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Large Cell Carcinoma

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Many non-small cell carcinomas arising in the lung are diagnosed by light microscopy as large cell carcinomas, but the term is imprecisely used, because any lung carcinoma that is not a small cell carcinoma, including well-differentiated adenocarcinoma or squamous cell carcinoma, is a large cell carcinoma. The term large cell carcinoma should be viewed as synonymous with large cell undifferentiated carcinoma, defined by the World Health Organization as a malignant epithelial tumor without the characteristic features of squamous cell carcinoma, small cell carcinoma, or adenocarcinoma.[1]

Ideally, the large cell undifferentiated category is reserved for tumors that totally lack evidence of differentiation, but minor degrees of maturation are readily overlooked in light microscopic sections, especially if a specimen is small, fragmented, or distorted, and many tumors that possess minimal differentiation are placed in the large cell undifferentiated group. Certain other tumors in the lung, including poorly differentiated nonepithelial, pleural, and metastatic neoplasms, can closely resemble a primary large cell undifferentiated carcinoma in routine light microscopic sections, making it even more difficult to keep the category pure.

Poorly differentiated carcinoma of the lung is also an abused term. It is tempting to a pathologist to resort to its use if there is a suspicion that some differentiation exists in a non–small cell carcinoma, but it is not clearly glandular or squamous. The assessment is to some degree subjective, because there are no reproducible criteria for the diagnosis. The management of a patient is not influenced by the information that the carcinoma is poorly differentiated, and the expression should be avoided. If convincing evidence of differentiation in a non–small cell lung carcinoma can not be detected after examination of slides stained with hematoxylin and eosin and with a mucin stain, the tumor is a large cell undifferentiated carcinoma and should be so designated.

At least 10% of primary lung tumors are large cell undifferentiated carcinomas. The incidence is higher if diagnoses are based on bronchoscopic or needle biopsies and lower in resection specimens. The rate is also lower if mucin stains are performed. In one series of 1336 successive lung cancer patients, 12% were large cell undifferentiated carcinomas.[2] Most patients are older adults, but among 22 patients 40 years of age or younger, 9 had large cell undifferentiated carcinomas.[3]

In this chapter, the light microscopic and ultrastructural features of large cell undifferentiated carcinomas of the lung are delineated and compared with those of poorly differentiated lung carcinomas and other neoplasms that enter into the differential diagnosis.

PATHOLOGY

Light Microscopy

The absence of an architectural pattern helps to separate large cell undifferentiated carcinoma from other non-small cell carcinomas of the lung, and certain cytologic features aid in differentiating the tumor from other types. Many of the tumors are composed of continuous sheets of closely packed mononuclear cells that are relatively uniform in size and shape, with consistent nuclear features. A variant composed of large, pleomorphic cells (*i.e.*, giant cell subset) may also have no evidence of differentiation.

In the compact type of large cell undifferentiated lung carcinoma, the cells are arranged in diffuse sheets or irregular, anastomosing, broad cords demarcated by zones of necrosis and fibrous stroma (Fig. 50-1). Fragments of residual lung structures may be entrapped within the tumor. A suggestion of grouping of the cells into small clusters can sometimes be detected (Fig. 50-2). Individual cells are usually fairly regular in size and shape, with the result that nuclei tend to be evenly spaced. Although the cells are often compactly arranged, they can also show various degrees of loss of cohesion (Fig. 50-3).

Individual cells are of medium size, larger than in a small cell carcinoma, and comparable in overall dimensions to those of poorly differentiated squamous and adenocarcinomas. Nuclei are round or oval and centrally positioned with clumped chromatin. Nucleoli are always obvious and often large, and nucleolar organizer region counts have been higher than in adenocarcinomas.[4,5]

The same nuclear features are evident in cytologic prepara-

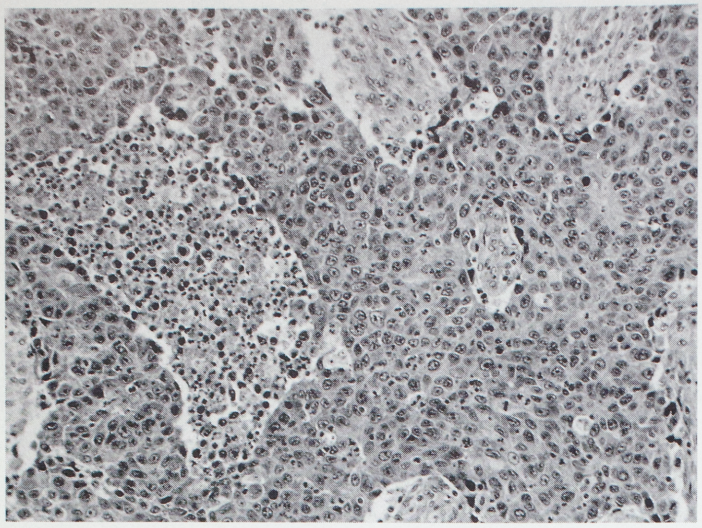

FIGURE 50-1. In this large cell carcinoma, broad cords of tumor cells are separated by zones of fibrous stroma and foci of necrosis. (H & E stain; low magnification.)

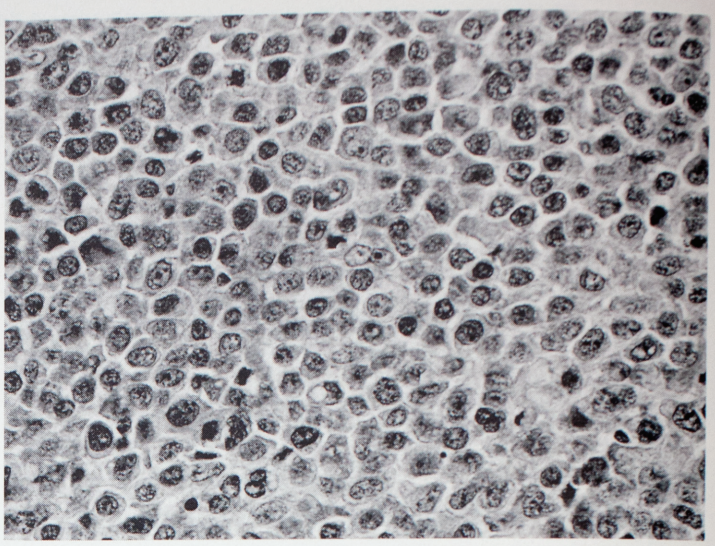

FIGURE 50-3. The uniform cells of a large cell carcinoma are loosely cohesive. They have moderate amounts of cytoplasm and nuclei with clumped chromatin and prominent nucleoli. There is no suggestion of an architectural pattern. (H & E stain; intermediate magnification.)

tions (Fig. 50-4). In smears, including those from fine needle aspiration biopsies, the cells can have moderate amounts of cytoplasm which may be slightly basophilic or eosinophilic, generally without a distinctive appearance. If the cells form continuous sheets, the margins of individual cells may not be clearly discernible (Fig. 50-5). The accuracy of typing large cell undifferentiated carcinomas in cytologic preparations is less than it is for the differentiated forms of non-small cell carcinoma.[6]

In the first WHO classification of lung tumors, one of the subcategories of large cell undifferentiated carcinoma was clear cell carcinoma with mucin production.[7] Because mucin formation is an indication of glandular differentiation, this form was appropriately changed to a subtype of adenocarcinoma in the 1981 revision.[1] The cells of some large cell undifferentiated carcinomas do have clear cytoplasm (Fig. 50-6), but mucin stains must be negative for the tumor to be retained in this subdivision.

Sarcomatoid changes can occur in large cell undifferentiated carcinomas.[8] The pleomorphic form of large cell carcinoma was called giant cell carcinoma by the WHO, following the observations of Hadley and Bullock in 1953 and the recommendation by Nash and Stout, who published 5 cases in 1958, that the tumor be accorded special recognition.[9,10] Hathaway and colleagues analyzed the 118 cases published up to 1969 and added 21 new examples.[11] It is more common to find this histology as a component of a dedifferentiating adenocarcinoma than of a squamous cell carcinoma.[12] The number of giant cells increases with tumor size and extent of necrosis.[13]

A diagnosis of pleomorphic variant of large cell carcinoma is more likely to be made on a small biopsy specimen, but an excision specimen, affording the opportunity for extensive microscopic analysis, may reveal areas of differentiation; the giant cell portion of the tumor should then be listed in the diagnosis as a component.

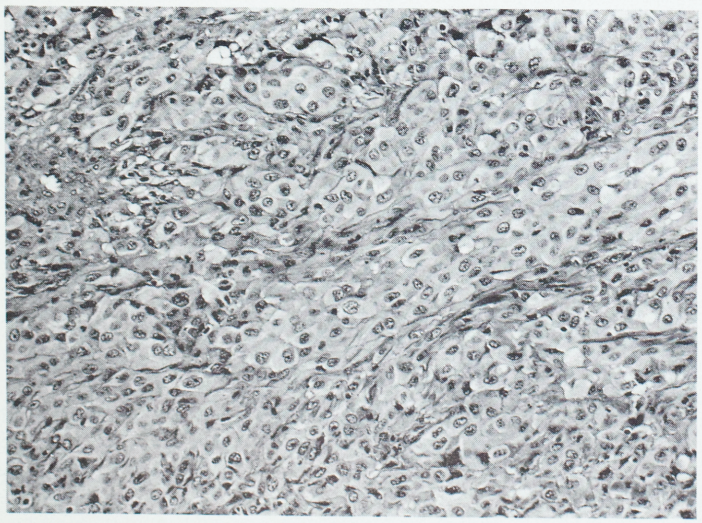

FIGURE 50-2. The large cell carcinoma is a cellular tumor with scanty stroma and a tendency for cell clustering. (H & E stain; intermediate magnification.)

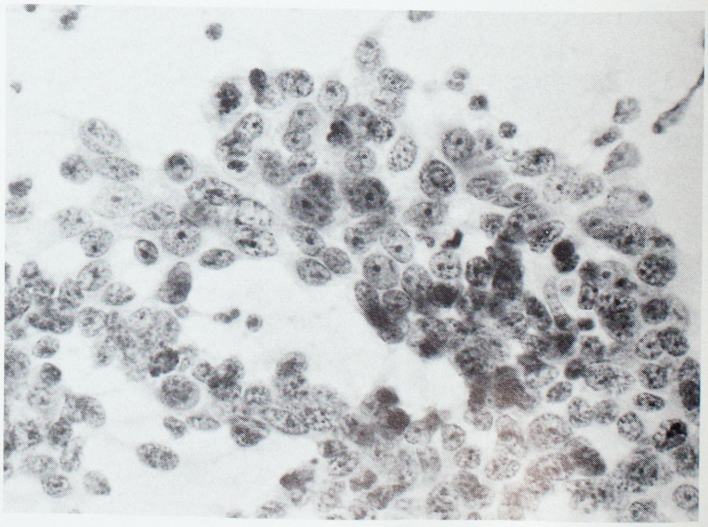

FIGURE 50-4. In this cytologic preparation of a large cell carcinoma, the nuclei are round to ovoid, and the nucleoli are prominent. (H & E stain; high magnification.)

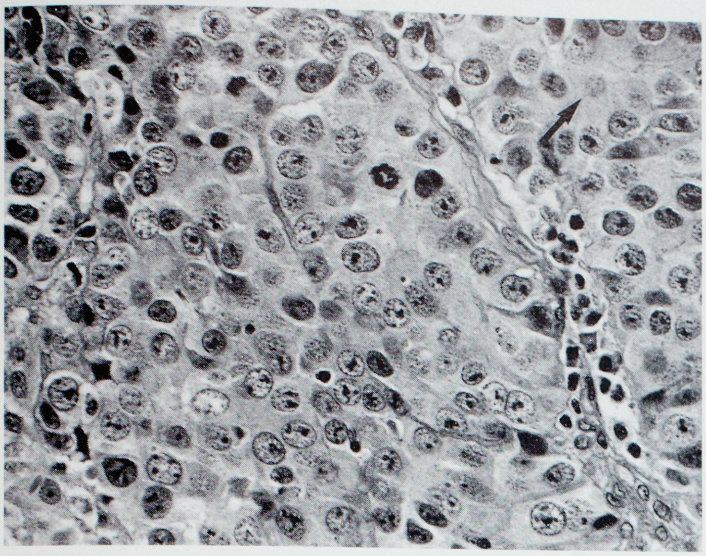

FIGURE 50-5. The spacing of the nuclei in a compact large cell carcinoma indicates the amount of cytoplasm. There was some suggestion of acinar grouping in this tumor (*arrow*). (H & E stain; high magnification.)

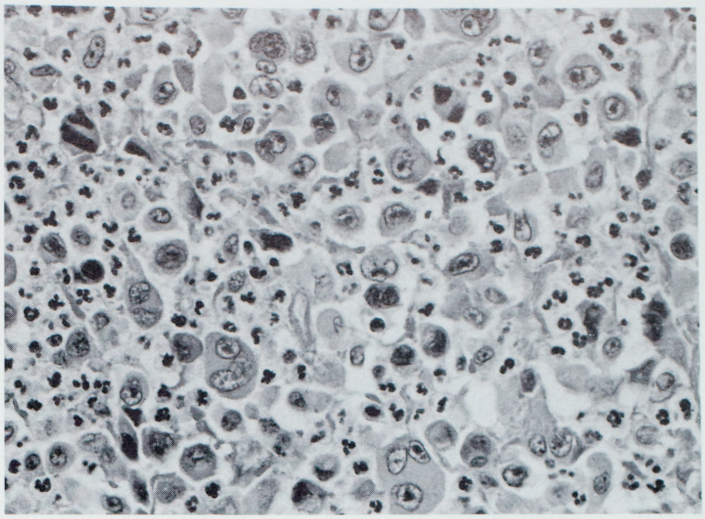

FIGURE 50-7. In this pleomorphic variant of a large cell carcinoma, the tumor cells have abundant cytoplasm and bizarre, multiple nuclei. Many neutrophils are seen. (H & E stain; high magnification.)

At least 30% of the cells in a tumor should be large and pleomorphic for it to qualify as a giant cell carcinoma.[14]

A spectrum of sizes and appearances between the small and large cells can often be seen in a tumor with a differentiated component. The pleomorphic cells are much larger than the mononuclear cells of the compact type of large cell undifferentiated carcinoma, and they have abundant cytoplasm. Loss of cohesion is the rule, and there are often zones of necrosis. It is customary to find many neutrophils infiltrating the pleomorphic form of large cell carcinoma (Fig. 50-7). The large tumor cell nuclei can have markedly irregular outlines, most nuclei are multilobated, and some cells contain more than one nucleus.

Ultrastructure

The uniform mononuclear cells in a large cell undifferentiated carcinoma show more variation in size and shape at the ultrastructural level than is generally perceived by light microscopy, but the features of the cells are similar throughout. Cell borders are smooth, and they may be intimately apposed (Fig. 50-8) or separated by clefts. Acinar lumens bordered by cells with tight junctions are not found, and microvilli are absent; few filopodia are seen. Where cells are in contact, attachment sites can be found, but they are sparse and poorly developed. Mature desmosomes should prompt a search for tonofilament bundles and other evidence of differentiation. A similar undifferentiated appearance is seen in the tumor cells if they are grown in culture, and the cells grow as solid tumors in nude mice and show little evidence of maturation by electron microscopy.[15]

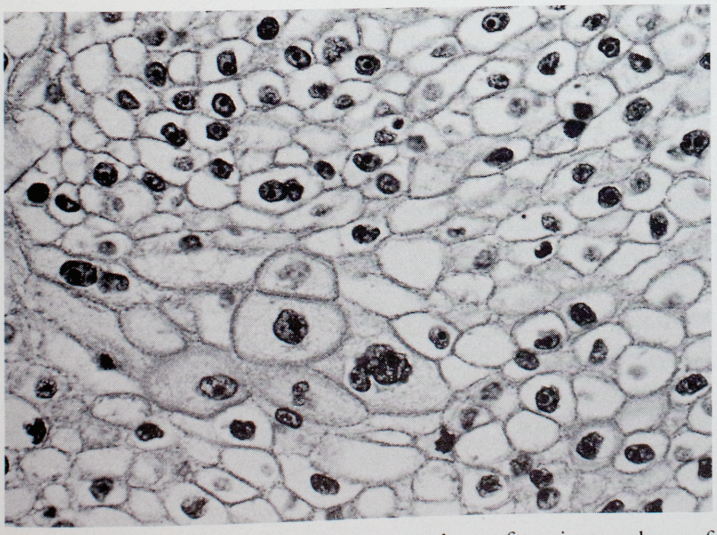

FIGURE 50-6. A large cell carcinoma made up of continuous sheets of cells with clear cytoplasm. The stains for mucin were negative. (H & E stain; high magnification.)

The cytoplasm often contains moderate numbers of organelles, aiding differentiation from small cell carcinoma, which is characterized by a paucity of organelles. A few mitochondria, scattered slender cisternae, and one or two lysosomes and lipid droplets are customary. Round, dense granules of the size seen in Clara cells are sometimes present, and these tumors are presumably dedifferentiated bronchioloalveolar adenocarcinomas. Rarely, a few granules of endocrine caliber are seen.[16]

Organelles can be numerous in the pleomorphic variant of large cell undifferentiated carcinoma[17], and the irregularity of the nuclear profiles is easily seen at the ultrastructural level (Fig. 50-9). Neutrophils may be detected within the large cells, and Wang has suggested that they enter by emperipolesis.[18]

Immunocytochemistry

The phenotypic heterogeneity of large cell undifferentiated carcinoma of the lung has been confirmed by immunostaining of tissue sections and cytologic preparations.[19] Histologic markers of epithelial differentiation were found more frequently in the compact growth type than in tumors with a looser structure.[20,21] The tumors can be subdivided into two groups according to their cytokeratin expression. Tumors with some glandular differentiation express cytokeratins of the type found in simple epithelia. Squamous differentiation is indicated by the expression of a stratified epithelium type of cytokeratin pattern, and these tumors stain for involucrin.[22]

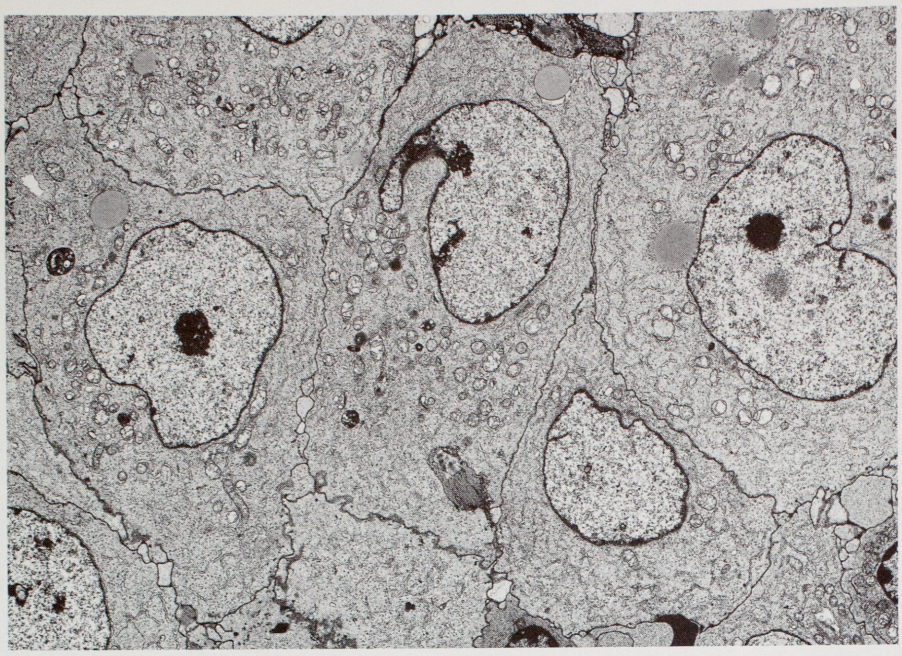

FIGURE 50-8. The carcinoma cells are closely apposed in large cell carcinoma. They contain moderate numbers of organelles and a few lysosomes and lipid droplets, but there is no suggestion of differentiation. (Original magnification × 4500.)

Large cell undifferentiated carcinomas may express vimentin. It was observed in 25% of anaplastic large cell carcinomas but in only 8.5% of adenocarcinomas and in none of the squamous carcinomas in one study.[23] Immunostaining for S-100 protein has been recorded.[24] Human chorionic gonadotropin has been found in all types of lung cancer, but the highest incidence is in large cell undifferentiated carcinomas.[25–27] In a patient with a preoperative α-fetoprotein–producing large cell undifferentiated lung carcinoma, the serum levels returned to normal postoperatively.[28]

A series of ten large cell undifferentiated carcinomas was studied for production of bombesin, and none displayed immunoreactivity, but seven showed a focal hybridization signal, indicating the presence of gastrin-releasing peptide mRNA and this was confirmed by Northern blot analysis.[29] P185NEU expression was not detected in large cell undifferentiated carcinomas in the study of Kern and associates, but Weiner and colleagues found it in cell lines of all histologic types of non-small cell carcinomas.[30,31]

Neuroendocrine differentiation has been detected in the differentiated forms of non-small cell carcinoma and in large cell carcinomas.[32] A correlation with nodal metastases, but not with survival, has been observed for non-small cell lung carcinomas with neuroendocrine differentiation.[33]

DIFFERENTIAL DIAGNOSIS

Many lung tumors called large cell carcinoma by conventional light microscopy are found on ultrastructural examination to possess evidence of maturation. This is strikingly demonstrated by the findings of Hammar and associates, who observed that approximately 80% of the tumors showed evidence of glandular differentiation, 10% showed evidence of squamous differentiation, and features of other tumors were found among the remaining 10%.[34,35] These results underscore the difficulty of making a confident

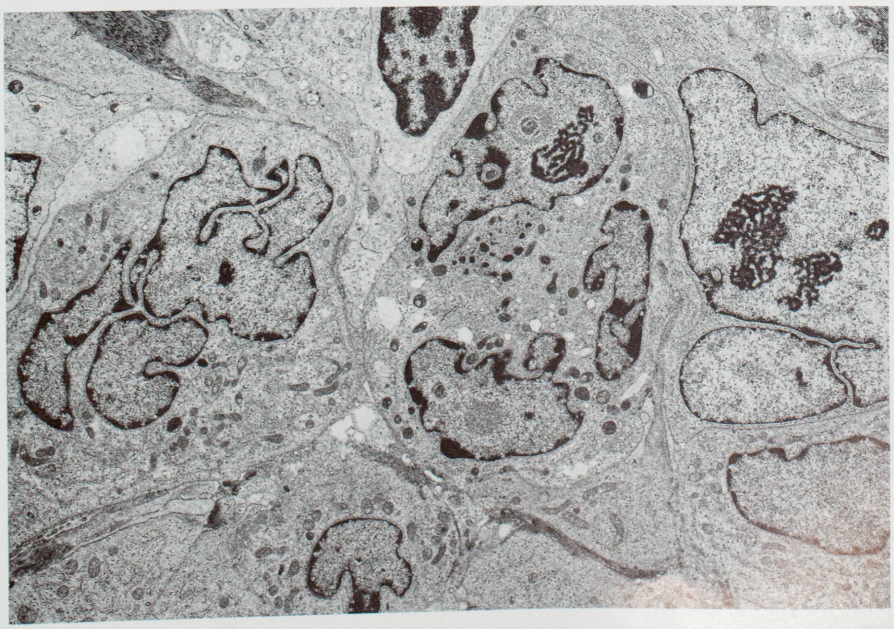

FIGURE 50-9. The nuclei of the cells are markedly irregular in this pleomorphic variant of large cell carcinoma, and the nucleoli are large. (Original magnification × 6200.)

diagnosis by light microscopy, although the minor levels of differentiation that elude detection even when good material is available and mucin stains are performed are of questionable clinical relevance.

The evidence for glandular differentiation that can be seen in large cell undifferentiated carcinomas by electron microscopy usually takes the form of small acini with microvilli and tight junctions or of slender clefts between the cells into which microvilli protrude (Fig. 50-10). The microvilli vary in length and spacing and do not as a rule have any visible internal structure, although cores of actin filaments and associated glycocalyceal vesicles are rarely seen; the latter are occasional findings in the bronchioloalveolar form of lung adenocarcinoma.

Squamous differentiation is not seen often, but it is indicated by frequent and better developed cell junctions with associated cytokeratin filament bundles; and the nuclei may be more irregular in profile than those of the surrounding undifferentiated cells (Fig. 50-11). Cytologic preparations can reveal the admixture of squamous and undifferentiated cells (Fig. 50-12). Distinctions between adenocarcinoma and squamous carcinoma become blurred in poorly differentiated tumors at the ultrastructural level.[36]

In a well-preserved biopsy or resection specimen, it is usually possible to differentiate small cell from large cell carcinomas, despite the fact that neither has an identifiable architectural pattern. However, even with optimal material, separation of the two can sometimes prove to be a problem, which is more likely to arise in a small biopsy sample. It can be insoluble if the cells are artifactually distorted, and then there may be no alternative to requesting a larger tissue specimen. The available biopsy fragments should be sectioned at intervals before it is concluded that a firm diagnosis can not be reached. Morphometric studies performed on low-magnification electron micrographs have confirmed that there is overlap in cell and nuclear size between small cell lung carcinoma cells and those of the non-small cell carcinomas, including large cell undifferentiated carcinoma.[37] The most revealing difference is the nuclear-cytoplasmic ratio, which is significantly higher in small cell tumors. In evaluating light microscopic preparations, an attempt should be made to assess the quantity of cytoplasm that the tumor cells possess. If there are many naked nuclei or distortion from crushing, this can be difficult, but where the cells are apposed within clusters, the spacing of the nuclei conveys an impression of how much cytoplasm the cells possess. A diagnosis of small cell carcinoma should be questioned if the cells have even moderate amounts of cytoplasm.

Markers for endocrine differentiation in lung cancer have clinical applications, but they are of limited utility for separating undifferentiated small cell and large cell carcinomas.[38] Chromogranin A is more frequently positive in the small cell tumors, but it marks about 10% of non-small cell lung carcinomas, and other endocrine markers have similar limitations. Neuron-specific enolase is nonspecific and virtually of no value in this diagnostic dilemma.

Electron microscopy has contributed to the solution of separating small and large cell undifferentiated lung carcinomas by delineating details of the morphology of the cells of the two tumors. Figure 50-13 shows the ultrastructural appearance of cells from a typical small cell lung carcinoma, and they can be compared with the cells in the illustrations of large cell carcinomas. The scanty cytoplasm and sparse organelles that are characteristic of small cell carcinoma can be appreciated; Figure 50-13 also shows that the nuclei are oval rather than spherical and that the nuclear chromatin is finely and evenly clumped throughout the nucleus. This is reflected in microscopic sections and smears by a homogeneous, moderately hyperchromatic appearance, and the nucleoli, typically small, are further obscured by the chromatin. There are exceptions; in approximately 10% of small cell lung carcinomas, the nuclear chromatin is fine, and the nucleoli are prominent.

With the electron microscope, small granules can sometimes be identified in the cytoplasm in small cell carcinoma. They occur in moderate numbers in about one third of the tumors and are sparse in another third. In some of the tumors, granules cannot be found even after a persistent search. Because an occasional large cell carcinoma also contains granules of endocrine caliber, they are not a reliable criterion to differentiate these tumors, but the granules in small cell carcinoma cells are uniformly small, about 120

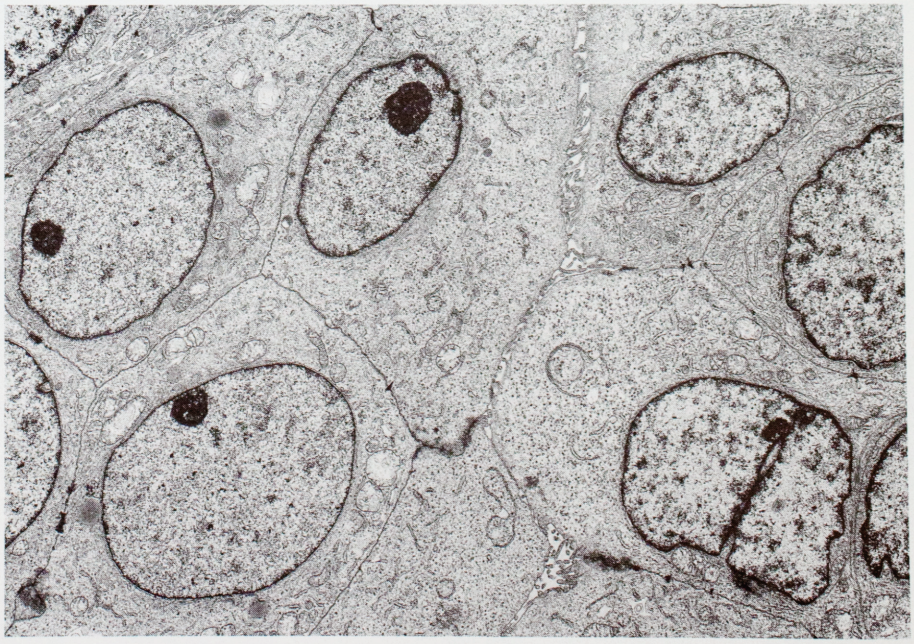

FIGURE 50-10. Although this poorly differentiated adenocarcinoma was diagnosed as a large cell carcinoma by light microscopy, the ultrastructural study revealed slender clefts containing microvilli. (Original magnification × 6200.)

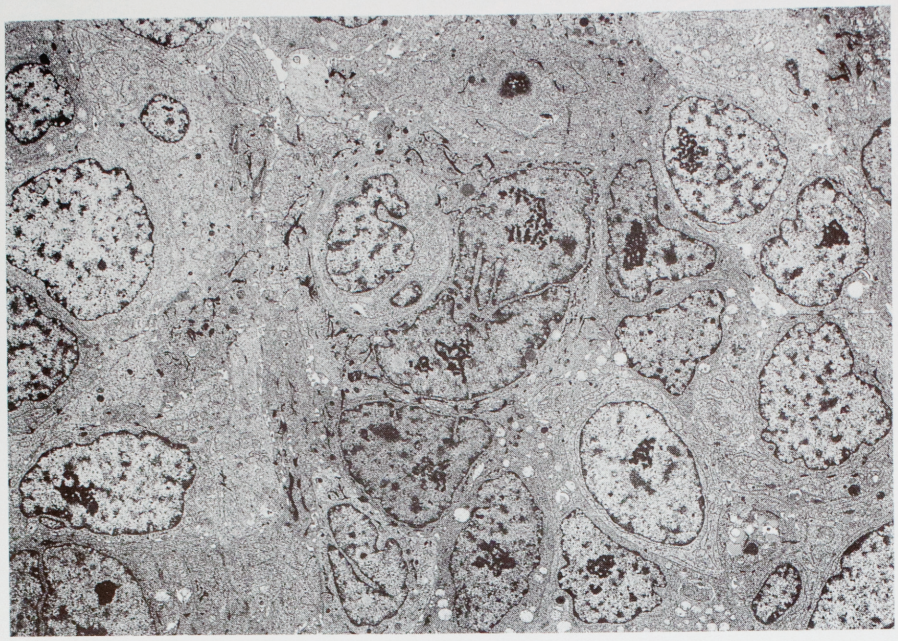

FIGURE 50-11. In this poorly differentiated squamous carcinoma, a small cluster of cells with cytokeratin filaments is surrounded by undifferentiated cells. (Original magnification × 3500.)

μm in diameter, and those in large cell carcinomas tend to be larger.

The clinical relevance of subtyping of small cell lung carcinomas is controversial. The pathology group of the International Association for the Study of Lung Cancer recommended that the adjectives "oat cell" and "intermediate" be abandoned, but they suggested that two variants be retained.[39] One of these, the combined form of small cell carcinoma in which a discrete, differentiated non-small cell carcinoma coexists with the small cell component, is widely accepted as an entity, albeit uncommon. The other variant, small cell and large cell carcinoma, is supposedly a mixture of undifferentiated large cell and small cell carcinoma with intimate intermingling of the two cell types. The existence of such a tumor would imply a shared histogenesis, and this contravenes current theories on the origin of the two tumor types. Identification of this variant has been based on light microscopy, and this is a dubious criterion because of the frequent distortion that mars paraffin sections of lung tumors. Artifactual damage can induce pyknotic changes in some of the cells within a large cell carcinoma, and these shrunken cells with hyperchromatic nuclei readily simulate small cell carcinoma.

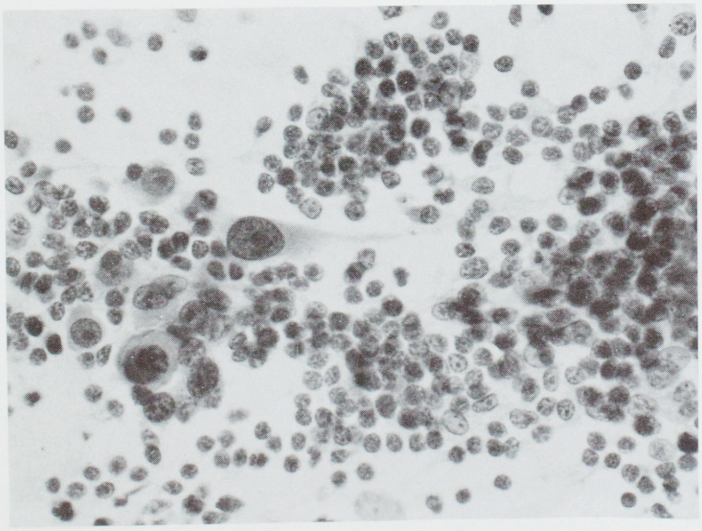

FIGURE 50-12. Scattered small foci of squamous differentiation were found in this otherwise undifferentiated large cell tumor. Both components can be seen in the cytologic preparation. (Papanicolaou stain; intermediate magnification.)

Some small cell carcinomas undergo morphologic transformation of their cells toward a larger cell type, particularly in response to therapy or in metastatic foci. Matthews and Gazdar found larger cells in one third of their autopsy cases.[40] Figure 50-14 illustrates the ultrastructural appearance of a lung tumor that was diagnosed by light microscopy as a large cell undifferentiated carcinoma. The smaller cells with high nuclear-cytoplasmic ratios simulate small cell carcinoma cells, but various degrees of transition between the large and small cells exist. In a study of 34 small cell lung carcinomas, 12 were considered to be of the mixed type, and they had fewer cells immunoreactive for chromogranin A and ultrastructurally had fewer granules and more desmosomes than in the pure subtype.[41] Proof of the existence of a small cell and large cell form of small cell carcinoma requires more convincing documentation than is available.

In most carcinoid tumors of the lung, the cells are arranged in patterns. These may take the form of clusters, cords, or glandlike aggregates. With dedifferentiation, the structure of a carcinoid tumor becomes obscured and ultimately lost, giving way to sheets of compact or loosely cohesive cells that display various degrees of cytologic atypia. The terms atypical carcinoid and large cell neuroendocrine carcinoma have been used. Because the cell size and nuclear-cytoplasmic ratio in these tumors can be the same as those of large cell undifferentiated carcinomas, the two tumors can be difficult to separate, particularly in small biopsies. However, endocrine differentiation in a carcinoid tumor is usually pronounced in the classic form and still detectable in atypical tumors, and chromogranin A and other endocrine markers are usually positive.

The limitations of these markers in the differential diagnosis of large cell undifferentiated lung carcinoma have been described. If electron microscopy is available, carcinoid tumors can usually be identified by their many endocrine granules, and although the number of granules diminishes in the more aggressive tumors, they should still be detectable. In carcinoid tumors, the cisternae

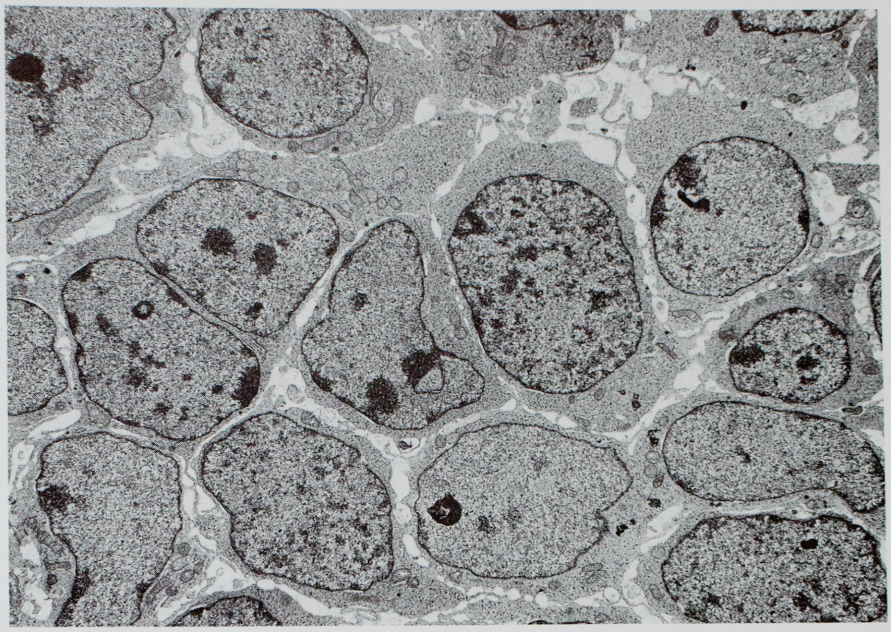

FIGURE 50-13. In this small cell lung carcinoma, the cells have sparse cytoplasm and few organelles, and the nuclear chromatin forms small clumps. (Original magnification × 5500.)

tend to form short stacks, and this is not a feature of large cell undifferentiated carcinomas, in which the endoplasmic reticulum is often sparse and haphazard in its distribution. The uniform structure of carcinoid cells, a round central nucleus, an even amount of cytoplasm, and round cell border are usually obvious to the electron microscopist; these are usually not features in large cell undifferentiated carcinomas. It may, however, be impossible to confidently separate a poorly differentiated endocrine tumor from large cell undifferentiated carcinoma of the lung by light or electron microscopy.

Among uncommon lung tumors, there are only a few that can be difficult to differentiate from large cell undifferentiated carcinoma, and with adequate material and the use of special stains, confusion is unlikely. The sheets of cells that occupy some areas of a sclerosing hemangioma do not have the cytologic atypia of the carcinomas. Loss of cohesion of cells in the carcinomas can simulate a large cell lymphoma, but the nuclear features and immunostaining for keratin and leukocyte common antigen suffice for the determination.

Some epithelial mesotheliomas closely resemble large cell undifferentiated carcinomas histologically. The radiologic findings may strongly suggest one or other diagnosis, but microscopic confirmation is always necessary. Mesothelioma cells are generally cuboidal; they form circles, nests, or cords; and the cell borders are usually distinct because of the many microvilli sandwiched between neighboring cells.[42] Immunostaining for keratin and carcinoembryonic antigen is the usual approach, but electron microscopy is often definitive. Mesothelioma cells have relatively few organelles compared with the carcinomas, and they may have perinuclear zones of intermediate filaments, not a feature of the carcinomas. The luxuriant profusion of long, slender, often branching microvilli coating many of the free surfaces of cells of an

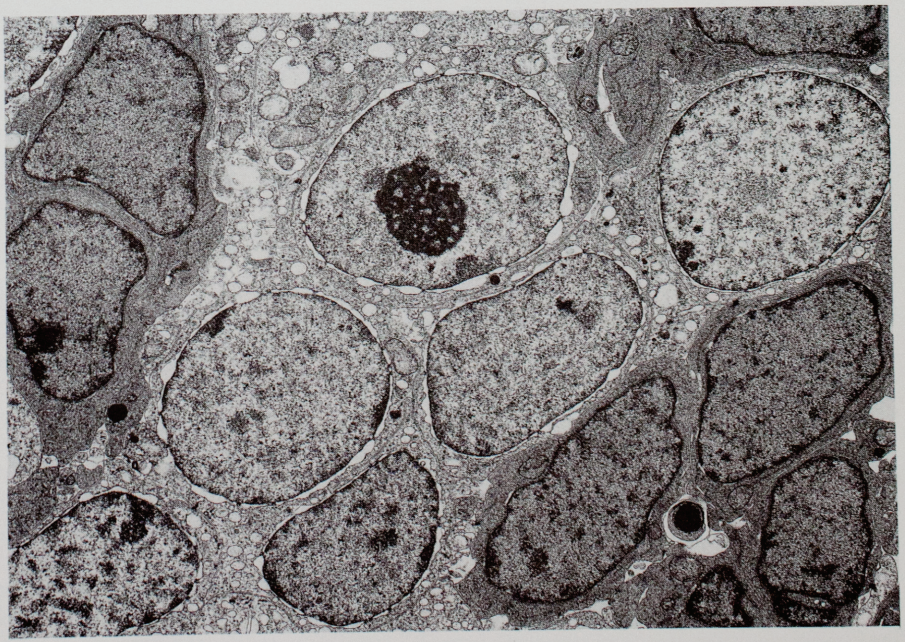

FIGURE 50-14. A large cell lung carcinoma with an admixture of smaller, darker cells. (Original magnification × 7600.)

epithelial mesothelioma is diagnostic. Separation from a poorly differentiated adenocarcinoma may not be easy if the microvilli are sparse, but undifferentiated carcinoma cells do not possess regular arrays of microvilli. It is not possible to differentiate between an undifferentiated epithelial mesothelioma and a large cell undifferentiated carcinoma by electron microscopy.

The clear cell form of large cell undifferentiated carcinoma of lung may contain some glycogen, and metastatic renal cell adenocarcinoma must be considered. Nuclei are smaller in renal cell tumors; lipid and microvilli can often be detected by electron microscopy; and the clinical history will probably be helpful. The rare benign clear cell tumor of the lung is composed of bland cells in sheets with a delicate vascular pattern and is never encountered by most pathologists.

The true nature of the pleomorphic form of large cell undifferentiated carcinoma may be recognized in resection specimens by the presence of a differentiated component, which is commonly adenocarcinoma. In a small biopsy specimen or cytologic preparation, the latter may not be detected, and the entire tumor may be made up of pleomorphic cells. Metastatic neoplasms composed of pleomorphic cells must then be considered, including soft tissue sarcomas, notably malignant fibrous histiocytoma, and melanoma. Because the ultrastructural features of pleomorphic lung carcinoma cells are nonspecific, electron microscopy is of limited value in making the determination, but if the tumor is a metastatic sarcoma, a primary tumor is likely to have been diagnosed earlier. Melanoma is usually positively immunostained with S-100 and HMB-45.

CLINICAL MANIFESTATIONS

Large cell undifferentiated lung carcinomas are often large tumors, and in keeping with the frequent finding by electron microscopy of minor degrees of adenocarcinomatous differentiation, the tumors are often peripheral.[43] However, there are no radiologic features that reliably separate the large cell undifferentiated tumors from adenocarcinomas. Etiologic factors are the same as for adenocarcinomas and squamous carcinomas of the lung, although an increased risk for large cell undifferentiated carcinoma with cigarette smoking was not observed in one study.[44]

As befits an undifferentiated tumor, the behavior of large cell undifferentiated carcinoma is typically aggressive, and the prognosis is poorer than for differentiated forms of non-small cell lung carcinoma.[45] Ishida and colleagues found that the patients with tumors with a compact structure had better survival rates than those with tumors in which cell cohesion was less apparent; the 5-year survival rates were 46% and 28%, respectively.[21] Survival was related to clinical stage. After apparent complete resection of the tumors in 53 patients, Huwer and associates found that the mean survival time for patients with stage I disease was 19 months and the 5-year survival rate was 30.1%, but for stage II tumors, the corresponding figures were 8 months and 10%; for stage IIIA disease, they were 6.5 months and 0%.[46]

Only 10 of a series of 96 consecutive patients had stage I lesions favorable for resection.[47] In an assessment of lung tumors larger than 10 cm in diameter, there was no significant difference between the large cell undifferentiated and differentiated types.[48] Many patients had regional lymph node metastases at the time of diagnosis. Those who did not have nodal spread lived longer, and an improved survival after chemotherapy was reported. The pleomorphic variant of large cell undifferentiated carcinoma is particularly aggressive.

REFERENCES

1. The World Health Organization histological typing of lung tumors, second edition. Am J Clin Pathol 1982;77:123.
2. Sridhar KS, Raub W Jr, Duncan RC, Hilsenbeck S, Richman SP. Lung carcinoma in 1,336 patients. Am J Clin Oncol 1991;14:496.
3. Sugio K, Ishida T, Kaneko S, Yokoyama H, Sugimachi K. Surgically resected lung cancer in young adults. Ann Thorac Surg 1992;53:127.
4. Burns TR, Underwood RD, Greenberg SD, Teasdale TA, Cartwright J Jr. Cytomorphometry of large cell carcinoma of the lung. Anal Quant Cytol Histol 1989;11:48.
5. Kaneko S, Ishida T, Sugio K, Yokoyama H, Sugimachi K. Nucleolar organizer regions as a prognostic indicator for stage I non-small cell lung cancer. Cancer Res 1991;51:4008.
6. DiBonito L, Colautti I, Patriarca S, Falconieri G, Barbazza R, Vielh P. Cytological typing of primary lung cancer: study of 100 cases with autopsy confirmation. Diagn Cytopathol 1991;7:7.
7. Kreyberg L. Histological typing of lung tumors. International histological classification of tumors. Geneva: World Health Organization, 1967:1.
8. Tou Y, Isobe M, Tutida I, Hyoudou S, Takeda J, Kakegawa T. Suspected primary tumor in the diaphragm revealing large cell carcinoma in the lung with sarcomatous change. Nippon Kyobu Geka Gakkai Zasshi 1990;38:1083.
9. Hadley GG, Bullock WK. Autopsy reports of pulmonary carcinoma. Calif Med 1958;79:431.
10. Nash AD, Stout AP. Giant cell carcinoma of the lung. Cancer 1958; 11:369.
11. Hathaway BM, Copeland K, Gurley J. Giant cell adenocarcinoma of the lung. Arch Surg 1969;98:24.
12. Mackay B, Lukeman JM, Ordonez NG. Tumors of the lung. Philadelphia: WB Saunders, 1991:197.
13. Cacic M, Oberman B, Dvornik G. Investigation of the applicability of histological classification of bronchial carcinoma according to the World Health Organization. Tumori 1989;75:580.
14. Mountain CF, Lukeman JM, Hammar SP, et al. Lung cancer classification: the relationship of disease extent and cell type to survival in a clinical trials population. J Surg Oncol 1987;35:147.
15. Anger B, Bockman R, Andreeff M, et al. Characterization of two newly established human cell lines from patients with large cell anaplastic lung carcinoma. Cancer 1982;50:1518.
16. Wick MR, Berg LC, Hertz MI. Large cell carcinoma of the lung with neuroendocrine differentiation: a comparison with large cell "undifferentiated" pulmonary tumors. Am J Clin Pathol 1992;97:796.
17. Mackay B, Lukeman JTM, Ordonez NG. Tumors of the lung. Philadelphia: WB Saunders, 1991:204.
18. Wang NS, Seemayer TA, Ahmed MN, Knaack J. Giant cell carcinoma of the lung: a light and electron microscopic study. Hum Pathol 1976;7:3.
19. Schulte MA, Ramzy I, Greenberg SD. Immunocytochemical characterization of large cell carcinomas of the lung. Role, limitations, and technical considerations. Acta Cytol 1991;35:175.
20. Ishida T, Yano T, Sugimachi K. Clinical applications of the pathological properties of small cell carcinoma, large cell carcinoma, and adenoid cystic carcinoma of the lung. Semin Surg Oncol 1990;6:53.
21. Ishida T, Kaneko S, Tateishi M, et al. Large cell carcinoma of the lung. Prognostic implications of histopathologic and immunohistochemical subtyping. Am J Clin Pathol 1990;93:176.
22. Said JW, Nash G, Sasoon AF, et al. Involucrin in lung tumors: a specific marker for squamous differentiation. Lab Invest 1983;49:563.
23. Upton MP, Hirohashi S, Tome Y, et al. Expression of vimentin in

surgically resected adenocarcinoma and large cell carcinomas of the lung. Am J Surg Pathol 1986;10:560.
24. Nakamura S, Suzuki R, Hirabayashi N. A case of S-100 protein-positive large cell carcinoma—its pathological study. Gan No Rinsho 1989;35:664.
25. Fukuda M, Sasaki Y, Morita M, et al. Large cell carcinoma of the lung secreting chorionic gonadotropin which responded to combination chemotherapy: case report. Jpn J Clin Oncol 1990;20:299.
26. Kasai K, Kameya T, Kadoya K, Wada C. A pulmonary large cell carcinoma cell line expressing neuroendocrine cell markers and human chorionic gonadotropin alpha-subunit. Jpn J Cancer Res 1991; 82:12.
27. Wachner R, Wittekind C, Kleitz S. Localization of CEA, β-HCG, SP1, and keratin in the tissue of lung carcinomas: an immunohistochemical study. Virchows Arch [A] 1984;402:415.
28. Okunaka T, Kato H, Konaka C, Yamamato H, Furukawa K. Primary lung cancer producing alpha-fetoprotein. Ann Thorac Surg 1992; 53:151.
29. Hamid QA, Corrin B, Dewar A, Hoefler H, Sheppard MN. Expression of gastrin-releasing peptide (human bombesin) gene in large cell undifferentiated carcinoma of the lung. J Pathol 1990;161:145.
30. Kern JA, Schwartz DA, Nordberg JE, et al. P185NEU expression in human lung adenocarcinomas predicts shortened survival. Cancer Res 1990;50:5184.
31. Weiner DB, Nordberg J, Robinson R, et al. Expression of the NEU gene-encoded protein (P185NEU) in human non-small cell carcinomas of the lung. Cancer Res 1990;50:421.
32. Visscher DW, Zarbo RJ, Trojanowski JQ, Sakr W, Crissman JD. Neuroendocrine differentiation in poorly differentiated lung carcinomas: a light microscopic and immunohistologic study. Mod Pathol 1990;3:508.
33. Sundaresan V, Reeve JG, Stenning S, Stewart S, Bleehen NM. Neuroendocrine differentiation and clinical behavior in non-small cell lung tumours. Br J Cancer 1991;64:333.
34. Hammar SP, Bolen JW, Bockus D, Remington F, Friedman S. Ultrastructural and immunohistochemical features of common lung tumors: an overview. Ultrastruct Pathol 1985;9:283.
35. Hammar S. Adenocarcinoma and large cell undifferentiated carcinoma of the lung. Ultrastruct Pathol 1987;11:251.
36. Van de Velde RL. Ultrastructural methods for the classification of malignant tumors of the lung. Lung Biol Health Dis 1990;44: 569.
37. Mackay B, Ordonez NG, Bennington JL, Dugan CC. Ultrastructural and morphometric features of poorly differentiated and undifferentiated lung tumors. Ultrastruct Pathol 1989;13:561.
38. Teeling M, McGing P, Johnston P, Carney DN. Clinical correlation of tumor endocrine markers in lung cancer. Cancer Treat Res 1989; 45:137.
39. Hirsch FR, Matthews MJ, Aisner S, et al. Histopathologic classification of small cell lung cancer: changing concepts and terminology. Cancer 1988;62:973.
40. Matthews MJ. Effects of therapy on the morphology and behavior of small cell carcinoma of the lung: a clinicopathologic study. In: Muggia M, Rozencweig M, eds: Lung cancer: progress in therapeutic research. New York: Raven Press, 1979:55.
41. Yokose T, Asami H, Ito Y. Immunohistochemical and ultrastructural study of mixed small cell/large cell carcinoma of the lung. Expression of Sialyl Lex-i antigens and scarcity of neuroendocrine characteristics. Acta Pathol Jpn 1991;41:540.
42. Hammar S. Pleural neoplasms. In: Hammar SP, Dail DH, eds. Pulmonary pathology. New York: Springer-Verlag, 1988:973.
43. Sider L. Radiographic manifestations of primary bronchogenic carcinoma. Radiol Clin North Am 1990;28:583.
44. Morabia A, Wynder EL. Cigarette smoking and lung cancer cell types. Cancer 1991;68:2074.
45. Campobasso O, Andrion A, Mancuso M, DeSimone M, Ribotta M. The postoperative survival in pulmonary carcinomas depending on the histological type and stage. Ann Osp Maria Vittoria Torino 1989;31:9.
46. Huwer H, Donie HW, Volkmer I, Seitz G. Large cell carcinoma of the lung: a contribution on prognosis after potentially curative resection. Thorac Cardiovasc Surg 1991;39:218.
47. Downey RS, Sewell CW, Mansour KA. Large cell carcinoma of the lung: a highly aggressive tumor with dismal prognosis. Ann Thorac Surg 1989;47:806.
48. Sano T, Naruke T, Kondo H, Goya T, Tsuchiya R, Suemasu K. Prognosis for resected lung cancer patients with tumors greater than ten centimeters in diameter. Jpn J Clin Oncol 1990;20:369.