The 2015 World Health Organization Classification of Lung Tumors

Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification

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On Behalf of the WHO Panel

Abstract: The 2015 World Health Organization (WHO) Classification of Tumors of the Lung, Pleura, Thymus and Heart has just been published with numerous important changes from the 2004 WHO classification. The most significant changes in this edition involve (1) use of immunohistochemistry throughout the classification, (2) a new emphasis on genetic studies, in particular, integration of molecular testing to help personalize treatment strategies for advanced lung cancer patients, (3) a new classification for small biopsies and cytology similar to that proposed in the 2011 Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification, (4) a completely different approach to lung adenocarcinoma as proposed by the 2011 Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification, (5) restricting the diagnosis of large cell carcinoma only to resected tumors that lack any clear morphologic or immunohistochemical differentiation with reclassification of the remaining former large cell carcinoma subtypes into different categories, (6) reclassifying squamous cell carcinomas into keratinizing, nonkeratinizing, and basaloid subtypes with the nonkeratinizing tumors requiring immunohistochemistry proof of squamous differentiation, (7) grouping of neuroendocrine tumors together in one category, (8) adding *NUT* carcinoma, (9) changing the term sclerosing hemangioma to sclerosing pneumocytoma, (10) changing the name hamartoma to "pulmonary hamartoma," (11) creating a group of PEComatous tumors that include (a) lymphangioleiomyomatosis, (b) PEComa, benign (with clear cell tumor as a variant) and (c) PEComa, malignant, (12) introducing the entity pulmonary myxoid sarcoma with an *EWSR1–CREB1* translocation, (13) adding the entities myoepithelioma and myoepithelial carcinomas, which can show *EWSR1* gene rearrangements, (14) recognition of usefulness of *WWTR1–CAMTA1* fusions in diagnosis of epithelioid hemangioendotheliomas, (15) adding Erdheim–Chester disease to the lymphoproliferative tumor, and (16) a group of tumors of ectopic origin to include germ cell tumors, intrapulmonary thymoma, melanoma and meningioma.

Key Words: WHO classification, Lung tumors, Lung cancer, Lung adenocarcinoma, Squamous cell carcinoma, Small cell carcinoma, Large cell carcinoma, Carcinoid.

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The 2015 World Health Organization (WHO) Classification of Tumors of the Lung, Pleura, Thymus and Heart has just been published (Table 1).[1] This follows previous WHO

TABLE 1. 2015 WHO Classification of Lung Tumors[a,b,c]

Histologic Type and Subtypes	ICDO Code
Epithelial tumors	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma[e]	8250/3[d]
Acinar adenocarcinoma	8551/3[d]
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma[e]	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma[e]	8253/3[d]
Mixed invasive mucinous and nonmucinous adenocarcinoma	8254/3[d]
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma[e]	8144/3
Minimally invasive adenocarcinoma[e]	
Nonmucinous	8256/3[d]
Mucinous	8257/3[d]
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0[d]
Adenocarcinoma in situ[e]	
Nonmucinous	8250/2[d]
Mucinous	8253/2[d]
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma[e]	8071/3
Nonkeratinizing squamous cell carcinoma[e]	8072/3
Basaloid squamous cell carcinoma[e]	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumors	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumors	
Typical carcinoid tumor	8240/3
Atypical carcinoid tumor	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0[d]
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinomas	
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and Unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma[e]	8023/3[d]
Salivary gland-type tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma[e]	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumors	
Pulmonary hamartoma	8992/0[d]
Chondroma	9220/0
PEComatous tumors[e]	
Lymphangioleiomyomatosis	9174/1
PEComa, benign[e]	8714/0
Clear cell tumor	8005/0
PEComa, malignant[e]	8714/3
Congenital peribronchial myofibroblastic tumor	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumor	8825/1
Epithelioid hemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with *EWSR1–CREB1* translocation[e]	8842/3[d]
Myoepithelial tumors[e]	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumors	
Extranodal marginal zone lymphomas of mucosa-associated Lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B cell lymphoma[e]	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim–Chester disease	9750/1
Tumors of ectopic origin	
Germ cell tumors	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8270/3
Meningioma, NOS	9530/0
Metastatic tumors	

[a]The morphology codes are from the ICDO.[2] Behavior is coded /0 for benign tumors, /1 for unspecified, borderline or uncertain behavior, /2 for carcinoma in situ and grade III intraepithelial neoplasia, and /3 for malignant tumors.

[b]The classification is modified from the previous WHO classification[3] taking into account changes in our understanding of these lesions.

[c]This table is reproduced from the 2015 WHO Classification by Travis et al.[1]

[d]These new codes were approved by the International Agency on Cancer Research/WHO Committee for ICDO.

[e]New terms changed or entities added since 2004 WHO Classification.[3]

LCNEC, large cell neuroendocrine carcinoma, WHO, World Health Organization; ICDO International Classification of Diseases for Oncology.

Classifications of Lung Tumors in 1967 and 1981, of Lung and Pleural Tumors in 1999 and Tumors of the Lung, Pleura, Thymus and Heart in 2004.[3–6] Due in part to remarkable advances in lung cancer genetics and therapy in the past decade, there are significant changes since the 2004 WHO classification that will be summarized in this review.[3] Compared with the 2004 WHO Classification, there are multiple major changes for the common lung cancers most of which follow the 2011 lung adenocarcinoma classification sponsored by the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS), which has essentially been adopted with only minor changes.[7] The most significant changes in this edition compared with 2004 involve (1) use of immunohistochemistry throughout the classification including for resected lung cancers, (2) a new emphasis on genetic studies, in particular integration of molecular testing to help personalize treatment strategies for advanced lung cancer patients, (3) a new classification for small biopsies and cytology as proposed by the 2011 IASLC/ATS/ERS Classification with a different approach to classification of resected lung cancers, (4) a completely different approach to lung adenocarcinoma as proposed by the 2011 IASLC/ATS/ERS Classification, (5) restricting the diagnosis of large cell carcinoma only to resected tumors that lack any clear morphologic or immunohistochemical differentiation with reclassification of the remaining former large cell carcinoma subtypes into different categories, (6) reclassifying squamous cell carcinomas into keratinizing, nonkeratinizing and basaloid subtypes with the nonkeratinizing tumors requiring immunohistochemistry proof of squamous differentiation, (7) grouping of neuroendocrine tumors together in one category, (8) adding nuclear protein in testis (NUT) carcinoma to a category of other and unclassified tumors, (9) changing the term sclerosing hemangioma to sclerosing pneumocytoma and moving this tumor to the adenoma category, (10) changing the name hamartoma to "pulmonary hamartoma," (11) creating a group of PEComatous tumors that include (a) lymphangioleiomyomatosis (LAM), (b) PEComa, benign (with clear cell tumor as a variant), and (c) PEComa, malignant, (12) introducing the entity pulmonary myxoid sarcoma with an *EWSR1–CREB1* translocation, (13) adding the entities myoepithelioma and myoepithelial carcinomas which can show *EWSR1* gene rearrangements, (14) recognition of usefulness of *WWTR1–CAMTA1* fusions in diagnosis of epithelioid hemangioendotheliomas (15) adding Erdheim–Chester disease to the lymphoproliferative tumors,[1] and (16) a new group of tumors of ectopic origin was created to include germ cell tumors, intrapulmonary thymoma, melanoma and meningioma.

Much of the work of this classification was accomplished through the Pathology Committee of the IASLC, who supported annual meetings of the committee over the past decade and an international multidisciplinary meeting in December of 2014 in New York. This included meetings of the IASLC/ATS/ERS lung adenocarcinoma classification between 2008 and 2010 in which major changes were based on a systematic review of the literature and consensus majority votes of the international multidisciplinary panel. For the WHO Book, lead authors were assigned to the major subchapter topics, and they coordinated the development of consensus and the writing assignments among the assigned coauthors. In addition, all significant changes from the 2004 book were discussed and approved by majority voting during a consensus meeting sponsored by the WHO and International Agency on Cancer Research in Lyon, France in April of 2014.

MORE EXPANDED USE OF IMMUNOHISTOCHEMISTRY

In prior WHO classifications lung cancer diagnosis was based mainly on light microscopy using routine hematoxylin and eosin and sometimes mucin stained slides. Immunohistochemistry was introduced for the first time in the 1999 WHO Classification and, even in the 2004 WHO classification, immunohistochemistry for lung cancer diagnosis was limited to large cell neuroendocrine carcinomas (LCNEC), sarcomatoid carcinomas, and carcinomas in the differential diagnosis with malignant mesothelioma.[3,6] However, throughout the 2015 WHO Classification, immunohistochemistry is now recommended, when possible, not only for small biopsies/cytology, but also for resected specimens in certain settings such as solid adenocarcinoma, nonkeratinizing squamous cell carcinoma, large cell carcinoma, neuroendocrine tumors, and sarcomatoid carcinomas. With certain drugs approved for specific subgroups of non–small cell lung cancers (NSCLC) patients (i.e., bevacizumab, pemetrexed for nonsquamous histologies), the requirement for more exact histopathological subtyping is mandatory. Whenever immunohistochemistry is used in diagnosis, care must be taken to ensure high-quality staining and participation in a quality assurance program is recommended. Furthermore, care must be taken in the use of different antibody clones and in the interpretation of different degrees of staining.

NEW IMPORTANCE OF HISTOLOGY AND GENETICS FOR PERSONALIZED MEDICINE IN ADVANCED LUNG CANCER

One of the great advances in the past decade in lung cancer diagnosis and treatment is the concept of personalized medicine, where therapeutic decisions are based on the specific histologic and genetic characteristics of the patient's tumor. This has given a new importance for pathologists to classify NSCLC further into specific pathologic subtypes (e.g., adenocarcinoma versus squamous cell carcinoma) as this determines eligibility for certain types of molecular testing and therapeutic strategies. Until the past decade, there have been no therapeutic implications to classify the NSCLC tumors further, so little attention was been given to the distinction of adenocarcinoma and squamous cell carcinoma in small tissue samples. This situation changed dramatically with the discovery of several therapeutic options that are only approved for treatment of patients with specific histologic types. Discovery that epidermal growth factor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements are effective targets for EGFR tyrosine kinase inhibitors or *ALK* inhibitors in patients with advanced lung adenocarcinoma has not only revolutionized therapeutic strategies, but transformed clinical practice for pathologists.[7] The new imperative for pathologists to distinguish between squamous cell carcinoma and adenocarcinoma was further emphasized by the observation that *EGFR* mutations and rearrangements of *ALK* and *ROS1* are found primarily in adenocarcinoma,

that pemetrexed is effective in patients with advanced lung adenocarcinoma rather than squamous cell carcinoma, and that bevacizumab is contraindicated in patients with squamous cell carcinoma, whereas Nivolumab (a programmed death-ligand [PDL] antibody) was most recently approved by the U.S. Food and Drug Agency in patients with advanced lung squamous cell carcinoma.[7,8] Because of the therapeutic implications, molecular testing for *EGFR* mutation and *ALK* rearrangement is today recommended by multiple leading clinical and pathology societies in tumors classified as adenocarcinoma and in cases where an adenocarcinoma component cannot be excluded.[7,9,10]

LUNG CANCER DIAGNOSIS IN SMALL BIOPSIES AND CYTOLOGY SPECIMENS

New criteria for the diagnosis of lung cancer based on small biopsies and cytology are proposed in the 2015 WHO classification. These guidelines are important because two thirds of lung cancer patients are presenting in advanced stages, and their diagnosis is usually established based on small biopsy and cytology specimens.[7] Furthermore, it might be anticipated with the introduction of lung cancer screening that more patients, also in early stages of the disease, will be diagnosed based on small specimens. Furthermore, these specimens are needed not only for an accurate pathologic classification, but these small tissue samples also need to be managed carefully for molecular testing.[7,9,10] This is the first WHO classification to provide standardized criteria and terminology for lung cancer diagnosis in small biopsies (bronchoscopic, needle, or core biopsies) and cytology (Tables 2 and 3).[7] The previous 1967, 1981, 1999, and 2004 WHO classifications addressed lung cancer classification based primarily on resection specimens.[3–46] Cytology was included for the first time in the 2004 WHO Classification; however, practical issues of diagnosing lung cancer in small biopsies were not addressed.[3] Furthermore, because there was no clinical need to classify NSCLC further, the diagnosis of NSCLC without further specification was encouraged to avoid discrepancies with subsequent resected specimens. In small biopsies, the percentage of NSCLC cases diagnosed as not otherwise specified (NOS) has been as high as 30% to 50%, and recent data from the Surveillance Epidemiology and End Results registry suggests the frequency of this NOS diagnosis has been increasing over time.[12–15] Until now, there have been no established standardized criteria or terminology for the diagnosis of lung cancer in small biopsies or cytology. However, over recent years, the situation has changed dramatically because of the major therapeutic implications of accurate histologic diagnosis and the need for molecular testing for eligibility to specific therapies. For this reason, it is recommended to reduce use of the term NSCLC NOS as much as possible and classify tumors according to their specific histologic subtype.[7,11]

TABLE 2. Terminology and Criteria for Adenocarcinoma, Squamous Cell Carcinoma, and NSCC NOS in Small Biopsies and Cytology Compared with Terms in Resection Specimens[a]

New Small Biopsy/Cytology Terminology	Morphology/Stains	2015 WHO Classification in Resection Specimens
Adenocarcinoma (describe identifiable patterns present)	Morphologic adenocarcinoma patterns clearly present	Adenocarcinoma predominant pattern: lepidic, acinar, papillary, solid, and micropapillary
Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)		Minimally invasive adenocarcinoma, adenocarcinoma in situ, or an invasive adenocarcinoma with a lepidic component
Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern)		Invasive mucinous adenocarcinoma
Adenocarcinoma with colloid features		Colloid adenocarcinoma
Adenocarcinoma with fetal features		Fetal adenocarcinoma
Adenocarcinoma with enteric features[b]		Enteric adenocarcinoma
NSCC, favor adenocarcinoma[c]	Morphologic adenocarcinoma patterns not present but supported by special stains (i.e., TTF-1 positive)	Adenocarcinoma (solid pattern may be just one component of the tumor)
Squamous cell carcinoma	Morphologic squamous cell patterns clearly present	Squamous cell carcinoma
NSCC, favor squamous cell carcinoma[c]	Morphologic squamous cell patterns not present but supported by stains (i.e., p40-positive)	Squamous cell carcinoma (nonkeratinizing pattern may be a component of the tumor)
NSCC NOS[d]	No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern	Large cell carcinoma

[a]Modified from the articles by Travis et al.[1,7,11]

[b]Metastasis of colorectal cancer should be carefully excluded with judicious immunohistochemical stains and clinical evaluation.

[c]These categories do not always correspond to solid adenocarcinoma or nonkeratinizing squamous cell carcinoma, respectively. Poorly differentiated components in adenocarcinoma or squamous cell carcinoma may be sampled.

[d]NSCC NOS pattern can be seen not only in large cell carcinomas but also when the solid poorly differentiated component of adenocarcinomas or squamous cell carcinomas is sampled but does not express immunohistochemical markers or mucin

NSCC, non–small cell carcinoma; NOS, not otherwise specified; TTF, thyroid transcription factor; WHO, World Health Organization.

TABLE 3. Diagnostic Terminology for Small Biopsy/Cytology Compared with the 2015 WHO Terms in Resection Specimens with Small Cell Carcinoma, LCNEC, Adenosquamous Carcinoma, and Sarcomatoid Carcinoma[a]

Small Biopsy/Cytology Terminology/Criteria	2015 WHO Classification in Resections
Small cell carcinoma	Small cell carcinoma
NSCC with NE morphology and positive NE markers, possible LCNEC	LCNEC
NSCC with NE morphology If negative NE markers comment: This is a NSCC where LCNEC is suspected, but stains failed to demonstrate NE differentiation.	Large cell carcinoma with NE morphology (LCNEM)
Morphologic squamous cell and adenocarcinoma patterns present: NSCC, NOS Comment that adenocarcinoma and squamous components are present and this could represent adenosquamous carcinoma.	Adenosquamous carcinoma (if both components ≥10%)
Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate glandular and adenocarcinoma components: NSCC, NOS Specify the results of the immunohistochemical stains and the interpretation and comment this could represent adenosquamous carcinoma.	Adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma or large cell carcinoma with unclear immunohistochemical features
NSCC with spindle cell and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)	Pleomorphic, spindle cell, and/or giant cell carcinoma

[a]Modified from the articles by Travis et al.[1,7,11]
LCNEC, large cell neuroendocrine carcinoma; NOS, not otherwise specified; NSCC, non–small cell carcinoma; NE, neuroendocrine; WHO, World Health Organization.

The specifics of the lung cancer classification in small biopsies and cytology are explained in more detail elsewhere.[7,11] Briefly, tumors that have clear morphologic patterns of adenocarcinoma (acinar, papillary, lepidic, micropapillary) or squamous cell carcinoma (unequivocal keratinization and well formed classical bridges) can be diagnosed as adenocarcinoma or squamous cell carcinoma, respectively, without immunohistochemistry, unless a pneumocyte marker such as thyroid transcription factor (TTF)-1 is desired to address primary versus metastatic adenocarcinoma (Table 2). However, in the setting of poorly differentiated tumors that do not show clear differentiation by routine microscopy, a limited immunohistochemical workup is recommended to allow for an accurate diagnosis and also to preserve as much tissue for molecular testing as possible. Most tumors can be classified using a single adenocarcinoma marker (e.g., TTF-1 or mucin) and a single squamous marker (e.g., p40 or p63). Non–small cell carcinomas (NSCC, without the L for lung) that show no clear adenocarcinoma or squamous cell carcinoma morphology or immunohistochemical markers are regarded as NSCC not otherwise specified (NOS). In this setting, it is recommended that pathologists use the term NSCC rather than NSCLC, because the lack of pneumocyte marker expression in small biopsies or cytology leaves open the possibility of a metastatic carcinoma and the determination of a lung primary must be established clinically after excluding other primary sites. If tumor with this morphology stains with pneumocyte markers (i.e., TTF-1), it is classified as NSCC, favor adenocarcinoma, and if it stains only with squamous markers (i.e., p40), it is classified as NSCC, favor squamous cell carcinoma (Table 2). In this way, application of immunohistochemistry increases the refinement of diagnosis so that a diagnosis of NSCC NOS can be avoided in up to 90% of cases.[13,14] In cases that meet criteria for NSCC NOS, consideration should be given for using a limited immunohistochemical panel to confirming a carcinoma (e.g., cytokeratin versus S100 or CD45) or a metastasis (estrogen receptor, prostate specific antigen, paired box 8). Terminology to be used in small biopsies for other major categories of lung cancer is summarized in Table 3.[7,11]

It is recognized that not all laboratories worldwide will have access to immunohistochemistry, or even a mucin stain, and in this setting, the diagnosis of NSCC NOS may remain frequent. However, the current classification still needs to encompass scientific advances where they can impact patient care. Accepted markers for identification of differentiation toward adenocarcinoma are TTF-1[13,14,16] and Napsin-A,[17] both of which are approximately 80% sensitive, although TTF-1 is easier to assess as a nuclear stain. In relation to squamous differentiation, P40 is reported as the most specific and sensitive squamous marker.[18–20] Other previously recommended antibodies include cytokeratin 5/6 and P63.[13,14] A reasonable recommendation is that, when immunohistochemistry is deemed necessary, at least one antibody each for squamous and glandular differentiation, but no more than two antibodies, should be used for an initial workup in each case (e.g., TTF-1 and P40 or P63).[11,21] Thus a simple panel of TTF-1 and p40 may be able to classify most NSCC NOS cases. If these stains are negative, further evaluation to confirm a diagnosis of carcinoma and to exclude a metastasis is appropriate. If TTF-1 reactivity is present in one population of tumor cells and another population is positive for squamous markers, this may raise the possibility of adenosquamous carcinoma, although this diagnosis can only be made based on a resection specimen.

Need to Apply New WHO Criteria in Future Clinical Trials and Genetic Studies

There is a great need for these new terminology and diagnostic criteria for small biopsies and cytology to be

applied in clinical trials of patients with advanced lung cancers.[22] Unfortunately, most of the existing clinical trial data regarding histology are based on studies where some cases would be reclassified if this new approach were applied. For example, some of the data regarding pemetrexed efficacy in cancers other than squamous cell carcinoma and regarding the toxicity of bevacizumab in squamous cell carcinomas need to be reevaluated with the new criteria.

In addition, future large-scale genetic studies such as The Cancer Genome Atlas need to incorporate the new criteria for both small biopsies and resection specimens, which now require immunohistochemistry to precisely classify poorly differentiated tumors such as solid adenocarcinoma or nonkeratinizing squamous cell carcinoma.[1] This was not possible with the recent lung squamous cell carcinoma and adenocarcinoma The Cancer Genome Atlas projects,[23,24] but, fortunately, this was done with the Clinical Lung Cancer Genome Project, which allowed for precise classification of the tumors that resulted in critical genetic data to guide some of the key revisions in the current WHO Classification, particularly for large cell carcinoma.[25]

Histologic Grading of Lung Cancer

There is no established histologic grading system for most lung cancers. Some tumors such as neuroendocrine tumors are inherently graded as they are classified with low-grade typical carcinoid, intermediate-grade atypical carcinoid, and high-grade LCNEC and small cell carcinoma. Other tumors such as large cell carcinoma and pleomorphic carcinoma are always high grade. In resection specimens, proposals have been made for grading lung adenocarcinoma using architectural versus nuclear approaches or a combination of both.[26–30] At the moment, grading according to the single most predominant pattern appears to be a simple and sufficient approach. Most studies show lepidic adenocarcinomas are low grade; acinar and papillary tumors are intermediate grade; solid and micropapillary tumors are high grade.[31,32] However, it would be useful to stratify further the intermediate-grade acinar and papillary adenocarcinomas, and this may be a good role for nuclear grading and mitotic counts.[27–29,33,34] However, more investigation is needed to address which approach is clinically relevant. For resected squamous cell carcinomas, there is very little data available, but nuclear diameter has been shown to be an independent predictor of worse outcome.[35] In one cytologic study, nuclear grading provided prognostic distinctions in aspiration biopsies.[36] Tumor budding has been recently reported to be an independent prognostic factor in both lung adenocarcinoma and squamous cell carcinoma.[35,37–39] In conclusion, there is a great need for additional studies of histological grading in lung cancer.

LUNG CANCER CLASSIFICATION IN RESECTION SPECIMENS

The remainder of this discussion regarding lung cancer primarily addresses diagnosis and classification in resection specimens. In some of these tumors such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), large cell carcinoma, adenosquamous carcinoma, and pleomorphic carcinoma, the diagnosis cannot be made without complete evaluation of the entire tumor histologically.

ADENOCARCINOMA

Major Changes in Adenocarcinoma Classification

In 2011, a new IASLC/ATS/ERS classification of lung adenocarcinoma proposed significant changes to the 2004 WHO classification for resected tumors including (1) discontinuing the terms bronchioloalveolar carcinoma (BAC) and mixed subtype adenocarcinoma; (2) the addition of AIS as a preinvasive lesion to join atypical adenomatous hyperplasia; (3) addition of MIA, (4) classification of invasive adenocarcinomas according to the predominant subtype after comprehensive histologic subtyping by semiquantitatively estimating the percentage of the various subtypes present in 5% increments; (5) use of the term "lepidic" for a noninvasive component (previously classified as BAC) present as part of an invasive adenocarcinoma; (6) introducing the term "invasive mucinous adenocarcinoma" for adenocarcinomas formerly classified as mucinous BAC, excluding tumors that meet criteria for AIS or MIA; (7) discontinuing the subtypes of clear cell and signet ring adenocarcinoma and recognizing these as a feature when any amount is present, however small; (8) discontinuing the term mucinous cystadenocarcinoma and including these under the category of colloid adenocarcinoma.[3,7,11,40]

Subsequent to the 2011 IASLC/ATS/ERS lung adenocarcinoma classification and with the development of the 2015 WHO classification, it was decided to classify tumors formerly called large cell carcinomas that have pneumocyte marker expression (i.e., TTF-1 and/or Napsin A), as solid adenocarcinoma even if mucin is absent.[1] Solid adenocarcinoma must be distinguished from squamous cell carcinomas and large cell carcinomas, both of which may show rare cells with intracellular mucin. Solid adenocarcinoma should show at least two high-power fields with five or more cells showing intracytoplasmic mucin. The expression of TTF-1 and/or Napsin-A is sufficient not only for diagnosing solid adenocarcinoma, but for separating it from squamous cell carcinoma.[41,42]

Criteria for diagnosis of AIS and MIA are summarized in Tables 4 and 5. With regard to the term lepidic, resected

TABLE 4. Adenocarcinoma In Situ[a]

Diagnostic criteria

- A small tumor ≤3 cm[a]
- A solitary adenocarcinoma
- Pure lepidic growth
- No stromal, vascular or pleural invasion
- No pattern of invasive adenocarcinoma (such as acinar, papillary, micropapillary, solid, colloid, enteric, fetal or invasive mucinous adenocarcinoma).
- No spread through air spaces
- Cell type mostly nonmucinous (type II pneumocytes or Clara cells), rarely may be mucinous (tall columnar cells with basal nuclei and abundant cytoplasmic mucin, sometimes resembling goblet cells).
- Nuclear atypia is absent or inconspicuous
- Septal widening with sclerosis/elastosis is common, particularly in nonmucinous adenocarcinoma in situ

[a]Modified from the articles by Travis et al.[1,7,11]

TABLE 5. Minimally Invasive Adenocarcinoma[a]

Diagnostic criteria

- A small tumor ≤3 cm
- A solitary adenocarcinoma
- Predominantly lepidic growth
- ≤0.5 cm invasive component in greatest dimension in any one focus
- Invasive component to be measured includes
  - Any histologic subtype other than a lepidic pattern (such as acinar, papillary, micropapillary, solid, colloid, fetal or invasive mucinous adenocarcinoma)
  - Tumor cells infiltrating myofibroblastic stroma
- Minimally invasive adenocarcinoma diagnosis is excluded if the tumor
  - Invades lymphatics. blood vessels, air spaces or pleura,
  - Contains tumor necrosis,
  - Spreads through air spaces
- The cell type mostly nonmucinous (type II pneumocytes or Clara cells), but rarely may be mucinous (tall columnar cells with basal nuclei and abundant cytoplasmic mucin, sometimes resembling goblet cells).

[a]Modified from the articles by Travis et al.[1,7,11]

primary lung adenocarcinomas that are lepidic predominant invasive adenocarcinoma should be called "adenocarcinoma, lepidic subtype" or "lepidic adenocarcinoma" with mention of the percentage of the lepidic component and listing of each of the other patterns present with their estimated percentage. Measurement of invasive size can be challenging in tumors with a lepidic component. If there is a single focus of invasion in a small tumor, it can be measured microscopically with a ruler on top of the slide on the microscope stage. If there are multiple foci of invasion or if the tumor does not fit onto a single slide, making ruler measurements difficult, recent data suggest that another way to estimate the invasive size is to sum the percentage of the invasive components and multiply this by the overall tumor diameter (i.e., a 2.0-cm total tumor size with 20% invasive components and 80% lepidic component would have an estimated invasive size of $2.0 \times 0.2 = 0.4$ cm).[43] In the differential with MIA, if the result is greater than 5 mm, a diagnosis of lepidic adenocarcinoma should be rendered. If there is doubt about tumor size after review of pathologic slides, correlation with a high-resolution computed tomography (CT) may be helpful to appreciate the amount of solid versus ground glass components in a lung nodule as these generally correspond to invasive versus lepidic components histologically.

The diagnosis of AIS or MIA can only be made in a resected tumor that has been submitted entirely for histologic evaluation, so complete histologic review can be performed to look for invasive foci. Therefore, when a small biopsy shows only a nonmucinous lepidic pattern, the diagnosis should be "adenocarcinoma with lepidic pattern" (Fig. 1*A*) adding a comment that this could be from a lesion that represents AIS, MIA, or invasive adenocarcinoma with a lepidic component (i.e., adenocarcinoma, lepidic subtype, or an invasive adenocarcinoma with a non-predominant lepidic component). Rarely, metastatic tumors may show a lepidic pattern, but they do not typically express TTF-1 in addition to the morphology of type II pneumocytes and/or club (Clara) cells. Correlation with CT findings can be informative to the likely final diagnosis (Fig. 1*B*). For example, if a biopsy shows a lepidic pattern and the CT shows a pure ground glass nodule, this would favor AIS or possibly MIA and less likely lepidic predominant adenocarcinoma (Fig. 1*B*), whereas if a mostly ground glass nodule also had a solid component measuring over 5 mm in size were present, this would favor lepidic predominant adenocarcinoma (Fig. 1*C*).[44–47] However, the final diagnosis of AIS or MIA requires a resection specimen, and these cannot be diagnosed in small biopsy specimens. It is reasonable to sample possible AIS or MIA lesions to save frozen tissue for research, but correlation with the CT findings should be made to be sure there are no suspicious solid areas for invasion. If suspicious areas are seen on CT and they are not represented in the histologic slides, the frozen sample may need to be processed for histologic examination to allow for a definitive diagnosis.

As most of the literature on MIA and AIS deals with tumors less than or equal to 2 to 3 cm, there is insufficient evidence that 100% disease-free survival can occur with such

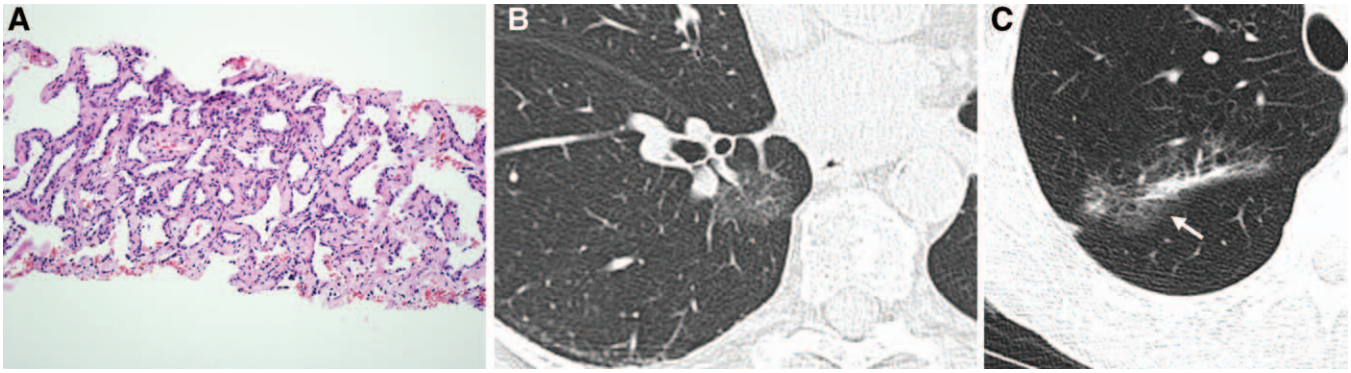

FIGURE 1. *A*, Core biopsy shows an "adenocarcinoma with a lepidic pattern." *B*, Correlation with the computed tomography (CT) scan shows a 2.5-cm pure ground glass nodule with no solid component, favoring a diagnosis of adenocarcinoma in situ (AIS), although a small invasive component or minimally invasive adenocarcinoma (MIA) cannot be excluded. *C*, This part solid nodule is from a resected lepidic predominant adenocarcinoma. If a core biopsy came from the ground glass area highlighted by the arrow, it could show the same pathologic findings as in *A*. It would be misleading to make a pathologic diagnosis of AIS in such a case as the entire lesion has not been sampled and the invasive component is not represented in the biopsy specimen.

tumors greater than 3 cm.[7,40] Therefore, if a tumor larger than 3 cm has been completely sampled histologically and shows either no invasion or less than or equal to 0.5 cm of invasion, the tumor should be classified as "lepidic adenocarcinoma, suspect AIS or MIA," respectively.

In the 2015 WHO classification, the term "predominant" is not listed in the name for the major adenocarcinoma subtypes as it was in the 2011 IASLC/ATS/ERS lung adenocarcinoma classification. However, these tumors still should be classified according to the predominant subtype after evaluation of the tumor using comprehensive histologic subtyping to make a semiquantitative estimate of all of the different histologic patterns present in 5% increments. Classification of tumors according to the predominant subtype should not be interpreted to imply these are specific entities. Because lung adenocarcinomas frequently are composed of complex heterogeneous mixtures of patterns with a continuum from one pattern to the next (i.e., lepidic to papillary or acinar), comprehensive histologic typing provides a useful tool to estimate not only the predominant pattern but also minor components. It is very useful to document these percentages in pathology reports as it helps to document cases where there are small amounts of the micropapillary pattern, which have been shown to be associated with poor prognosis even in small amounts as it helps to compare multiple adenocarcinomas to document whether the percentages of patterns is similar or different.[48] Even though it is theoretically possible to have equal percentages of two prominent components, in practice, a single predominant component should be chosen. Recording of these percentages in a pathologic diagnosis in such a case makes it clear to the reader of a report when a tumor has relatively even mixtures of several patterns versus a clear single predominant pattern. One point of frequent questioning is when an area of adenocarcinoma shows an acinar or lepidic pattern, and there are tumor cells within air spaces in a micropapillary pattern; this should be classified as micropapillary and not acinar or lepidic (Fig. 2). Several studies have shown that the cribriform pattern is associated with worse prognosis.[49–51] Recognition of this pattern may be a way to recognize a higher grade of tumors with acinar growth.

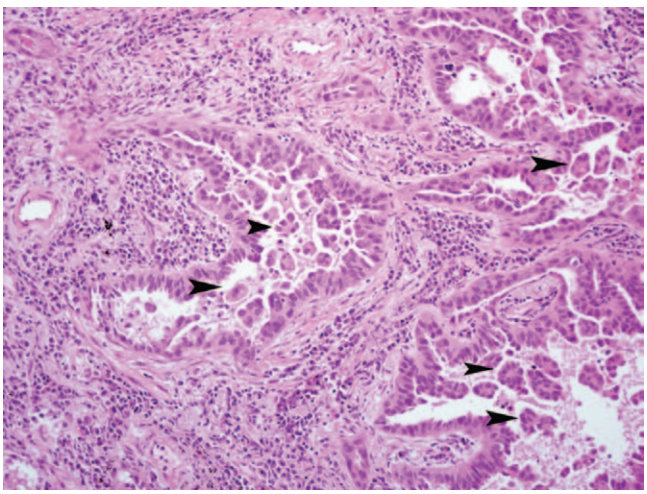

FIGURE 2. Adenocarcinoma with micropapillary pattern. When an airspace contains a micropapillary pattern (arrowheads), even if it is surrounded by lepidic or acinar structures, it should be classified as a micropapillary pattern.

A reproducibility study of classical and difficult selected images of the major lung adenocarcinoma subtypes circulated among a panel of 26 expert lung cancer pathologists documented κ- values of 0.77 ± 0.07 and 0.38 ± 0.14, respectively.[52] A study of reproducibility for predominant pattern showed moderate to good κ-values of 0.44 to 0.72 for pulmonary pathologists. For untrained pathologists, κ-values were expectedly lower ranging from 0.38 to 0.47, but these improved after a training session to 0.51 to 0.66 and reevaluation by the same reviewers led to very high κ-values between 0.79 and 0.87.[53]

Spread Through Air Spaces

Since the 2011 IASLC/ATS/ERS lung adenocarcinoma classification was published, an additional pattern of invasion is now more clearly recognized consisting of spread through air spaces (STAS). STAS consists of micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma (Fig. 3). It probably contributes to the significantly increased recurrence rate for patients with small stage 1 adenocarcinomas who undergo limited resections[54] and the worse prognosis observed by others.[55–57] As this represents a manifestation of tumor spread, this is not included in the percentage measurement of subtype patterns in comprehensive histologic typing or in measurement of invasive size. STAS is now incorporated into the definition of invasion that is used to separate lepidic adenocarcinomas from MIA and AIS. STAS is a pattern of invasion to be reported similar to visceral pleural and vascular invasion.

Comparing Multiple Lung Adenocarcinomas

Comprehensive histologic subtyping can be useful in comparing multiple lung adenocarcinomas in a single patient to distinguish multiple primary tumors from intrapulmonary metastases. This has a great impact on staging for patients with multiple lung adenocarcinomas. Recording the percentages of the various histologic subtypes in 5% increments, not just the most predominant type, allows these data to be used to compare multiple adenocarcinomas, particularly if the slides of a previous tumor are not available at the time of review of the additional lung tumors. In addition to comprehensive histologic subtyping, other histologic features of the tumors such as cytologic (clear cell or signet ring features) or stromal (desmoplasia or inflammation) characteristics may be helpful to compare multiple tumors.[48] It is likely that poorly differentiated components such as solid and micropapillary may be enriched in some metastatic foci, so one does not necessarily expect an identical percentage distribution of patterns in intrapulmonary metastases, and in such cases, other stromal or cytologic characteristics may play a more important role. Nevertheless this is a powerful tool for morphologic comparison of multiple tumors. Several genetic studies have addressed this problem,[48,58–63] but the role of molecular studies including what platform to utilize and how to interpret the results remains to be established. Ultimately, a multidisciplinary

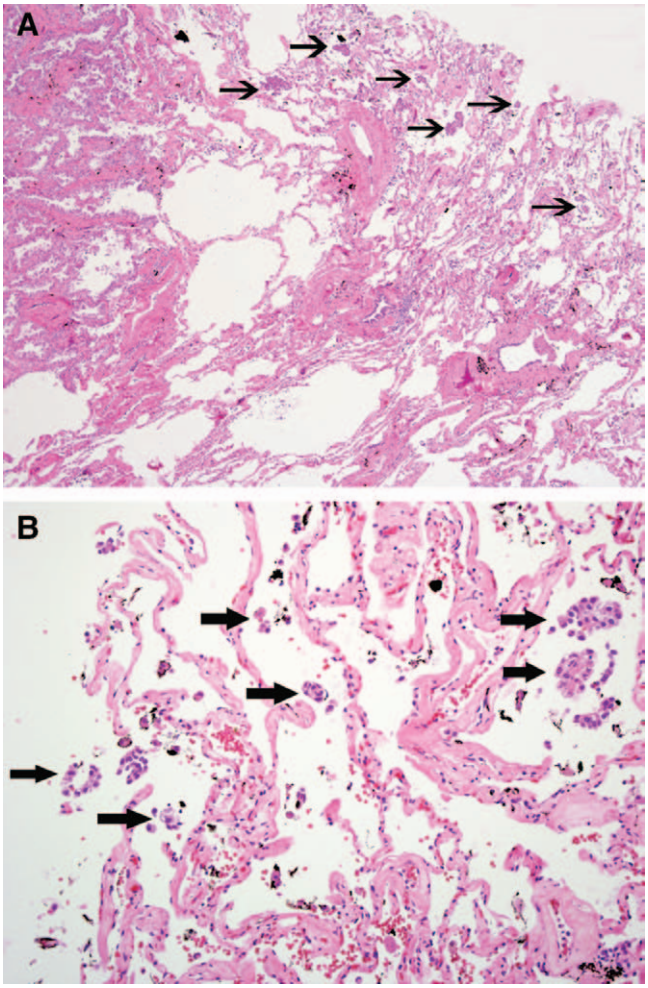

FIGURE 3. Invasion of adenocarcinoma in the pattern of spread through air spaces (STAS). *A,* Tumor cells are present within airspaces in the lung parenchyma beyond the edge of the tumor (arrows). *B,* These consists of micropapillary clusters and single cells (arrows).

approach is needed to address this problem incorporating clinical, radiologic, molecular, and pathologic information.

Prognostic and Predictive Implications of Adenocarcinoma Comprehensive Subtyping

Despite the challenges in distinguishing some patterns from each other, since the principle of comprehensive histologic subtyping was introduced in the 2011 IASLC/ATS/ERS classification, there are a growing number of studies of resected lung adenocarcinomas that have demonstrated its utility in identifying significant prognostic subsets and molecular correlations according to the predominant patterns.[31,32,43,64–69] The prognosis for lepidic predominant adenocarcinoma in stage I patients is excellent[31,32,43,69,70]; most of those tumors that recur have some high risk factor such as a close margin in limited resection and presence of a micropapillary component or invasion of blood vessels and/or pleura.[43] The solid and micropapillary subtypes are associated with poor prognosis.[64,66–68,70,71] The presence of the micropapillary subtype is a poor prognostic factor for overall survival[72] and for recurrence in patients with limited resections.[73] Solid predominant subtype has also been shown to be an independent predictor of early, extrathoracic, multisite recurrence, and poor postrecurrence survival.[74]

New data suggest that micropapillary or solid predominant subtyping predicts improved responsiveness to adjuvant chemotherapy compared with acinar or papillary predominant tumors in surgically resected lung adenocarcinoma patients when analyzed by disease-free survival and specific disease-free survival.[75]

SQUAMOUS CELL CARCINOMA

The terminology and criteria for squamous cell carcinoma diagnosis in small biopsies are discussed above, and the comments below refer to these issues in resection specimens. In the 2004 WHO classification, the major subtypes included papillary, clear cell, small cell, and basaloid carcinoma. However, this was not very meaningful as the papillary, clear cell, and small cell subtypes are very uncommon.[35] In retrospect, the term small cell variant of squamous cell carcinoma was probably not a good choice because if it were used in clinical practice, it could be confused with small cell carcinoma, so this term is now discontinued. As with lung adenocarcinoma, clear cell change is now regarded as a cytologic feature that can occur in keratinizing or nonkeratinizing squamous cell carcinoma, so this is no longer recognized as a formal subtype, although it can be referred to in a diagnosis as "with clear cell features" with the amount mentioned even if in a small percentage. In addition, with the new importance of separating adenocarcinoma and squamous cell carcinoma, it was learned through molecular and immunohistochemical studies that some adenocarcinomas have a very squamous-like morphology.[41,42] So in the absence of unequivocal keratinization, immunohistochemistry with positive squamous markers such as p40 or p63 is required to diagnose surgically resected nonkeratinizing squamous cell carcinoma. Furthermore, with the recognition that the former basaloid carcinomas actually express squamous markers, these tumors were moved from the category of large cell carcinoma to become a subtype of squamous cell carcinoma. Genetic data also support that basaloid squamous cell carcinomas show a specific mRNA expression profile, factors controlling cell cycle, transcription, chromatin, and splicing with prevalent expression in germ line and stem cells and underexpress typical genes seen in other squamous cell carcinomas.[76] For these reasons, the subtyping of squamous cell carcinoma was modified to consist of keratinizing, nonkeratinizing, and basaloid subtypes, similar to the Head and Neck WHO Classification of nasopharyngeal carcinomas (Table 1).[77] Tumors are classified as keratinizing subtype if any amount of keratinization is present and basaloid squamous cell carcinoma if this component is greater than 50% of the tumor, regardless of the presence of any keratinization. In tumors with 50% or less of a basaloid component, this can be acknowledged in the diagnosis "with basaloid features."[1] There does not seem to be prognostic significance to keratinizing versus nonkeratinizing squamous carcinomas.[35] Some studies suggest a poorer prognosis for basaloid squamous cell carcinomas,[76,78,79] but other data do not support this.[35,80,81]

There is currently no clear clinical implication to the subtyping of squamous cell lung cancer. However, there is an increasing amount of clinical data on new therapies for this tumor (e.g., immunotherapy and new targeted therapies).[82]

LARGE CELL CARCINOMA

The entity large cell carcinoma can only be diagnosed in a surgical resected tumor, so this term should not be applied to small biopsies or cytology (see above). In the 2004 WHO classification, large cell carcinoma included several variants such as LCNEC, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype.[3] In addition, in the 2004 WHO Classification, there was no role for immunohistochemistry using adenocarcinoma or squamous markers in assessing these tumors. However, in the 2015 WHO Classification, carcinomas showing a solid pattern are now reclassified as solid adenocarcinoma or nonkeratinizing squamous cell carcinoma, if they show positive staining for markers such as TTF-1 or p40, respectively.[1] This decision was based on genetic and immunohistochemical studies indicating that tumors previously classified as large cell carcinomas were a heterogeneous group of tumors with adenocarcinoma, squamous cell differentiation, or a null immunophenotype and genotype.[21,83,84] Poorly differentiated carcinomas are regarded to have a null immunophenotype if they lack clear pneumocyte (i.e., TTF-1), squamous (p40), or neuroendocrine (chromogranin, synaptophysin, CD56) marker staining patterns. Tumors with adenocarcinoma or null immunophenotype typically showed an adenocarcinoma genetic profile, and those with a squamous immunophenotype showed a squamous genetic profile.[21,83–85] Furthermore, epidemiologic evidence from the National Cancer Institute (NCI) Surveillance Epidemiology and End Results registry indicated that the diagnosis of large cell carcinoma started to decline about the time that TTF-1 was introduced into clinical diagnosis, so this probably reflects that practicing pathologists started to reclassify large cell carcinomas.[86]

The other large cell carcinoma subtypes from the 2004 WHO classification are reclassified as follows. LCNEC is now grouped with the other neuroendocrine tumors. Basaloid carcinoma is moved to a subtype of squamous cell carcinoma. Lymphoepithelioma-like carcinoma is moved to a group of "other and unclassified carcinomas." Clear cell carcinoma and rhabdoid phenotype are now regarded as a cytologic features rather than a specific histologic subtype, as these can occur in a variety of histologic types including adenocarcinoma or squamous cell carcinoma (Table 1).

NEUROENDOCRINE TUMORS

In the 1981, prior WHO classifications the carcinoid tumors, small cell lung carcinoma (SCLC) and LCNEC were grouped separately. However, in the current classification they are grouped together.[1] The tumors are listed in the order of their frequency with SCLC first as it is the most common. Although some have suggested there should be a uniform neuroendocrine tumor classification system throughout the body including the lung, similar to the one used in the gastrointestinal tract and pancreas, a leading organization, the European Neuroendocrine Tumor Society, has endorsed the WHO classification for pulmonary neuroendocrine tumors.[87]

Despite the grouping of these tumors together, it is clear that the carcinoids have major clinical, epidemiologic, histologic, and genetic differences compared with the high-grade SCLC and LCNEC. Carcinoid patients are significantly younger, have a better prognosis, and lack the strong association with smoking that applies for SCLC and LCNEC. Also compared with carcinoid tumors, SCLC and LCNEC have much higher mitotic rates, more necrosis and can show combinations with other lung cancer types including adenocarcinoma or squamous cell carcinoma.[87] Carcinoid tumors also have very few genetic abnormalities compared with SCLC and LCNEC.[85,88]

Although, in many cases, SCLC and carcinoid tumors can be diagnosed on good quality tumor material with a high-quality hematoxylin and eosin–stained section and in well preserved cytologic samples, immunohistochemistry can be very helpful in diagnosing pulmonary neuroendocrine tumors. The role of Ki-67 is mainly to separate the high-grade SCLC and LCNEC from the carcinoid tumors, especially in small biopsies with crushed and/or necrotic tumor cells.[89,90] Data are conflicting regarding its use in separating typical from atypical carcinoid tumors, so it is not recommended in this setting.[87,89,91]

Mitosis counting methods were not specified in the 2004 WHO Classification, but more detail is provided in the 2015 book. Careful counting of mitoses is essential as it is the most important histologic criteria for separating typical from atypical carcinoid and the carcinoids from the high-grade SCLC and LCNEC. Mitoses should be counted in the areas of highest activity and per 2 mm^2 rather than 10 high-power fields. Because of the differences in microscope models, adjustments need to be made in the number of high-power fields reviewed to assess a 2 mm^2 area of tumor.[92] In tumors that are near the cutoffs of 2 or 20 mitoses per 2 mm^2, at least three sets of 2 mm^2 should be counted and the mean used for determining the mitotic rate, rather than the single highest rate. For typical and atypical carcinoid tumors, mitotic rate and necrosis status should be included in pathology reports.

Because of recognition of the potential overlap in the morphology of LCNEC and basaloid squamous cell carcinoma, it can be helpful to confirm negative squamous markers (i.e., p40) in TTF-1–negative tumors that otherwise meet criteria for LCNEC. In 10-20% of NSCC, neuroendocrine differentiation can be demonstrated. This is not formally recognized as class of tumors in the 2015 WHO Classification, as there is no proven clinical significance to this finding.[1,3,7]

SARCOMATOID CARCINOMA

Sarcomatoid carcinoma is a general term that includes pleomorphic carcinoma, carcinosarcoma, and pulmonary blastoma. For this reason, it is best to use the specific term for these entities whenever possible rather than the general term. This also may avoid any confusion with a true sarcoma. These tumors are rare accounting for less than 1% of all lung cancers.[93] There are no major changes in the terminology or diagnostic criteria for these tumors since the 2004 Classification. One new aspect is the recommendation for molecular testing according to known genetic abnormalities associated with histologic components (i.e., tumors with an adenocarcinoma component should be

tested for *EGFR* mutation and *ALK* rearrangement). The diagnoses of pleomorphic, spindle cell, or giant cell carcinoma cannot be made on small biopsies or cytology, and recommendations for diagnostic terminology in these types of specimens are discussed above. It is very difficult to diagnose carcinosarcoma or pulmonary blastoma in small biopsies and cytology, but if material is obtained that fulfills diagnostic criteria, it is possible. Prognosis for all these tumors is poor.

Pleomorphic carcinoma is a poorly differentiated NSCC namely a squamous cell carcinoma, adenocarcinoma, or undifferentiated NSCC that contains at least 10% spindle and/or giant cells or a carcinoma consisting only of spindle and giant cells. The prevalence of *KRAS* (in up to 38% of cases)[94,95] and *EGFR* mutations (in up to 25% of cases)[96–98] partially reflects the tumor components (i.e., adenocarcinoma), patient ethnicity, and smoking habits.[99]

Spindle cell carcinoma consists of an almost pure population of epithelial spindle cells, with no differentiated carcinomatous elements.

Giant cell carcinoma consists almost entirely of tumor giant cells (including multinucleated cells), with no differentiated carcinomatous elements. Definite diagnosis may only be made on a resected tumor. The specific histological components should be mentioned in the diagnosis.

Carcinosarcoma is a malignant tumor that consists of a mixture of NSCLC (typically squamous cell carcinoma or adenocarcinoma) and sarcoma-containing heterologous elements, such as rhabdomyosarcoma, chondrosarcoma, and osteosarcoma. Carcinosarcomas are clonal tumors[100–102] developing through sarcomatoid change in a carcinoma.[100,102] *TP53* mutations are often present in carcinosarcoma,[101,103] whereas *KRAS* mutations occur less frequently,[101,103] and *EGFR* mutations are very uncommon.[103,104]

Pulmonary blastoma is a biphasic tumor that consists of fetal adenocarcinoma (typically low grade) and primitive mesenchymal stroma. Foci of specific mesenchymal differentiation (osteosarcoma, chondrosarcoma, or rhabdomyosarcoma) may also be present but are not required for the diagnosis. Pulmonary blastoma and well-differentiated fetal adenocarcinoma (a putative precursor lesion) are frequently associated with missense mutations in exon 3 of *CTNNB1*, responsible for activation of the Wnt pathway through aberrant nuclear/cytoplasmic localization of β-catenin protein.[103,105–107] *TP53* mutation and both p53 and MDM2 protein accumulation are occasionally detected in pulmonary blastoma.[101,103,108]

NUT CARCINOMA

Carcinomas associated with chromosomal rearrangement in the NUT gene are called NUT carcinomas. These are poorly differentiated carcinomas genetically defined by the presence of *NUT* gene rearrangement.[109,110] This consists of a chromosomal translocation between the *NUT* gene (*NUTM1*) on chromosome 15q14 and other genes: *BRD4* on chromosome 19p13.1 (70%), *BRD3* on chromosome 9q34.2 (6%), or an unknown partner gene (24%).[111] Fewer than 100 cases of NUT carcinoma have been reported. Although it was originally thought to be a disease of children and younger adults, NUT carcinoma can affect people of any age, affecting males and females equally.[109,110]

This tumor was recognized in the thymus in the 2004 WHO classification as a carcinoma with t(15;19) translocation, and it is also referred to as NUT midline carcinoma. Pathologically, it consists of sheets and nests of small-sized to intermediate-sized undifferentiated cells with a monomorphic appearance (Fig. 4*A*).[110] Nuclei have irregular contours and granular to coarse chromatin. Foci of abrupt keratinization are often present. Immunohistochemistry is positive in more than 50% of tumor cells with a speckled nuclear positivity (Fig. 4*B*).[112] NUT carcinoma is a very aggressive tumor with a median survival of 7 months.[113]

TUMORS OTHER THAN LUNG CANCER WITH SIGNIFICANT CHANGES FROM THE 2004 WHO CLASSIFICATION

Sclerosing Pneumocytoma

In this classification, sclerosing hemangioma is moved from a group of "Miscellaneous tumors" where it was

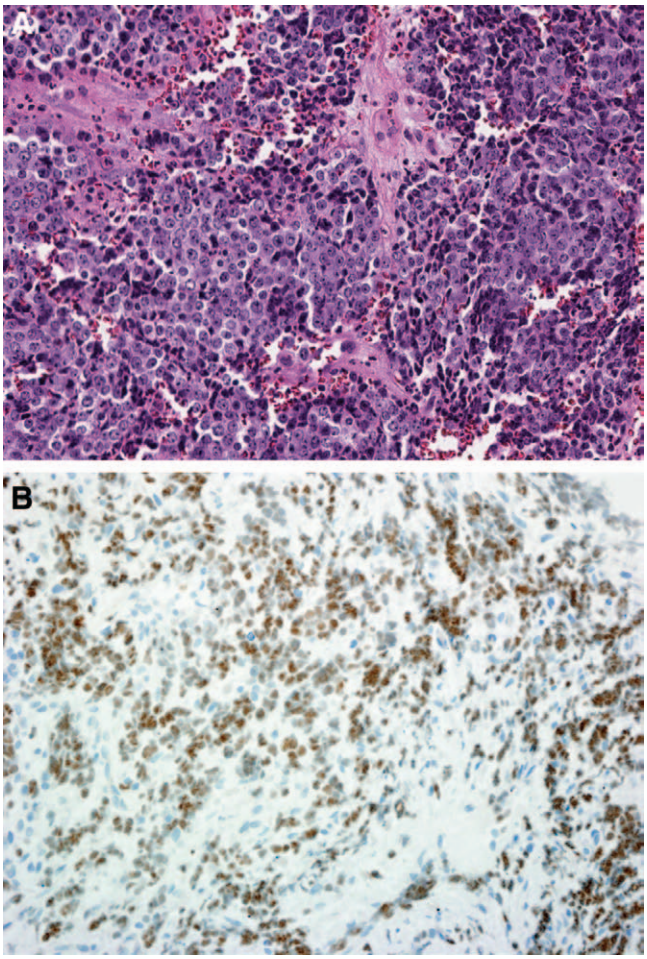

FIGURE 4. Nuclear protein in testis (NUT) carcinoma. *A,* This poorly differentiated carcinoma consists of large cells with moderate eosinophilic cytoplasm and prominent nucleoli. No clear glandular or squamous differentiation is seen. *B,* Immunohistochemistry with NUT antibody shows diffuse strong staining with a granular nuclear pattern.

classified in both the 1999 and 2004 WHO Classifications[3,6] to the group of "Adenomas" in the current classification. It has been recognized for many years that sclerosing hemangioma is not a vascular tumor. Multiple papers have documented that this tumor is actually derived from primitive respiratory epithelial cells that express TTF-1 in the solid as well as surface tumor cells.[114,115] This tumor characteristic has become widely recognized and accepted making it an appropriate time to reclassify this tumor as an adenoma. Sclerosing pneumocytoma is a tumor of pneumocytic origin with a dual population of surface cells resembling type II pneumocytes and round cells, with slightly different histogenetic profiles. Most tumors have at least three of four primary growth patterns: solid, papillary, sclerosing, and hemorrhagic. The key feature of sclerosing pneumocytoma is the presence of two cell types: cuboidal surface cells and stromal round cells, both of which are considered to be neoplastic.[116] The surface cells are cuboidal and morphologically similar to type II pneumocytes. These tumors can be very challenging to diagnose in frozen section, small biopsies, and cytology where they can easily be mistaken for adenocarcinoma or carcinoid tumors. Despite the very rare frequency of metastases, these tumors typically have a benign clinical course.[114]

Pulmonary Hamartoma

Pulmonary hamartomas are neoplasms composed of varying amounts of at least two mesenchymal elements (such as cartilage, fat, connective tissue, and smooth muscle), combined with entrapped respiratory epithelium. Because hamartomas in other parts of the body are generally not regarded to be neoplasms, there was a debate if hamartomas in the lung should have an International Classification of Diseases for Oncology code in this classification. However, because multiple genetic studies have established that these are true neoplasms, they have been assigned a new International Classification of Diseases for Oncology code and the diagnostic term is "pulmonary hamartoma," rather than just hamartoma. Pulmonary hamartomas have a high frequency of the translocation t(3;12)(q27-28;q14-15), resulting in gene fusion of the high mobility group protein gene *HMGA2* and the *LPP* gene. The *HMGA2–LPP* fusion gene usually consists of exons 1–3 of *HMGA2* and exons 9–11 of *LPP* and seems to be expressed in all tumors with this translocation.[117–119]

Pulmonary hamartomas are composed predominantly of chondroid or chondromyxoid tissue intermixed with variable proportions of other mesenchymal components, including fat, myxoid fibrous connective tissue, smooth muscle, and bone. Clefts of normal respiratory epithelial cells represent entrapment by the expanding mesenchymal growth. Endobronchial pulmonary hamartomas may have a prominent adipose tissue component. Immunohistochemical stains show reactivity for mesenchymal markers and sex steroid receptors, but immunohistochemistry is not usually necessary for diagnosis.[120]

PEComatous Tumors

PEComatous tumors are thought to arise from perivascular epithelioid cells. In the lung, they can take several forms: (1) a diffuse multicystic proliferation termed LAM; (2) more rarely, a benign localized mass termed a clear cell tumor or PEComa; and (3) exceptionally, a diffuse proliferation with overlapping features between LAM and clear cell tumor. These lesions are part of the spectrum of PEComatous tumors that arise at several sites throughout the body, originating from the perivascular epithelioid cells, although no counterpart in normal tissue has yet been identified. In the 1999 WHO[6] Classification, LAM was classified under tumor-like lesions, and in 2004,[3] it was moved to mesenchymal tumors. In both 1999 and 2004 WHO Classifications, clear cell tumors were grouped under "Miscellaneous tumors." However, in the 2015 WHO Classification, these lesions are grouped together under the title "PEComatous tumors" with three groups of tumors: (1) LAM, (2) PEComa, benign including clear cell tumor, and (3) PEComa, malignant.[1] Historically LAM was considered an interstitial lung disease but it is now considered to be a low-grade destructive metastasizing neoplasm, as the lesional cells usually have growth-promoting biallelic mutations in the tuberous sclerosis gene *TSC2*. Lymphangioleiomyomatosis cells also show evidence of clonal origin, as well as invasive and metastatic potential further supporting the theory of a neoplastic underpinning.[121–124] There is a very rare association between clear cell tumors and tuberous sclerosis.[125] Isolated cases with more diffuse features that overlap with LAM have also been described,[126] called diffuse PEComatosis.[127]

Lymphangioleiomyomatosis consists of a proliferation of plump spindle-shaped myoid cells with typically pale eosinophilic cytoplasm. These are usually found in the walls of the cystic air spaces, where their growth may be overt and nodular, although some cases may be very subtly infiltrative, to the extent that multiple levels are required to identify the lesional cells. Lesional cells may infiltrate blood vessels and lymphatics, causing secondary pulmonary hemorrhage. Lymphangioleiomyomatosis can be associated with micronodular type II pneumocyte hyperplasia, particularly in individuals with tuberous sclerosis.[128] Clear cell tumors consist of rounded or oval cells with distinct cell borders and abundant clear or eosinophilic cytoplasm. There is mild variation in nuclear size, and nucleoli may be prominent, but mitoses are usually absent.[129,130] The presence of necrosis is extremely rare and should lead to consideration of malignancy,[126,129,131] as should significant mitotic activity and an infiltrative growth pattern. Thin-walled sinusoidal vessels are characteristic. Because of the glycogen-rich cytoplasm, there is usually strong periodic acid–Schiff positivity that is removed with diastase digestion.[132] Cases with diffuse PEComatosis show features overlapping between LAM and clear cell tumor.[127] Both LAM and clear cell tumor stain most consistently for HMB45, melan A, and microphthalmia transcription factor. Clear cell tumors may also stain for S100. Lymphangioleiomyomatosis stains for smooth muscle actin and is S100-negative; some cases also stain for the estrogen and progesterone receptors. The *TSC* mutations that occur in LAM result in abnormal signaling through the mammalian target of rapamycin (mTOR) pathway.[133]

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma is a low-grade to intermediate-grade malignant vascular tumor composed of solid nests and short cords of epithelioid endothelial cells in a myxohyaline stroma.[134,135] The new information regarding this tumor is recognition of a translocation involving the *WWTR1* and *CAMTA1* genes and prognostic factors. The details of the histologic features are described previously.[3,134,135] They may be low or intermediate grade with the latter distinguished by the presence of necrosis, increased mitotic activity (mean 2/2 mm^2), and greater nuclear atypia.[134] The vascular markers CD31, CD34, and FLI1 are more sensitive than factor VIII, and most epithelioid hemangioendothelioma expresses these markers. Focal cytokeratin expression is present in 25% to 30% of cases.[134] A recurrent t(1;3)(p36.3;q25) chromosomal translocation is characteristic of epithelioid hemangioendothelioma.[134,136] The translocation involves two genes, *WWTR1* (3q25), which encodes a transcriptional coactivator that is highly expressed in endothelial cells, and *CAMTA1* (1p36), a DNA-binding transcriptional regulatory protein that is normally expressed during brain development.[137–139] A subset of epithelioid hemangioendothelioma occurring in young adults shows recently described *YAP1–TFE3* fusions.[140] Epithelioid hemangioendothelioma is a low-grade to intermediate-grade malignant tumor with metastatic potential and a 5-year survival rate of 60%. Prognosis is worse for intermediate grade compared with low-grade tumors and can be as low as 20%.[134] Negative prognostic indicators include extensive intrapulmonary and pleural spread, weight loss, anemia, and hemorrhagic pleural effusions.[141]

Pulmonary Myxoid Sarcoma with an *EWSR1–CREB1* Translocation

Primary pulmonary myxoid sarcoma is a malignant tumor that typically arises in the airways. It predominantly consists of lobules of delicate, lacelike strands, and cords of mildly atypical round and spindle cells within a prominent myxoid stroma. Primary pulmonary myxoid sarcoma was first described in 1999.[142] It is seen most often in young adult females, but fewer than 15 cases have been published.[143,144] The tumor is characterized by distinct histological features and an *EWSR1–CREB1* fusion (Fig. 5). Although *EWSR1–CREB1* is also found in other tumors (such as angiomatoid fibrous histiocytoma[144] and clear cell sarcomas),[145] primary pulmonary myxoid sarcomas are morphologically different from these entities. At low power, pulmonary myxoid sarcomas have a lobulated architecture, with an endobronchial location. A fibrous pseudocapsule may be present. Tumors are typically composed of spindle, stellate, and polygonal cells, with a predominant reticular network of delicate lacelike strands and cords within a prominent myxoid stroma that may be lightly basophilic, although more solid areas may be found. A minority have a predominantly solid architecture with a more patternless distribution of cells within the myxoid stroma, which may be focally fibrous (Fig. 5*A*). In one case, cells showed focal multinucleation. Cellular atypia is generally mild to moderate in extent, although rare cases have shown focal marked atypia and multinucleation. Mitotic rates of up to 32 mitoses per 2 mm^2 with atypical forms are described, although the majority shows less than 5 mitoses per 2 mm^2. Necrosis is seen in about 50% of tumors and tends to be focal. Most cases

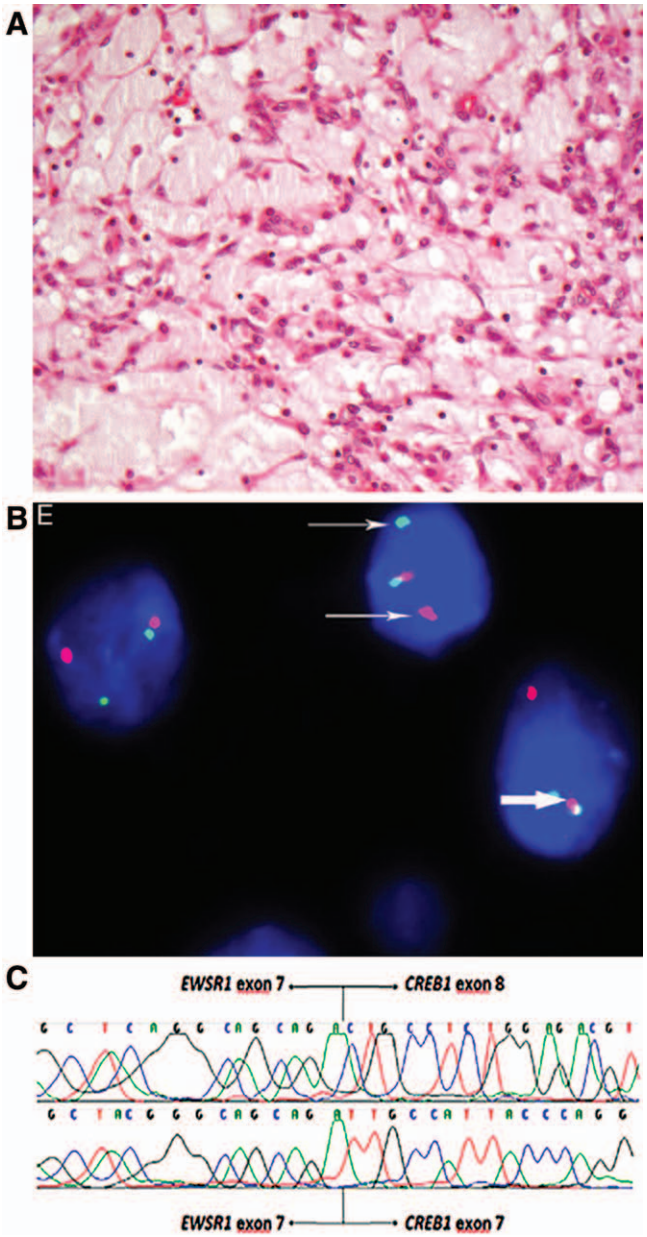

FIGURE 5. Primary pulmonary myxoid sarcoma. *A*, Spindle and rounded cells with typically bland nuclei show a lacelike or reticular architecture within sparsely cellular myxoid stroma, with a mixed chronic inflammatory infiltrate. *B*, Fluorescent in situ hybridization shows split red and green signals (thin arrows) with *EWSR1* break-apart probes in tumor nuclei, consistent with the presence of rearrangements of this gene, contrasting with the fusion signal in a non-rearranged gene (thick arrow). *C*, Direct sequencing confirms the presence of *EWSR1–CREB1* fusions, which predominantly involve exon 7 of each gene (lower diagram), or more rarely occur between exon 7 of *EWSR1* and exon 8 of *CREB1* (upper diagram). *B* and *C*, Reprinted from Thway et al.[143]

have a patchy background chronic inflammatory cell infiltrate of mainly lymphocytes and plasma cells. Vascular invasion is rare.[143] All tumors express vimentin, and 60% show weak and focal staining for epithelial membrane antigen. Other common markers are negative, in particular cytokeratins, S100, smooth muscle actin, desmin, CD34, and neuroendocrine markers. The myxoid stroma is positive for Alcian blue, with staining sensitive to treatment with hyaluronidase.[142]

EWSR1 rearrangements are detectable by fluorescent in situ hybridization, with real-time reverse transcriptase polymerase chain reaction analysis showing *EWSR1–CREB1* fusion transcripts that have been confirmed with direct sequencing (Fig. 5, B and C). In assessable cases, the break point in *EWSR1* involved exon 7, whereas for the *CREB1* gene, exon 7 was involved in six cases and exon 8 in one. Cases have been assessed for fusion transcripts of *NR4A3EWSR1* and *NR4A3TAF15*, but neither were detected.[143]

Myoepithelial Tumors

Myoepithelial tumors of the lung are rare, but they are gaining increasing recognition with the discovery of EWSR1 gene rearrangements as a marker. These tumors show predominant or exclusive myoepithelial differentiation, and malignant myoepithelial tumors are classified as myoepithelial carcinomas. Myoepithelial tumors differ from mixed tumors, in that mixed tumors also show ductal differentiation. Histologically, the tumors show a spectrum of trabecular or reticular patterns, with abundant myxoid stroma (Fig. 6).[146–151] The tumor cells are epithelioid or spindled, and the nuclei are uniform, with eosinophilic or clear cell cytoplasm (Fig. 6). Cells with a plasmacytoid appearance and cytoplasmic hyaline inclusions can be present.[146,147] Myoepithelial carcinomas also show malignant features, such as a high mitotic rate, necrosis, or nuclear atypia.[148,151] Immunohistochemistry shows that most tumors stain positively for keratin, S100, calponin, and glial fibrillary acidic protein. Smooth muscle actin and p63 (or p40) may also be positive. Staining for desmin and CD34 is negative.[134,146,147] *EWSR1* gene rearrangement can be found in pulmonary myoepithelial tumors

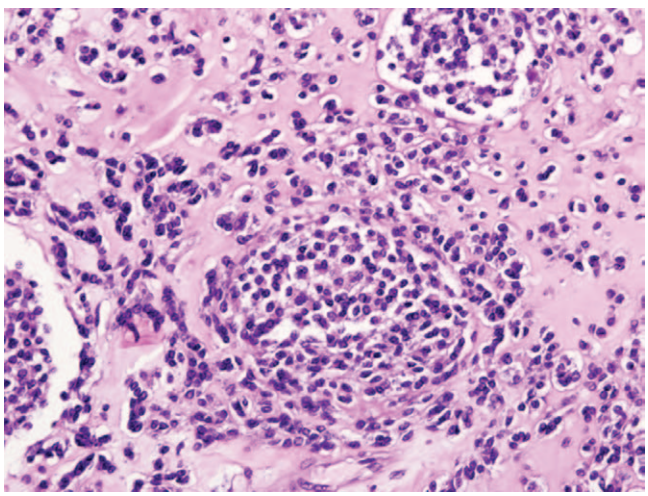

FIGURE 6. Myoepithelioma. The tumor shows clusters of small round cells with focal hyaline stroma.

EWSR1–ZNF444, and *FUS* gene rearrangements were found in two malignant tumors that showed clear cell and spindle cell morphology.[152]

Erdheim–Chester disease

Erdheim–Chester disease is newly added to the classification of lymphoproliferative disorders as it has become better characterized clinically, pathologically, and genetically. It is a rare xanthogranulomatous histiocytosis characterized by infiltration of the skeleton and viscera by lipid-laden histiocytes. In the lung, this leads to interstitial fibrosis with a perilymphatic distribution. Erdheim–Chester disease involves the lungs in 20% to 30% of patients,[153,154] and there is a slight male predominance. Peak incidence occurs within the fifth to seventh decade, with a range of 4 to 87 years and a mean age at diagnosis of 53 years.[153–156] Pulmonary symptoms are typically cough and dyspnea, although pulmonary involvement may also be asymptomatic.[153] Pleural effusions occur in about 20% of patients.[155] General symptoms consist of mild bone pain (occasionally

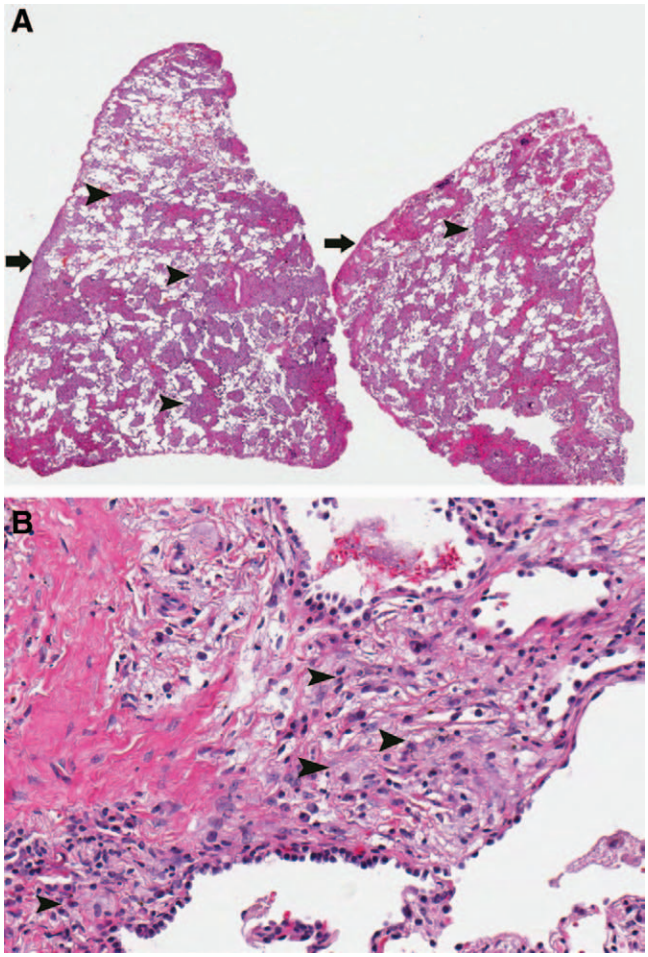

FIGURE 7. Erdheim–Chester disease. *A*, Low power shows diffuse interstitial infiltrates along lymphatic routes: the pleura (arrows) and bronchovascular bundles (arrowheads mark a few of the many affected bronchovascular bundles). *B*, High power shows thickening of the interstitium by sheets of histiocytic cells (arrowheads) adjacent to areas of fibrosis.

associated with soft tissue swelling), fever, weight loss, and weakness. Other manifestations include exophthalmos, diabetes insipidus, kidney failure, and cardiac or neurological symptoms. The serum lipid profile is relatively normal. The lung is involved in more than half of all cases with thoracic involvement, with septal and subpleural thickening, poorly defined centrilobular nodular, and ground-glass opacities, and lung cysts being reported.[155,157] Mediastinal infiltration, pleural thickening, and effusions are also commonly seen.[157] Architecturally, histiocytic infiltration and fibrosis predominate along the distribution of the pulmonary lymphatics (visceral pleura, bronchovascular bundles, and interlobular septa; Fig. 7*A*). Histiocytes are typically foamy, with Touton giant cells often seen (Fig. 7*B*). This is associated with variably dense fibrosis, lymphocytes, plasma cells, and eosinophils. Immunohistochemistry confirms the monocyte/macrophage lineage of the lipid-laden foamy histiocytes and giant cells by their expression of Factor XIIIa, lysozyme, MAC387, CD68 (KP1), CD4, alpha-1 antichymotrypsin, alpha-1 antitrypsin, and S100 protein (variable).[158] They are negative for CD1a. B-rapidly accelerated fibrosarcoma (*BRAF*) V600E mutations have been detected in 54% of patients,[159] and the histiocytic proliferation has been shown to be clonal in some studies[160,161] but not in others.[162] Sustained responses to vemurafenib, a BRAF inhibitor, have been reported in patients with *BRAF* (V600E) mutated Erdheim–Chester disease.[163,164]

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