2001), whereas three types are now described in the 1999 WHO/IASLC classification (Travis et al. 1999). In addition to bronchial squamous dysplasia and carcinoma in situ (WHO 1981), two new lesions have been described, one for peripheral adenocarcinoma, the atypical adenomatous hyperplasia (AAH) (Mori et al. 1993), and one thought to be a preinvasive condition for carcinoids, the diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (Aguayo et al. 1992). According to the concept of field cancerization, preinvasive lesions are multicentric processes, distal or peripheral, and usually multiple. The pathology of preinvasive lesions for lung cancer has attracted increasing interest in recent years because of the growing importance of early detection through the screening of high risk patients using fluorescence bronchoscopy (Lam et al. 1998) and low-dose spiral or helical CT (Gartenschlager et al. 1998; Itoh et al. 1998).

3.2.1 Squamous Dysplasia and Carcinoma in Situ

Bronchial carcinogenesis is now conceptualized as a multi-step, multicentric process involving transformation of the normal bronchial mucosa through a continuous spectrum of lesions, including basal cell hyperplasia, squamous metaplasia, mild, moderate or severe dysplasia and carcinoma in situ (Auerbach et al. 1957; Becci et al. 1978; Carter 1978; Bennett et al. 1993; Woolner 1993; Colby et al. 1995; Brambilla et al. 1998).

According to the thickness and the severity of cytologic atypia within the bronchial epithelium, dysplasia is subclassified as mild, moderate or severe for the lower-third, two-thirds or all thicknesses, respectively, of the bronchial epithelium that's involved (Travis et al. 1999; Travis 2001). Carcinoma in situ shows full-thickness involvement of the epithelium and marked cytologic atypia. It differs from severe dysplasia by the lack

of visible maturation and by the orientation of the cells from the basal to luminal part of the epithelium. Although these morphologic changes are part of a progressive continuum, they can be separated into categories with a rather good reproducibility following the definition given in the new WHO classification. Dysplasia should not be confused with reactive atypia, which is secondary to inflammation. The term, *microinvasive squamous cell carcinoma*, is not recommended since microinvasive tumors are T1 squamous cell carcinomas and should be distinguished from carcinomas in situ with involvement of submucosal glands (Travis et al. 1999; Travis 2001).

3.2.2

Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia (AAH) is a millimetric lesion that is considered a preinvasive state for bronchioloalveolar carcinoma. AAH is a bronchioloalveolar proliferation that resembles but falls short of criteria for BAC of the nonmucinous type (Fig. 3.1) (Noguchi and Shimosato 1995). This finding was an incidental discovery during a histologic examination of a lung cancer resection specimen (Miller 1990; Kitamura et al. 1999; Travis et al. 1999). The incidence of AAH varies from 5.7 to 21.4%, depending on the size of the sample and the criteria used for diagnosis, as well as on the range of ages in reported autopsy studies (Nakani-

shi 1990; Miller 1990; Carey et al. 1992; Weng et al. 1992). Most lesions are less than 5 mm in diameter and are multiple. Histologically, AAH consists of a focal proliferation of slightly atypical cuboidal to low-columnar epithelial cells along alveolar walls and respiratory bronchioles (Fig. 3.1). Alveolar septa may present slight thickening and discrete lymphoid infiltration.

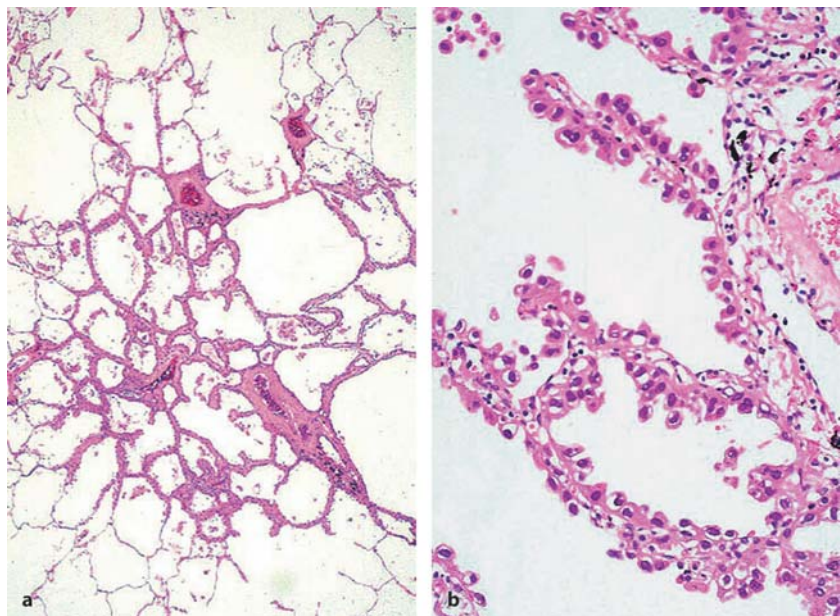
Atypical adenomatous hyperplasia must be distinguished from bronchiolization, which is a colonization of peribronchiolar alveoli by bronchial epithelial cells, essentially seen in cases of interstitial lung fibrosis. AAH should also be distinguished from BAC (Mori et al. 1996), although a considerable overlap exists between these two types of lesion (Mori et al. 1993; Kitamura et al. 1999; Ritter 1999; Travis et al. 1999). BAC lesions are usually more than 5 mm in diameter and present more severe atypical cells, with no gaps between adjacent epithelial cells. It has not been proven that patients with lung cancer associated with AAH (having one or several lesions) have any different prognosis from those with lung cancer without associated AAH (Suzuki et al. 1997).

3.2.3

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is thought to represent a precur-

Fig. 3.1. Atypical alveolar hyperplasia. **A** This millimeter-sized bronchioloalveolar proliferation is well defined with mild thickening of the alveolar walls (HES $\times 40$). **B** Hyperplastic pneumonocytes show minimal atypia and leave gaps between them (HES $\times 200$)



sor lesion for carcinoid tumors because a subset of patients afflicted with this condition present with one or more carcinoid tumors (Travis et al. 1999). It is a rare condition involving peripheral airways at the level of terminal and respiratory bronchioles characterized by linear neuroendocrine cell hyperplasia and tumorlets (Aguayo et al. 1992). Patients with DIPNECH may present with a form of interstitial lung disease with small airway obstruction caused by the frequent association of the disease with bronchiolar obstructive fibrosis (Aguayo et al. 1992). Some patients, however, do not have any type of fibrosis. In most cases where neuroendocrine cell hyperplasia and tumorlets are encountered, they are secondary to airway inflammation or fibrosis and do not belong to this idiopathic type (Whitwell 1955; Ranchod 1977; Pelosi et al. 1992; Canessa et al. 1997). Neuroendocrine hyperplasia is often observed in close vicinity with carcinoids, which, again, are not considered to be DIPNECH, *per se*.

3.3 Squamous Cell Carcinoma

Squamous cell carcinoma accounts for approximately 30% of all lung cancers in the United States (Travis et al. 1995) and 45% in Europe. Twenty years ago, it was

the most frequent histological type of lung cancer in Europe. Since then, it has progressively decreased, whereas adenocarcinoma has increased in incidence. Two-thirds of squamous cell carcinomas present as central tumors, whereas one-third presents in the form of peripheral tumors, although the primary bronchial site may be easily detected at histology (Tomashefski et al. 1990; Colby et al. 1995). The morphologic features that characterize squamous differentiation include intercellular bridging and keratinization (or individual cell keratinization or squamous pearl formation) (Fig. 3.2). These features are readily apparent in well-differentiated tumors, but difficult to detect in poorly-differentiated tumors (Carlile and Edwards 1986). However, this spectrum of differentiation has not been demonstrated to correlate with the prognosis in lung squamous cell carcinoma. Segmental bronchi, more often than lobar and mainstem bronchi, are the primary site of squamous cell carcinoma (Melamet et al. 1977). Variants described in the WHO classification include papillary, clear cell, small cell (Churg et al. 1980) and basaloid subtypes (Travis et al. 1999). This last variant has a dismal prognosis, compared with poorly-differentiated squamous cell carcinoma (Moro et al. 1994; Brambilla et al. 1992a). Papillary squamous cell carcinoma often shows a pattern of exophytic endobronchial growth (Sherwin et al. 1962; Dulmet-Brender et al. 1986).

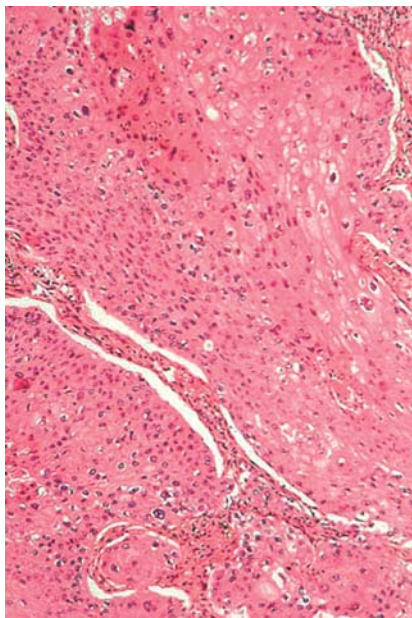


Fig. 3.2. Squamous cell carcinoma, well differentiated. Keratinized cytoplasm and keratin pearls are characteristic of squamous differentiation (HES $\times 100$)

3.4 Adenocarcinoma

Adenocarcinomas account for about 30% of lung cancer in Europe as well as in the United States (Travis et al. 1995). Most primary pulmonary adenocarcinomas, in contrast with metastases, are highly heterogeneous and consist of a mixture of histologic subtypes. This justified the addition of a new subtype in the 1999 WHO classification called *mixed subtype*. The other four major subtypes include acinar (gland forming), papillary, bronchioloalveolar and solid with mucous formation, and were recognized in the 1981 WHO classification.

Most adenocarcinoma lesions are histologically heterogeneous, consisting of two or more of the histologic subtypes. Eighty percent of all lung adenocarcinoma diagnosed today is classified as this mixed subtype. The acinar and papillary (Fig. 3.3) subtypes are recognized by their architectural pattern of tumor cell growth and invasion. A substantially different definition has been given to bronchioloalveolar carcinoma (BAC subtype) which should be restricted to tumors

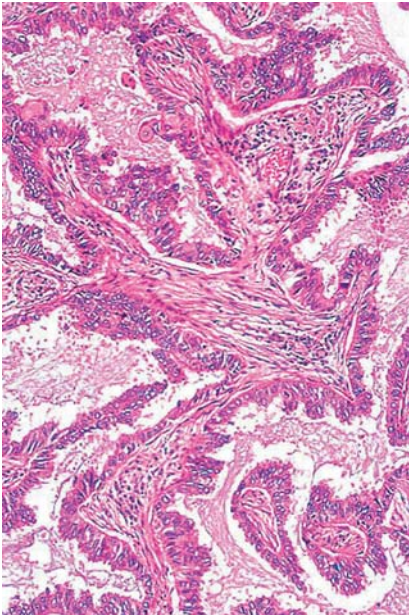


Fig. 3.3. Adenocarcinoma, papillary subtype. The malignant epithelial cells form papillary structures along the surface of thick fibrovascular cores (HES $\times 100$)

that grow in a purely lepidic fashion. The solid type is a poorly differentiated carcinoma presenting intracytoplasmic mucins that should be at least of five mucin droplets in two different high-power fields. The mucin stains recommended are PAS (periodic acid-Schiff) with diastase digestion and Kreyberg staining with alcian blue. It is common to observe central scars in pulmonary adenocarcinoma that contain invasive components and a focal BAC-like pattern at the periphery of the tumor.

Bronchioloalveolar carcinoma is uncommon, and probably restricted to fewer than 3% of all lung malignancies (Travis et al. 1995). In the new 1999 WHO/IASLC classification, BAC is defined as a tumor showing lepidic growth along respected alveolar septa, with intact elastic and basal lamina frames and without invasive growth (Fig. 3.4). The lack of invasive growth was added as an essential criterion (Travis et al. 1999), based on clinico-pathological data indicating that in patients with lesions smaller than 2 cm, BAC may be curable by economic surgical resection (Noguchi et al. 1995). As a result of the definition, this tumor can be considered to be a carcinoma in situ at alveolar site. As a consequence of this revised definition of BAC, the literature dealing with these tumors needs complete re-evaluation. Indeed, before the most recent classifica-

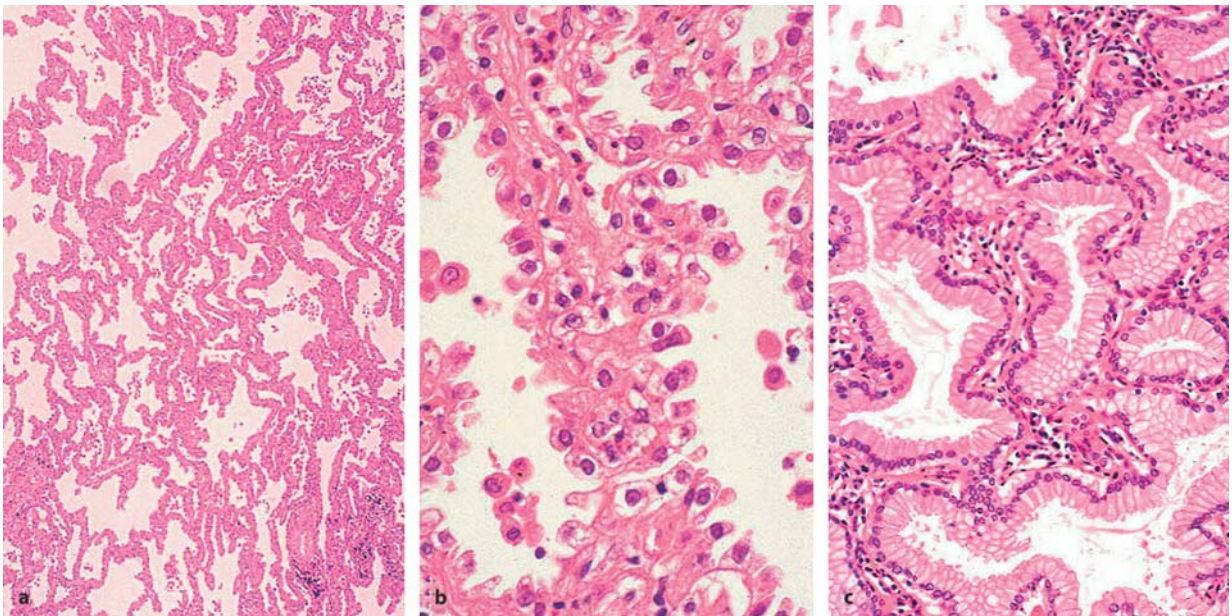


Fig. 3.4. Bronchioloalveolar carcinoma. **A** At low magnification, uniform cells proliferate along alveolar septa, the architecture of which is preserved (HES $\times 40$). **B** Non mucinous bronchioloalveolar carcinoma: cuboidal cells with a hobnail appearance proliferating along normal

alveolar walls (HES $\times 400$). **C** Mucinous bronchioloalveolar carcinoma. The tumor consists of tall columnar cells with basally oriented nuclear and abundant apical cytoplasmic mucin (HES $\times 200$)

tion, BAC included tumors with obvious invasive growth (WHO 1957, 1981; Barsky et al. 1994).

BAC is not a unique feature for lung adenocarcinoma, since about 15% of digestive mucinous carcinoma metastases might mimic the histologic appearance of BAC. TTF-1 immunostaining restricted to primary lung adenocarcinoma is of great help in making this distinction.

More than 50% of previously identified BACs present focal central desmoplastic scarring tissue or intraalveolar complex papillary growth, while the lepidic growth starts around the edge of the scar (Fig. 3.5A) (Daly et al. 1991). For tumors showing malignant tumor cell nests in a desmoplastic stromal reaction, the diagnosis is adenocarcinoma *mixed subtype*; and the various subtypes present (such as acinar, papillary or BAC) should be mentioned. They are no longer considered to be pure BAC (Fig. 3.5B) (Daly et al. 1991; Colby et al. 1995).

BACs have two major cytological subtypes: nonmucinous (see Fig. 3.4B) and mucinous (see Fig. 3.4C) (Travis et al. 1999). They are rarely mixed (i.e. a combination of mucinous and nonmucinous cells (Travis et al. 1999). The majority of BACs are mucin-producing, followed by the nonmucinous type, while only about 12% are a mixture of both (Manning et al. 1984; Daly et al. 1991).

The nonmucinous BACs are more likely than the mucinous type to be solitary (Manning et al. 1984). These tumors are composed of cuboidal cells prolifera-

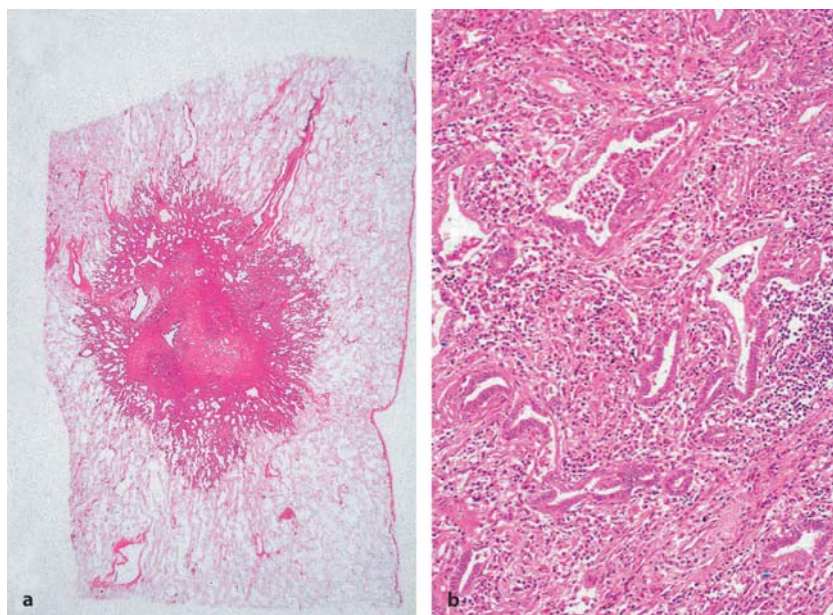
ting along alveolar septa (see Fig. 3.4B) and exhibiting a hobnail appearance. Specific nuclear inclusions are apparent in half of the nonmucinous tumor cells stained with diastase digested PAS and immunohistochemically for surfactant apoprotein. At electron microscopy, these inclusions form a network of 40-nm diameter microtubules (Clayton 1986; Singh et al. 1986). Nonmucinous BACs consist of Clara cells and type II pneumocytes, which are a common type of stem cell for distal bronchioles and alveoli identified in fetal lung.

The mucin-producing BACs tend to be more multicentric and characteristically exhibit mucin production (Manning et al. 1984). They may cause lobar consolidation resembling pneumonia on gross examination. Histologically, these tumors consist of tall columnar cells with abundant apical cytoplasmic mucin and small basally-oriented regular nuclei (see Fig. 3.4C) lining thin alveolar septa. The alveolar and bronchiolar spaces are filled with abundant mucin.

According to the 1999 WHO/IASLC classification, a final diagnosis of BAC can only be achieved on examination of a surgical resection specimen. Small biopsies obtained by bronchoscopy or fine needle sampling may show a lepidic growth pattern suggesting the possibility of BAC, but such samples are not sufficient to exclude the presence of an invasive growth.

Several important clinico-pathological studies have shown the clinical significance of BAC (Noguchi et al. 1995; Suzuki et al. 2000; Yokose et al. 2000).

Fig. 3.5. Adenocarcinoma, mixed subtype. **A** This adenocarcinoma has extensive bronchioloalveolar growth at the periphery (HES $\times 20$). **B** An invasive growth is observed in the central scarring area (HES $\times 200$)



Noguchi et al. (1995) reported on a large series of 236 smaller than 2 cm. peripheral lung adenocarcinoma cases where the patients had 100% 5-year survival. These were identified as pure BAC, in contrast to “invasive BAC,” which is associated with higher mortality and reduced survival. Suzuki et al. (2000) demonstrated that the size of the fibrotic scar in a series of 100 less than 3 cm peripheral adenocarcinoma cases was correlated with 100% 5-year survival associated with a scar size of 5 mm or less, in contrast to 70% for patients with larger scars (5 to 15 mm) and 40% survival for patients with larger than 15 mm central scars. In this study, the size of central fibrosis was an independent prognostic factor on multivariate analysis ($p=0.01$), as significant as vascular invasion ($p=0.024$) and lymph node metastasis ($p=0.024$). Later, Yokose et al. (2000) studied multiple pathologic factors for in the prognostic assessment in 200 patients. They found that 100% 5-year survival was associated with at least one of the following features: (1) a pattern of lepidic growth of more than 75%, (2) central scar measuring 5 mm or less, and (3) lack of destruction of the elastic fiber framework by tumor cells. The most significant determinants of shorter survival in the multivariate analysis were vascular invasion ($p<0.001$) and more than 25% papillary or invasive growth ($p=0.043$).

Several additional unusual variants also were recognized, such as well-differentiated fetal adenocarcinoma (Kodama et al. 1984a), mucinous (“colloid”) adenocarcinoma (Moran et al. 1992), mucinous cystadenocarcinoma (Kragel et al. 1990, 1991; Higashiyama et al. 1992), signet ring carcinoma (Kish et al. 1989) and clear cell adenocarcinoma (Travis et al. 1999). Two unusual gross patterns of adenocarcinoma include the endobronchial polypoid adenocarcinoma (Kodama et al. 1984b) and pseudomesotheliomatous adenocarcinoma (Harwood et al. 1976; Lin et al. 1980; Koss et al. 1992).

3.5 Small Cell Carcinoma

Small cell lung carcinoma accounts for 25% of all lung cancers in the United States as well as in Europe (Travis et al. 1995). Two-thirds of SCLC are proximal and present as a perihilar tumor. They occur in a bronchial location, infiltrate the bronchial submucosa and subsequently lead to bronchial obstruction by circumferential compression. SCLCs are not commonly observed in a surgical specimen since extensive lymph node metastasis is common and the tumor is not surgically curable. Macroscopically, the tumor is soft, friable, white-

tan and extensively necrotic. Extensive lymph node metastasis is highly frequent and fewer than 5% of cases present as a solitary coin lesion (Gephardt et al. 1988; Kreisman et al. 1992).

The 1999 WHO/IASLC classification presents only two types of SCLC, SCLC (with pure SCLC histology) and combined SCLC (combined with any non-small cell type – see Table 3.1) (Travis et al. 1999). The two subtypes, oat cell carcinoma and intermediate cell type, that were proposed in the 1981 WHO classification, as well as the category of mixed small cell/large cell proposed in 1988 by the IASLC recommendation, were discarded from the new classification because of difficulties in the reproducibility of these subtypes and the lack of confirmation that these patients had different prognoses (Hirsch et al. 1988; Fraire et al. 1992).

Small cell lung cancer has a distinctive histological appearance. Tumor cells are small, not exceeding the size of 3 lymphocytes. They have a round or fusiform shape, scant cytoplasm with a nuclear-to-cytoplasmic ratio of 9 to 10, a fine, granular nuclear chromatin (salt and pepper appearance) and absent or inconspicuous nucleoli (Fig. 3.6) (Travis et al. 1999). Owing to the scarcity of cytoplasm, nuclear molding and smearing of nuclear chromatin is frequent, caused by crush artifact. There is usually an extensive necrosis and a mitotic rate exceeding 20 and reaching 100 mitosis per 2 mm² area.

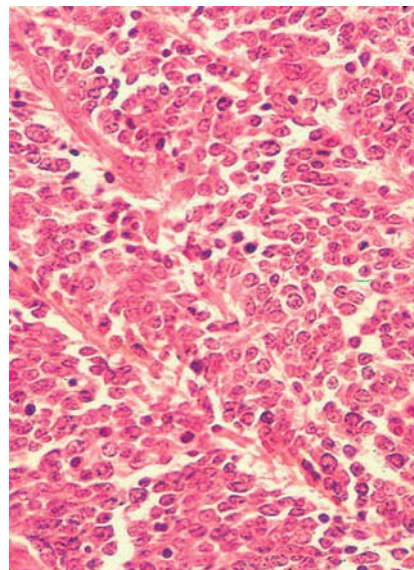


Fig. 3.6. Small cell carcinoma. This tumor consists of densely packed small tumor cells with scant cytoplasm, finely granular nuclear chromatin, inconspicuous or absent nucleoli and multiple metastases (HES $\times 400$)

Most often, the growth pattern consists of diffuse sheets, although endocrine differentiations with rosettes, palisading, ribbons and organoid nesting might be present (Azzopardi 1959). The basophilic encrustation of vessel walls is known as the *Azzopardi effect* in necrotic areas (Azzopardi 1959).

Depending on the biopsy specimens, the tumor cell size of SCLCs might appear larger (this is often the case in well-fixed open biopsies).

3.5.1

Combined Small Cell Lung Cancer

The frequency of combined-SCLC depends on the extent of histologic sampling and on the extent of the associated component. Combined-SCLC represents about 10% (Hirsch et al. 1988) of SCLC if small biopsies are considered. However, in a recent study of surgically treated SCLC, using a conservative estimate of 10% of tumors showing non-small cell lung carcinoma for subclassifying a tumor as a combined variant of SCLC, 28% of the cases of SCLC showed a combination with non-small cell lung carcinoma, more commonly with large cell lung carcinoma, followed by adenocarcinoma and squamous cell carcinoma (Mangum et al. 1989; Hirsch et al. 1988; Mangum et al. 1989; Fraire et al. 1992; Mangum et al. 1989; Nicholson et al. 2002). Small cell lung cancer can also be associated with spindle cell carcinoma (Tsubota et al. 1992; Fishback et al. 1994), giant cell carcinoma (Fishback et al. 1994) and carcinosarcoma (Sümmermann et al. 1990). Immunohistochemistry might help to recognize the associated components. Cytokeratin antibody cocktails, for instance, tends to stain non-small cell lung carcinoma components, a good example of which is cytokeratin 1, 5, 10, 14 recognized by 34 β E12 (Sturm et al. 2001). However, evidence is lacking that pure small cell lung carcinoma and combined small cell lung carcinoma behave differently in terms of prognosis and response to therapy (Mangum et al. 1989). Following chemotherapy, a mixture of large cells, squamous cell and adenocarcinoma or giant cells with SCLC may be seen in 15 to 45% of the cases (Bégin et al. 1983; Sehested et al. 1986; Bepler et al. 1989; Brambilla et al. 1991).

3.5.2

Differential Diagnosis

Because SCLC has distinctive clinical properties and an aggressive clinical course, with frequent widespread

metastasis of presentation, common paraneoplastic syndrome and responsiveness to chemotherapy, the histologic classification of lung cancer often is simplified into SCLC versus NSCLC. A constellation of criteria are applied for the distinction between SCLC and LCNEC, including cell size, nucleoli, nuclear-to-cytoplasmic ratio, nuclear chromatin pattern, nuclear molding, cell shape (fusiform versus polygonal) and *Azzopardi phenomenon* (Table 3.2) (WHO 1981; Vollmer 1982; Travis et al. 1991; Travis et al. 1999).

Because of the unique properties of SCLC, agreement in regard to the distinction between SCLC from NSCLC is common among pathologists. Roggli et al. (1985) found 93% concordance for the diagnosis of SCLC among five observers and 98% among at least four of the five (Roggli et al. 1985). Disagreement among expert lung cancer pathologists over this distinction occurs in up to 10% of cases (Roggli et al. 1985; Vollmer et al. 1984), owing to the fact that sometimes LCNEC may adopt the nuclear features of SCLC. With the new description of LCNEC, the main differential resides in the distinction of SCLC from LCNEC (Table 3.2).

Crush artifact is common in small biopsy specimens, owing to the scarcity of stromal protection. This also can be seen in carcinoid tumors, lymphocytic infiltrates and poorly differentiated NSCLC. In these cases, cytology specimens might be helpful because the morphology may be more diagnostic than in a small biopsy specimen. Immunohistochemistry for neuroendocrine differentiation, keratins and common leukocyte antigen (lymphoid marker) can be useful in marking SCLC versus lymphoid cells (Marchevsky et al. 1984). Recently, TTF-1 has been shown to be of great help in distinguishing SCLCs, which are 85% positive for TTF-1 nuclear staining, from other small cell proliferations, such as the small cell variant of squamous cell carcinoma and basaloid carcinoma, both of which are always TTF-1 negative (Ordonnez 2000; Sturm et al. 2001).

The most useful and specific neuroendocrine markers for distinguishing SCLC in formalin-fixed, paraffin-embedded tissue sections are chromogranin A, synaptophysin and neural cell adhesion molecule, especially the 123C3 clone and CD56 (Travis et al. 1991; Brambilla et al. 1992b; Guinee et al. 1994; Kaufmann et al. 1997; Lantuejoul et al. 1998; Linnoila et al. 1988). NCAM is of great value in separating NSCLC from SCLC, owing its surprising resistance to crush artifact (Lantuejoul et al. 1998). Twenty-five percent of all cases were found to be negative for the three neuroendocrine markers, chromogranin, synaptophysin and Leu-7 by Guinee et al.

Table 3.2. Light microscopic features for distinguishing small cell carcinoma from large cell neuroendocrine carcinoma^a

Histologic feature	Small cell carcinoma	Large cell neuroendocrine carcinoma
Cell Size	Smaller (less than diameter of 3 lymphocytes)	Larger
Nuclear/Cytoplasmic Ratio	Higher	Lower
Nuclear Chromatin	Finely granular, uniform	Coarsely granular or vesicular Less uniform
Nucleoli	Absent or Faint	Often (not always) present May be prominent or faint
Nuclear Molding	Characteristic	Less prominent
Fusiform Shape	Common	Uncommon
Polygonal shape with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear	Frequent	Uncommon
Basophilic staining of vessels and stroma	Occasional	Rare

^a From: Travis WD, Linnoila RI, Tsokos MG, et al. (1991) Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol* 15:529–533, with permission

(1994). This percentage has dropped considerably to less than 3% with the addition of NCAM to the panel of specific neuroendocrine markers for the diagnosis of SCLC (Lantuejoul et al. 1998). Although neuron-specific enolase (NSE) has been advocated as a useful marker for neuroendocrine differentiation, it is relatively nonspecific due to the fact that 60% of NSCLCs stain with NSE antibodies (Travis et al. 1991; Brambilla et al. 1992b). Keratin (AE1/AE3) and epithelial membrane antigen (EMA), as well as TTF-1 (Thyroid Transcription Factor-1), stain virtually all SCLCs in open lung biopsy and transbronchial biopsy specimens (Travis et al. 1991; Guinee 1994; Ordonnez 2000; Sturm et al. 2001). In contrast, a specific set of cytokeratins never expressed in neuroendocrine proliferations (CK 1, 5, 10, 14) called *34βE12* is always absent in pure SCLC. In the cases where common cytokeratins are negative in a

suspected SCLC, the pathologist should exclude other possibilities such as chronic inflammation, lymphoma (CD45 positive), primitive neuroectodermal tumor and small cell round sarcoma. One difficulty resides in the fact that a large proportion of SCLCs express the antigen MIC-2, as do primitive neuroectodermal tumors and small round cell sarcoma. It is important to recognize that this distinction is based primarily on light microscopy (Table 3.2) (Travis et al. 1999). Since no single monoclonal antibody can reliably distinguish SCLC from NSCLC (Tome et al. 1990; Brambilla et al. 1992b), a set of reliable markers should be considered (Table 3.3).

3.6 Large Cell Carcinoma

Large-cell carcinoma is a tumor that shows no differentiation pattern for allowing classification into squamous cell carcinoma, adenocarcinoma or small cell carcinoma. These poorly-differentiated tumors most often arise in the lung periphery, although they may be located centrally. They frequently appear at gross examination as large, necrotic tumors. Histologically, they consist of sheets or nests of large polygonal cells with vesicular nuclei and prominent nucleoli (Fig. 3.4) (WHO 1981). Although they are undifferentiated by light microscopy, features of squamous cell or adenocarcinoma might be found at electron microscopy ex-

Table 3.3. Histochemical differential diagnosis between small cell lung carcinoma, basaloid carcinoma and large cell neuroendocrine carcinoma

	NE Markers	TTF-1	Cytokeratins 1, 5, 10, 14
SCLC	+	+	–
Basaloid carcinoma	–	–	+
LCNEC	+	+/-	–

amination (Churg 1978; Horie and Ohta 1981; Kodama et al. 1985).

There are several variants of large cell carcinoma, some of which are of high clinical significance, as recognized in the new WHO/IASLC histologic classification of lung cancer (Table 3.1) (Travis et al. 1999). These include LCNEC (Travis et al. 1991, 1998, 1999), basaloid carcinoma (Brambilla et al. 1992a; Moro et al. 1994; Brambilla 1997), lymphoepithelial-like carcinoma (Butler et al. 1989; Pittaluga et al. 1993; Chan et al. 1995), clear cell carcinoma (Katzenstein et al. 1980) and large cell carcinoma with rhabdoid phenotype (Cavazza et al. 1996). Lymphoepithelial-like carcinoma is described as an Epstein-Barr virus- (EBV) dependent epithelial proliferation, more commonly seen in the upper respiratory tract.

Because lung cancers are classified according to the best-differentiated component, and areas of large cell carcinoma are frequently observed in poorly differentiated adenocarcinoma or squamous cell carcinoma, it is difficult to specifically and appropriately classify many lung cancers, in which only small pieces of tissue are available, owing to the common heterogeneity of these cancers. In such cases, the best diagnosis might be “non-small cell carcinoma” with the specification of the most obvious component (Auerbach et al. 1982; Chuang et al. 1984; Haratake et al. 1987).

3.6.1

Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinoma is a variant of large cell carcinoma. It is a high grade non-small cell neuroendocrine carcinoma that differs from atypical carcinoid and small cell carcinoma. Histologic criteria include: (1) neuroendocrine morphology (organoid, palisading, trabecular or rosette-like growth patterns – see Fig. 3.7); (2) non-small cell cytologic features (large size, polygonal shape, low nuclear-to-cytoplasmic (N/C) ratio, coarse or vesicular nuclear chromatin and obvious nucleoli); (3) high mitotic rate (≥ 11 per 2 mm^2) with a mean of 60 mitoses per 2 mm^2 ; (4) frequent necrosis and (5) at least one positive neuroendocrine immunohistochemical-specific marker or neuroendocrine granules by electron microscopy (Travis et al. 1991, 1999). It is difficult to diagnose LCNEC based on small biopsy specimens, because of the frequent lack of neuroendocrine morphology, without a substantial sampling of the tumors. Some criteria have been proposed based on cytology (Wiatrowska et al. 2001).

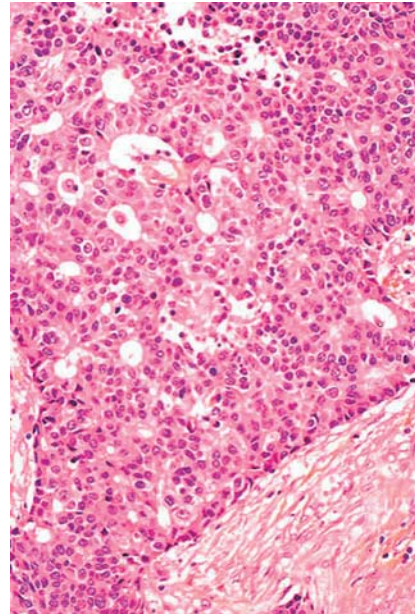


Fig. 3.7. Large cell neuroendocrine carcinoma. Numerous rosettes give this tumor a neuroendocrine morphologic appearance. Mitotic rate is high (HES $\times 200$)

The term *combined LCNEC* is used for tumors associated with other histologic types of NSCLC, such as adenocarcinoma or squamous cell carcinoma (Table 3.1) (Travis et al. 1999). Any combination of LCNEC with SCLC is diagnosed as *SCLC combined* (Travis et al. 1999). A variety of criteria must be used to separate SCLC from LCNEC (Table 3.2).

3.6.1.1

Clinical Features

Patients with LCNEC have a median age of 62 years (range 33–87 years) and are typically heavy cigarette smokers (Travis et al. 1991). They have a poor prognosis, with a survival rate of 5 to 10 years in, respectively, 27 and 11% of all cases, a significantly worse prognosis than patients with atypical carcinoid (AC) (Travis et al. 1998).

Iyoda et al. (2001) found the survival at 5 to 10 years to be 35.3% and 31.7%, respectively. In this study, a worse survival was observed for LCNEC, compared with classical large cell carcinoma NOS ($p=0.031$). Jiang et al. (1998) found a worse probability of survival for LCNEC compared with non-small cell carcinomas ($p=0.046$). It must be noted that the series are short and include several different stages and in particular few

stage I-II cases. For the moment, it has not been possible to show a difference in survival rates between LCNEC and SCLC (Travis et al. 1998; Beasley et al. 2000). Surgical resection is recommended, but it remains to be proved whether adjunctive radiation or chemotherapy are effective.

3.6.1.2

Differential Diagnosis

In 10% of the cases of NSCLC lacking neuroendocrine morphology, immunohistochemical neuroendocrine markers or neuroendocrine granules by electron microscopy can be demonstrated. Such tumors are called *non-small cell carcinomas* (adenocarcinoma, squamous cell carcinoma or large cell carcinoma) *with neuroendocrine differentiation* (NSCLC-NED) (Travis et al. 1991; 1999). Although Iyoda et al. (2001) found that the tumor size of large cell carcinomas with neuroendocrine differentiation was significantly larger than that for LCNECs, the survival was no different in this series from patients with LCNEC. At present time, the clinical significance of the diagnosis of NSCLC-NED is not known. Whether these tumors are responsive to SCLC chemotherapy regimens (Graziano et al. 1989; Linnoila et al. 1989; Gazdar et al. 1992) or whether expression of neuroendocrine markers may be an unfavorable prognostic factor (Berendsen et al. 1989; Kibbelaar et al. 1991; Skov et al. 1991; Carles et al. 1993; Pujol et al. 1993; Kiriakogiani-Psaropoulou et al. 1994; Linnoila et al. 1994; Schleusener et al. 1996) remains to be determined.

3.6.2

Basaloid Carcinoma

Basaloid carcinoma is the most prominent variant of large cell carcinoma after LCNEC (Moro et al. 1994; Brambilla 1997; Travis et al. 1999). Basaloid carcinoma comprises 3 to 4% of NSCLC in Europe. It occurs only in males and most of the tumors develop in proximal bronchi, where they frequently have an endobronchial component. Two-thirds of these tumors arise from long areas on bronchial mucosa and show prolonged and laterally extended in situ carcinoma. About half of the tumors present with a pure basaloid pattern that belongs to a variant of large cell carcinoma. The remaining cases have minor (less than 50%) of the components of squamous cell carcinoma or, more rarely, adenocarcinoma, and are thus classified as squamous cell carcinoma (basaloid variant) or adenocarcinoma, respectively. These tumors consist of a lobular, trabecular or palisading gross pattern of relatively small

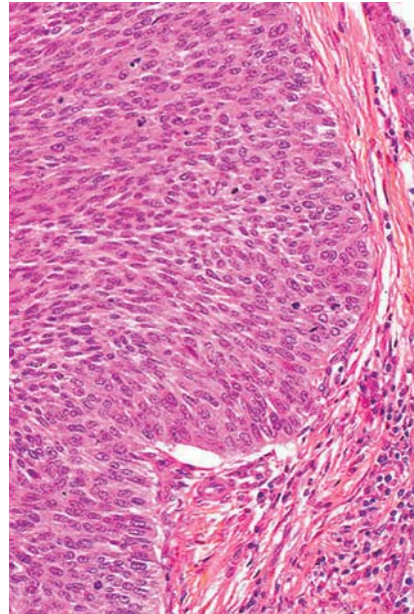


Fig. 3.8. Basaloid carcinoma. This tumor consists of lobules of rather small uniform cells with peripheral palisading, and a high rate of mitosis (HES $\times 200$)

monomorphic cuboidal to fusiform cells, with moderately hyperchromatic nuclei, finely granular chromatin, absent or only focally conspicuous nucleoli, scant cytoplasm but a nuclear-to-cytoplasmic ratio lower than that of SCLC and a high mitotic rate of 20 to 100 mitosis per 2 mm^2 (Fig. 3.8). Neither intercellular bridges nor individual cell keratinization are present, which allows basaloid carcinomas to be distinguished from poorly differentiated squamous cell carcinoma. Patients with basaloid carcinoma have a significantly shorter survival than those with poorly differentiated squamous cell carcinoma and therefore the disease deserves this differential diagnosis (Brambilla et al. 1992a; Moro et al. 1994; Brambilla 1997).

3.6.2.1

Differential Diagnosis

Because comedo-type necrosis is common, palisading is a characteristic feature of basaloid carcinoma (BC), and rosettes can be identified in about one-third of the cases; the main differential diagnosis resides in the distinction from LCNEC. Immunohistochemical stains for neuroendocrine markers are negative in basaloid carcinoma and positive in LCNEC. No secretory granules have been seen by electron microscopy in BC. Two anti-

bodies are helpful in making the distinction on small biopsies between basaloid carcinoma, SCLC and LCNEC. The specific cytokeratin 1, 5, 10, 14 recognized by 34 β E12 show no staining in small cell, large cell and LNEC, whether it stains quite all basaloid carcinoma[?]. TTF-1 is never present in basaloid carcinoma, but it is present in the majority of SCLCs and LCNECs (Table III) (Sturm et al. 2001, 2002).

3.7 Adenosquamous Carcinoma

Adenosquamous carcinoma accounts for 0.6 to 2.3% of all lung cancers (Fitzgibbons and Kern 1985; Naunheim et al. 1987; Takamori et al. 1991; Ishida et al. 1992; Sridhar et al. 1992). It is defined as a lung carcinoma having at least 10% of squamous cell or adenocarcinoma components (Travis et al. 1999). Adenosquamous carcinoma should not be confused with mucoepidermoid carcinoma, a malignant epithelial tumor characterized by the presence of squamoid cells, mucin-secreting cells and cells of an intermediate type identical to the same tumors encountered in the salivary glands. Mucoepidermoid carcinoma of high grade malignancy is differentiated from adenocarcinoma by a variety of features, including a mixture of mucin-containing cells and squamoid cells, transition areas from classical low grade mucoepidermoid carcinoma and the lack of keratinization.

3.8 Carcinomas with Pleomorphic Sarcomatoid, or Sarcomatous Elements

This group of lung carcinomas is poorly differentiated and expresses a spectrum of pleomorphic, sarcomatoid and sarcomatous elements. These elements express the features and the biological behavior of epithelial cells that adopt an epithelial-to-mesenchymal transition in certain instances of cultures in vitro. Pleomorphic carcinomas tend to be large, peripheral tumors that invade bronchial lumens, forming endobronchial growth. They often invade the chest wall and are associated with a poor prognosis (Fishback et al. 1994). Because of the characteristic histologic heterogeneity of this tumor, adequate sampling is required and should consist of at least one section per centimeter of the tumor diameter. To be in this category, a pleomorphic carcinoma should have at least a 10% component of spindle or giant cells associated with other histological types,

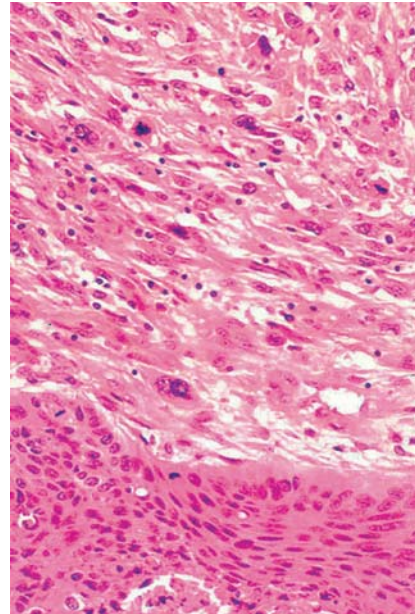


Fig. 3.9. Pleomorphic carcinoma. This tumor is composed of a squamous cell carcinoma (bottom) and an extensive proliferation of malignant spindle and giant cells (HES $\times 250$)

such as adenocarcinoma or squamous cell carcinoma (Fig. 3.9) (Travis et al. 1999).

Rarely, carcinomas present with a pure giant cell or spindle cell pattern and deserve the term *giant-cell* or *spindle cell-carcinoma*. Giant cell carcinoma consists of huge, bizarre pleomorphic and multinucleated tumor cells that engulf numerous inflammatory cells, particularly polymorphonuclear leukocytes, in their cytoplasm (Addis et al. 1988; Chejfec et al. 1991; Ginsberg 1992; McCaughan et al. 1985). They are discohesive and separated by an important infiltration of inflammatory cells. This type of tumor is defined as a carcinoma not only by light microscopy, but also by immunohistochemistry and epithelial markers such as keratins, which are quite helpful in confirming their epithelial nature (Travis et al. 1999).

3.8.1 Carcinosarcoma and Pulmonary Blastoma

Carcinosarcoma is a tumor composed of a mixture of carcinoma and sarcoma. It should be noted that cartilage, bone, and skeletal muscle are heterologous elements and do not display cytokeratin staining (Travis et al. 1999). Experience proves that these cases are extremely rare.

Pulmonary blastomas are defined as biphasic tumors in association with a glandular component that resembles well-differentiated fetal adenocarcinoma; pulmonary blastomas also have a primitive sarcomatous or mesenchymal component (Travis et al. 1999). Well-differentiated fetal adenocarcinoma is no longer regarded as the epithelial pattern of monophasic pulmonary blastoma but, rather, as a variant of adenocarcinoma (Travis et al. 1999).

3.9 Typical and Atypical Carcinoid

Carcinoid tumors account for 1 to 2% of all invasive lung malignancies (Travis et al. 1995). The majority of patients are asymptomatic at presentation (McCaughan et al. 1985). Symptoms include hemoptysis, post-obstructive pneumonitis, dyspnea and paraneoplastic syndrome, including carcinoid, Cushing's syndrome (Ricci et al. 1972; McCaughan et al. 1985; Pass et al. 1990) and acromegaly (Scheithauer et al. 1984). There is no gender predilection (McCaughan et al. 1985; el-Naggar et al. 1991). There is no association with smoking, since 40% of patients with carcinoid are non smokers, which is the proportion of non smokers within the general population. The mean age is 55 years, with a range up to 82 years (McCaughan et al. 1985). This is the most common lung tumor in childhood (Lack et al. 1983).

The treatment of choice of pulmonary carcinoids is surgical resection (McCaughan et al. 1985; Stamatis et al. 1990). Patients with typical carcinoid (TC) have an excellent prognosis and rarely die from their tumors (McCaughan et al. 1985; Warren and Gould 1990). However, metastases do not disqualify the diagnosis of typical carcinoid. Five to ten percent of TCs have regional lymph node involvement, which does not, however, affect their clinical outcome (Colby et al. 1995). Compared with TC, AC presents with a larger tumor size, a higher rate of metastases and a significantly reduced survival. Most series where the diagnosis was based on actual accepted criteria reported a mortality of 27 to 47% (Arrighi et al. 1972; McCaughan et al. 1985; Paladugu et al. 1985; Bonato et al. 1992).

Carcinoid tumors are most often centrally located and have a polypoid endobronchial obstructive component. When peripheral carcinoids occur, they are more often of the spindle-cell type. Both TC and AC are characterized histologically by endocrinoid, organoid growth pattern and uniform cytologic features, consisting of moderate eosinophilic, finely granular cytoplasm, a nucleus with a fine, granular chromatin (Table IV), inconspicuous nucleoli that can be discretely more prominent in AC. A variety of histologic patterns may occur in AC and TC, including trabecular, palisading, rosette-like, papillary, sclerosing papillary, glandular, paragangliomatous, spindle cell and follicular patterns (Travis et al. 1991). More rarely, the tumor cells of pulmonary carcinoid tumors may have oncocytic, acinic

Table 3.4. Typical and atypical carcinoid: distinguishing features

Histologic or clinical feature	Typical carcinoid	Atypical carcinoid
Histologic Patterns: Organoid, Trabecular, Palisading and Spindle cell	Characteristic	Characteristic
Mitoses	Absent or < 2 per 2 mm ² area of viable tumor (10 high power fields on some microscopes)	2–10 per 2 mm ² or area of viable tumor (10 high power fields on some microscopes)
Necrosis	Absent	Characteristic, usually focal or punctate
Nuclear pleomorphism, hyperchromatism	Usually absent, not sufficient by itself for diagnosis of AC	Often present
Regional lymph node metastases at presentation	5–15%	40–48%
Distant metastases at presentation	Rare	20%
Survival at 5 years	90–95%	58%
Disease free survival at 10 years	90–95%	35%

cell-like, signet ring, mucin-producing or melanocytic features (Travis et al. 1991).

The most distinguishing feature between typical and atypical carcinoid is the rate of mitosis and the presence or absence of necrosis. Typical carcinoids show fewer than 2 mitosis per 2 mm² area of viable tumor (10 high power field) and no necrosis. The presence of mitosis between 2 to 10 per 2 mm² or the presence of necrosis (Travis et al. 1998) define the diagnosis of atypical carcinoids. The presence of features such as cell pleomorphism, vascular invasion or increased cellularity are of no help in separating TC from AC or in allowing stratification of patients for prediction of survival (Travis et al. 1998). TC may well show focal cytologic pleomorphism, as do paraganglioma in the head and neck area (Arrigoni et al. 1972; Travis et al. 1991). The necrosis in AC usually consists of small foci centrally located within organoid nests of tumor cells.

3.10 Conclusions

The histologic subclassification of lung tumors is usually based on light microscopy in order to ensure the comparability and consistency of data worldwide. Nonetheless, techniques such as immunohistochemistry, electron microscopy, tissue culture and molecular biology might provide valuable information on carcinogenesis, histogenesis and differentiation. It is universally recognized that immunohistochemistry or electron microscopy may detect differentiation, specifically in regard to the histological heterogeneity of lung cancer that cannot be seen by routine light microscopy. Hence, electron microscopy techniques are occasionally required for precise classification. An example of this is LCNEC and malignant mesothelioma, which require appropriate immunohistochemical and/or electron microscopy findings to confirm the diagnosis.

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