Review Article

An Update on the Classification of Lung and Pleural Tumors

Liang Lu[1] and Haodong Xu[1,2*] [ID]

[1]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA; [2]Department of Pathology, Wake Forest University, Winston Salem, NC, USA

Abstract

The World Health Organization (WHO) recently published new guidelines for the diagnosis and classification of lung and pleural tumors. This review provides a concise overview of the key updates, including discussions of histologic features and recommended terminology for small diagnostic lung samples, the revised grading system for lung adenocarcinoma with inclusion of complex glandular and filigree micropapillary patterns, and molecular features of large cell neuroendocrine carcinoma. Additionally, rare neoplasms such as bronchiolar adenoma/ciliated muconodular papillary tumor, SMARCA4-deficient undifferentiated thoracic tumor, and primary pulmonary hyalinizing clear cell carcinoma are described in terms of their diagnostic approaches and molecular features. This review also includes discussion of the diagnostic algorithm for malignant epithelioid mesothelioma.

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Introduction

Lung cancer ranks among the leading causes of cancer morbidity and mortality worldwide, with an estimated 2.2 million new cases diagnosed and 1.8 million deaths reported every year.[1] The interpretation of lung biopsies and large resection specimens (wedge resection, segmentectomy, lobectomy, and pneumonectomy) can be challenging due to common confounding factors including the level of experience/subspecialty training of the pathologist, the quality and quantity of the specimens provided by the clinician, and the availability of clinical, imaging, and laboratory testing information.

Within the thoracic space, mesothelioma is the most common primary tumor of the pleura. Mesothelioma has been associated with occupation and environmental exposure to asbestos.[2] The challenges in diagnosing malignant mesothelioma stem from the morphologic variants (deciduoid, clear cell, small cell, signet ring cell, pleomorphic, adenomatoid-like, lymphohistiocytoid, etc.), the availability of diagnostic markers at the local institution, and difficulty with interpreting ancillary studies, which are further exacerbated by the potential medicolegal consequences of this diagnosis.

The World Health Organization (WHO) Classification of Tumors published in 2015 expanded our knowledge of the diagnosis, classification, and genetics of lung tumors and pleural mesotheliomas. This provided us new information about novel immunohistochemical markers, improved understanding of underlying molecular biology, and refined diagnostic stratification of tumor types. However, the WHO published new guidelines on the Classification of Thoracic Tumors in 2021. The aim of this review is to provide a summary of this updated information regarding the new concepts, diagnostic criteria, and guidelines for practicing anatomic pathologists, cytopathologists, pathology trainees, and clinicians.

Highlights of New WHO Classification of Lung Tumors

Small diagnostic samples

Accurate pathologic diagnosis of small samples is essential for guiding clinical therapy of lung cancer. Providing a precise diagnosis based on small biopsy samples requires the pathologist to strike a balance between the clinical need for detailed classification and the limited tissue sample size, which can be further hampered by scant viable tumor cells and/or poorly differentiated tumor morphology. While the optimal approaches to obtaining diagnostic materials differ among institutions, routine methods include imaging guided biopsies and exfoliative specimens such as sputum, bronchial washings/secretions, bronchial brushings, and bronchoalveolar lavages.

Diagnoses of small cell carcinoma, squamous cell carcinoma, and adenocarcinoma with specific growth pattern(s) can be made based on morphological analysis of small biopsies. The use of certain terms for small samples of lung specimens is discouraged in the WHO 2021 guidelines.[3] The term "non-small cell lung carcinoma-not other specified (NSCLC-NOS)" should be minimized, and NSCLC must be further classified as adenocarcinoma or squamous cell carcinoma whenever possible. The term "NSCLC-non-squamous cell carcinoma" should be avoided as a histopathologic diagnosis, as this entity is used by clinicians to describe a heterogeneous group
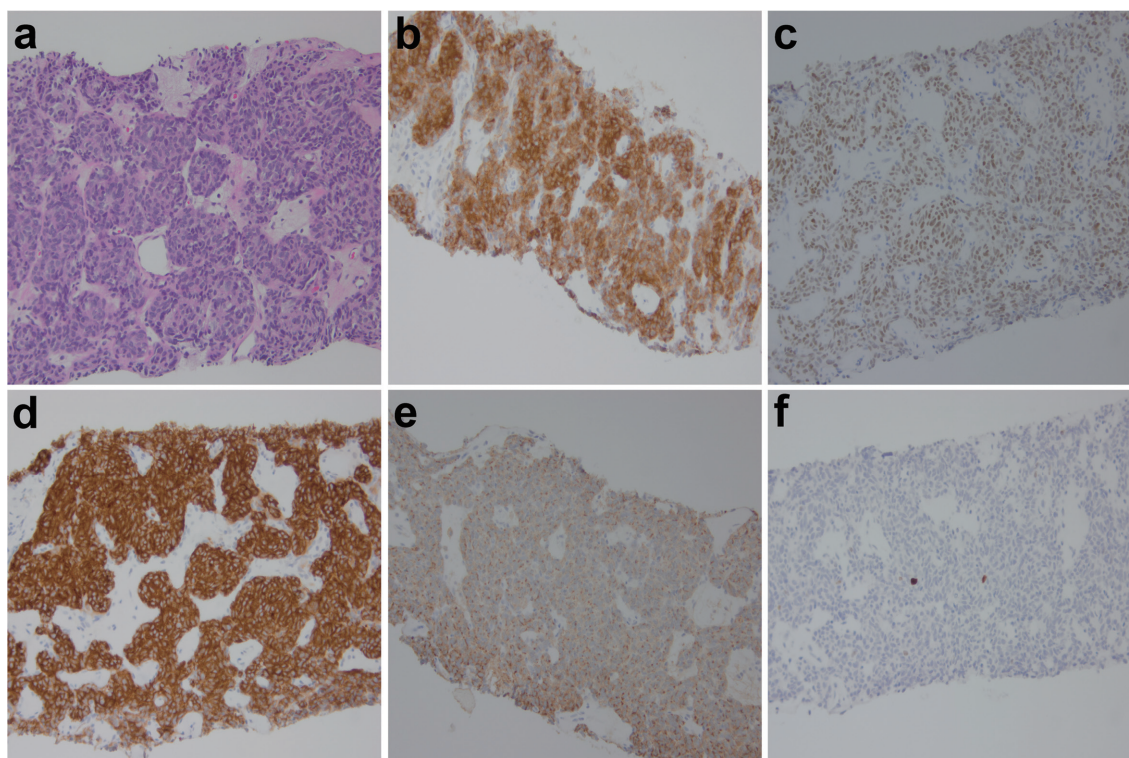
Fig. 1. Typical carcinoid tumor. (a) Tumor cells are uniform with round to oval nuclei and inconspicuous nucleoli, arranged in a nested/organoid pattern. Other growth patterns include pseudoglandular, trabecular, and follicular with rosette formation. There is moderate to abundant eosinophilic cytoplasm (×20). (b) Tumor cells typically show immunoreactivity to CAM5.2, which is helpful to distinguish carcinoid tumor from paraganglioma (×10). (c) TTF-1 would help establish a pulmonary lineage and tend to be focal and weak (×20). Neuroendocrine markers (d) synaptophysin and (e) chromogranin are positive in tumor cells (×20), and (f) proliferation labeling index with Ki-67 should be low in typical carcinoid tumor (×20).

of tumors for clinical trials.[4–6] A few entities require a resection specimen to diagnose, including adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma; in these scenarios, the tumor should be diagnosed as adenocarcinoma with a lepidic growth pattern only if a noninvasive pattern is present, with a comment that definitive diagnosis is deferred to a larger specimen.

When evaluating a biopsy with malignant cells and no clear evidence of glandular formation, squamous differentiation, or neuroendocrine morphology, immunohistochemical analysis, including TTF1 and p40, could be helpful. A diagnosis of NSCLC, favoring adenocarcinoma, can be made based on positive TTF1 staining, and a diagnosis of NSCLC, favoring squamous cell carcinoma, would be supported by immunoreactivity with p40. Adenocarcinoma with a solid pattern should be ruled in/out with special stains, such as mucicarmine, Kreyberg, and PAS-D, to highlight cytoplasmic mucin in the neoplastic cells to be classified as adenocarcinoma. Large cell carcinoma cannot be diagnosed in small samples, as the tumor must be thoroughly sampled in a resection to exclude a different component and determine the proportion of each component. When both TTF1 and p40 staining are negative in the absence of definitive cytoplasmic mucin, NSCLC-NOS can be diagnosed, with a comment in the diagnostic report of the possibility of large cell carcinoma in the resection specimen. Pleomorphic carcinoma (more than 10% spindle or giant cell or combined components in the background of NSCLC), mixed mucinous and non-mucinous adenocarcinoma (more than 10% of each component), and adenosquamous cell carcinoma (more than 10% of each

component) should not be diagnosed based on small biopsies, because the percentage of component cannot be precisely determined based on limited sampling. Of note, reporting the relative proportion of each pattern is discouraged due to possible misrepresentation of a larger tumor in a small biopsy/cytology specimen.

When sarcomatoid features (nuclear pleomorphism, malignant giant cells, or spindle cell morphology) are present in biopsies, the tumor should be classified based on the carcinomatous component (squamous cell carcinoma, adenocarcinoma, or NSCLC, favor adenocarcinoma/squamous cell carcinoma) with a comment describing the sarcomatoid features. In addition, immunohistochemical studies with neuroendocrine markers should be performed only in cases with sufficient neuroendocrine features based on histology/nuclear features (Fig. 1). Carcinoid tumor NOS is used when the tumor exhibits carcinoid morphology with <2 mitoses in a 2 mm^2 region. Ki67 is especially useful in distinguishing carcinoid tumors from small and large cell neuroendocrine carcinoma, particularly in the presence of crush artifacts. Small and large cell neuroendocrine carcinoma should be considered if the tumor has neuroendocrine features with a Ki-67 proliferative index higher than 50%.

Precursor glandular lesions

"Precursor glandular lesions" is listed under epithelial tumors in the 5th edition of WHO, while "precursor lesions" is discussed under adenocarcinomas in the 4th edition of WHO. Precursor lesions of the lung include atypical adenomatous hyperplasia (AAH) and AIS, mucinous and non-mucinous
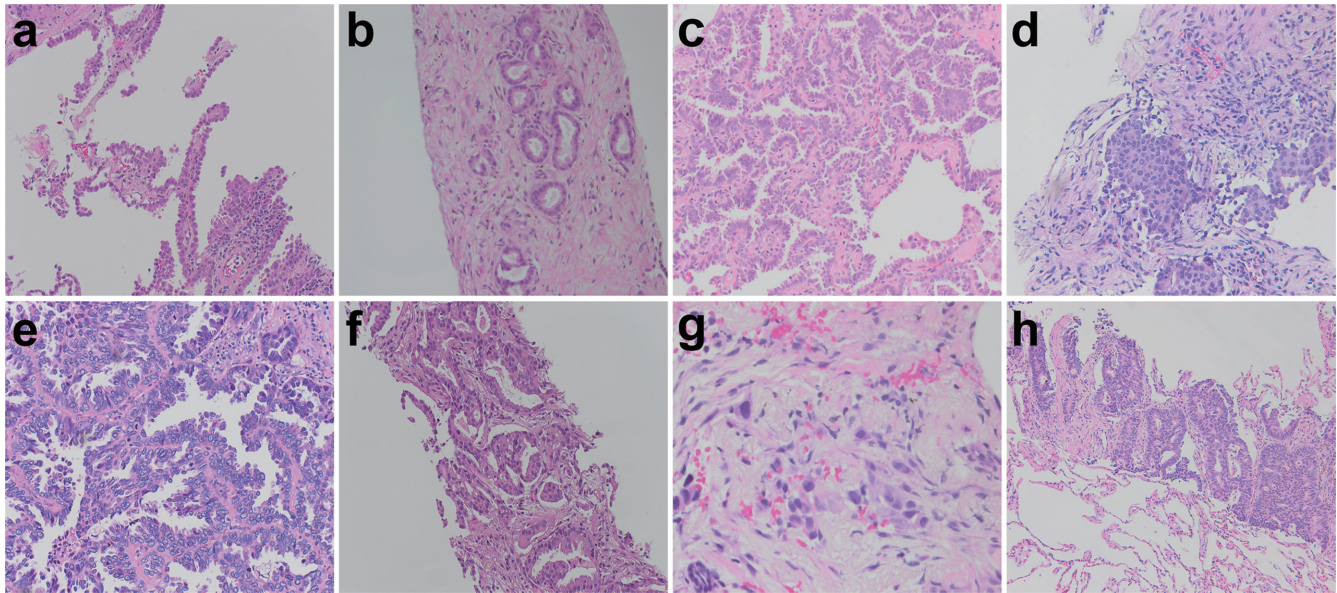
Fig. 2. Primary lung adenocarcinoma growth patterns. (a) Lepidic: atypical pneumocytes lining with preserved alveolar architectures (×20). (b) Acinar: infiltrative well-defined glands (×10). (c) Papillary: true fibrovascular cores (×20). (d) Solid (×10), (e) Micropapillary: tufting of tumor cells with no true fibrovascular core (×20). (f) Complex glandular-poorly formed and fused glands (×10), (g) Complex glandular-infiltrative single cells (×20), (h) Complex glandular-cribriform (×10).

types. Recent studies on tumorigenesis have suggested the step-wise progression from AAH to AIS, and subsequent development into minimally invasive adenocarcinoma and overt invasive adenocarcinomas.[7] AIS is defined as a sole lepidic growth pattern, with atypical pneumocytes lining the preserved alveolar architectures (Fig. 2a). The size must be no greater than 3.0 cm, with no desmoplastic reaction or other invasive growth patterns such as acinar, papillary, micropapillary, solid, or complex glandular. AIS has no tumor necrosis, visceral pleural invasion, or lymphovascular invasion. AAH presents with atypical pneumocytes lining the alveolar septa with a cutoff size at 0.5 cm.

New high-grade patterns of lung adenocarcinoma

For staging purposes, the size of the invasive components (i.e. any growth patterns other than lepidic) must be documented, and the percentage of each growth pattern should be included. In general, invasive tumors with micropapillary (Fig. 2e) and solid (Fig. 2d) growth patterns are clinically more aggressive compared to those with acinar- (Fig. 2b) and papillary-predominant (Fig. 2c) growth.[8,9] Studies have revealed that filigree and complex glandular patterns (Fig. 2h) are considered high-grade patterns and have significant impacts on clinical outcomes in patients with lung adenocarcinomas.[8,10,11]

Filigree pattern as a subtype of micropapillary growth pattern

The filigree micropapillary growth pattern has recently been defined as "tumor cells growing in delicate lace-like narrow stacks of cells without fibrovascular cores".[12] The filigree pattern differs from the classical micropapillary pattern by the absence of floret tufts (Fig. 3). Once this diagnostic criterion is incorporated, tumors conventionally recognized as lepidic, acinar, or papillary surrounded by filigree growth would have been reclassified as micropapillary, and these tumors have been shown to be associated with higher risk of recurrence, advanced stage, lymphovascular invasion,

and solid tumor growth.[12]

Complex glandular pattern (CGP)

CGP is a newly recognized high-grade growth pattern in the 2021 WHO lung tumor classification and is defined as "fused glands (Fig. 2f) or single cells (Fig. 2g) infiltrating in a desmoplastic stroma".[3] While the cribriform pattern was initially included in the 2015 WHO classification system as a subtype of acinar growth pattern with no further discussion of CGP, there has been increasing evidence that CGP-predominant tumors are associated with worse clinical outcome compared to acinar-predominant tumors and frequently harbor ALK rearrangement and HER2 mutation.[10] Histologically, high-grade features, including higher mitotic rate, more extensive tumor necrosis, and lymphovascular invasion, are seen in CGP-predominant tumors.[13,14] In the 2021 WHO classification, CGP has been recognized as one of the high-grade patterns on par with solid and micropapillary growth.

More recent studies suggest a further refined stratification scheme. Specifically, cribriform (Fig. 2h) as a predominant pattern has been shown to be associated with poor prognosis akin to solid and micropapillary patterns, whereas the 5-year survival for patients with fused gland-predominant adenocarcinomas ranked between papillary- and micropapillary-predominant tumors.[11] Histologically, cribriform-predominant adenocarcinoma is associated with larger tumor size, more frequent pleural involvement, lymphovascular invasion, and spread through airspaces (STAS), and recurrent tumors with cribriform pattern may have therapeutic implications with tyrosine kinase inhibitors in a small subset of patients.[15] These data suggest that the cribriform pattern could be recognized as a stand-alone aggressive subtype, and such classification would further stratify the prognostic values of the complex glandular pattern and potentially provide guidance for targeted therapy.

Updates on grading

The conventional grading system for nonmucinous adenocarcinomas consistently correlates with prognosis and pre-
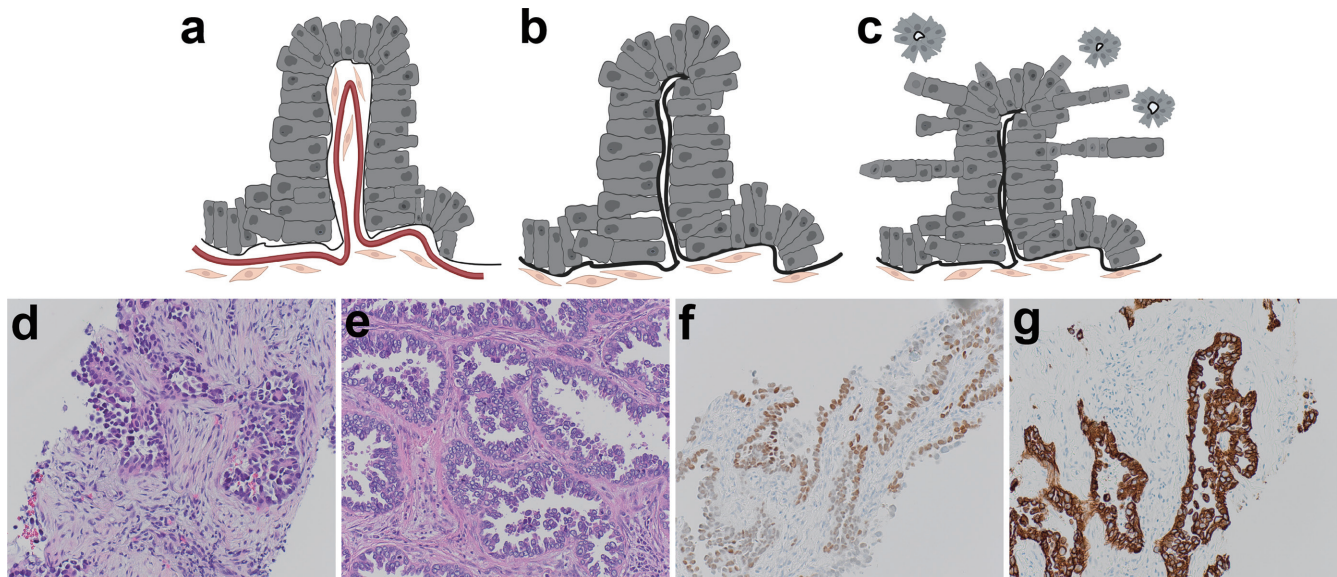
Fig. 3. Micropapillary growth pattern and the concept of filigree growth pattern. (a) True papillary growth pattern: fibrovascular core consisting of a fibrovascular core with stromal cells (fibroblasts) and feeding vessel. (b) Conventional micropapillary pattern: tufting structure with tumor cells grown on the basement membrane with no definitive fibrovascular core. (c) Filigree growth pattern: tumor cells grown in a delicate, narrow stacking pattern. (d) Conventional micropapillary pattern (×20). (e) Filigree micropapillary growth pattern (×20). Before the introduction of a filigree growth pattern as a new form of micropapillary growth, such histologic features would have been otherwise classified as acinar growth pattern. (f) Immunohistochemical stain with TTF1 (×20). (g) Immunohistochemical stain with CK7 (×20). Conceptual drawings (a–c) created with BioRender.com.

dicts tumor response to adjuvant chemotherapy. In general, lepidic predominant tumors are considered low grade; acinar or papillary predominant adenocarcinomas are more aggressive and thus considered intermediate grade, while micropapillary and solid-predominant tumors have the worst prognosis and are classified as high grade. However, a specific drawback on the prognostic value, based solely on the "predominant growth pattern," is the omission of the "non-predominant", or secondary growth pattern, which can be associated with worse prognosis, especially with regards to the micropapillary pattern. To account for the more aggressive minor growth patterns, a formal three-tier grading system has been developed to incorporate secondary high-grade patterns (Table 1[3,16]). Micropapillary, solid, cribriform, and complex glandular patterns (Fig. 2) must be included based on the current grading scheme if they comprise at least 20% of the tumor in resected specimens.[16]

Tumor cell STAS is defined as the spread of lung cancer cells into air spaces in the lung parenchyma beyond the edge of the main tumor. STAS encompasses three histologic patterns, namely micropapillary, solid nests/tumor islands, and discohesive single cells.[17] STAS tumor cells can be distinguished from alveolar macrophages and detached reactive type pneumocytes by the lack of cytoplasmic pigment or foamy cytoplasm, higher degree of nuclear atypia and hyperchromasia, and more prominent nucleoli. Artifacts constitute another potential confounding phenomenon, which are featured by (1) the presence of tumor cell clusters randomly scattered in tissue distant from the main tumor, lacking evidence of continuous spread of tumor; (2) tumor cell clusters at the edge of a resection specimen; (3) jagged edges of tumor cell clusters (tumor fragmentation, or carry-over from a knife during grossing); and (4) linear strips of tumor cells lifted off alveolar walls. STAS is associated with a more aggressive clinical course, especially in patients undergoing limited resection compared with lobectomy. STAS should not be included in the tumor size for staging or the percentage of growth patterns, as it is considered a feature of tumor spread rather than a component of the invasive tumor.

Molecular alterations in large cell neuroendocrine carcinoma (LCNEC)

Recent genetic and molecular studies have advanced our knowledge about the etiology and pathophysiology of neuroendocrine neoplasms of the lung. While the 2021 WHO classification did not specifically account for the molecular characteristics of each entity, certain molecular alterations are seen consistently in a subset of lung tumors. To subclassify pulmonary neuroendocrine tumors, incorporating molecular changes into the diagnostic approach can further improve the precision and further guide the development of targeted therapies. Carcinoid tumors are clinically indolent neuroendocrine tumors with low mutation rates and usually harbor mutations in *MEN1, EIF1AX, PSIP1, KMT2C, and ARI-*

Table 1. Grading of lung adenocarcinomas based on growth patterns[3]

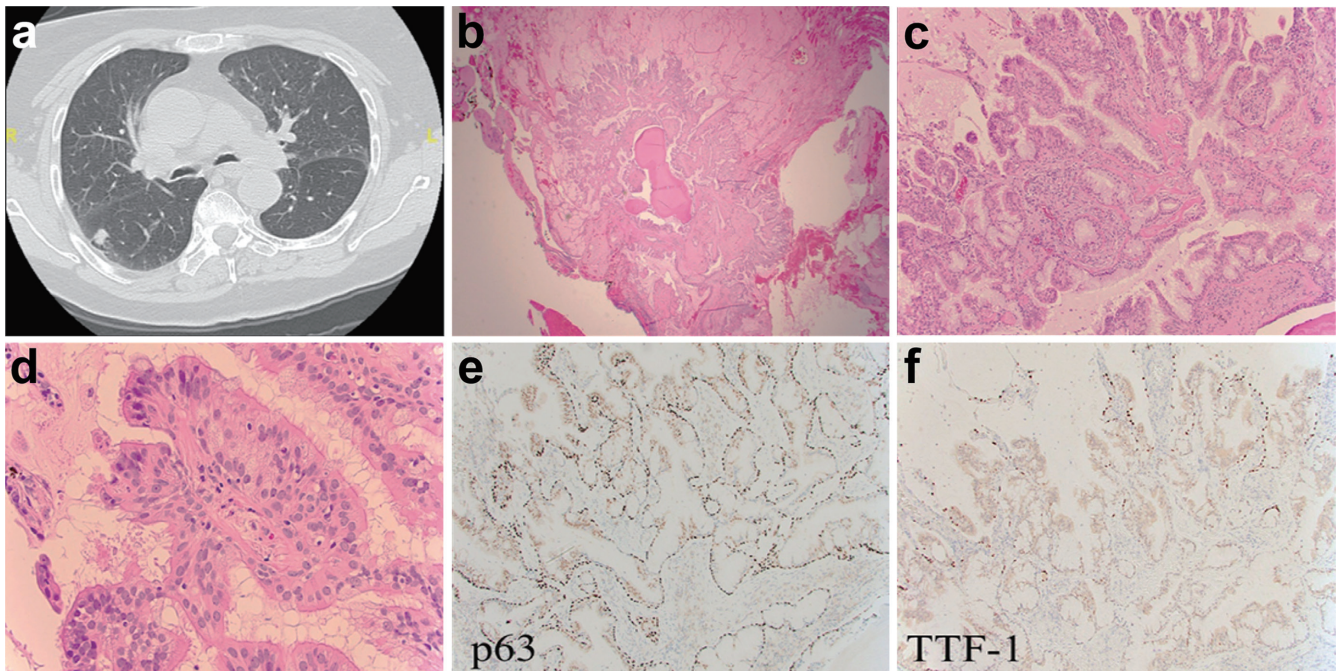| Grade	Predominant Pattern	Secondary Pattern
Grade 1: Well differentiated	Lepidic	<20% high-grade pattern
Grade 2: Moderately differentiated	Acinar, Papillary	<20% high-grade pattern
Grade 3: Poorly differentiated	High grade pattern ≥20%; Micropapillary, solid, cribriform, complex glandular	

Fig. 4. BA/CMPT. (a) BA/CMPT can present as an irregular, solid nodule on computed tomography images. (b) On low power (×5), BA/CMPT typically exhibits papillary and glandular growth patterns. (c) The apical cell layer consists of copious amounts of mucinous epithelial cells with an underlying basal cell layer (×20). (d) On higher power (×40), three types of cells are present: ciliated columnar cells, mucous cells, and basal cells. The nuclear features appear bland. (e) Basal cell layer is highlighted by p63 immunohistochemical staining (×20). (f) Luminal cells are negative for TTF1 staining (×20).

D1A genes, most of which are involved in chromatin remodeling.[18,19] In contrast, LCNEC usually have a higher mutation burden and smoking-related mutation signature. Genomic and transcriptomic analysis further subdivided LCNECs into two major and one minor groupings based on their mutation characteristics. One major group of LCNECs shows bi-allelic TP53, STK11/KEAP1, and KRAS alterations, frequently observed in adenocarcinomas and squamous cell carcinomas, whereas the other major group with RB1 alterations and TP53 inactivation displayed molecular features similar to SCLC.[19] A minor group of LCNECs shows a MEN1 mutation, which represents a small group of tumors with carcinoid morphology but exceeds the proliferative threshold for lung carcinoids (*i.e.* 10 mitoses/2 mm^2). Although a Ki-67 labeling index greater than 30% is considered a supportive diagnostic feature for LCNEC,[20,21] its definitive diagnostic utility and the precise cutoff warrant further investigation.[20]

Bronchiolar adenoma/ciliated muconodular papillary tumor (BA/CMPT)

BA/CMPT was included as a new entity in the 2021 WHO classification and is usually defined as a tumor with subpleural localization less than 2.0 cm (Fig. 4) Histologic features of BA/CMPT include bland, bilayered bronchiolar-type epithelium arranged in a nodular architecture. Luminal epithelial cells can be ciliated, mucinous, or flat, with no atypia or increased mitotic activity. BA/CMPTs are further categorized into proximal and distal types.[22] The proximal type usually has more ciliated and/or mucinous cells with a morphologic resemblance to proximal airway, and the distal type tends to have cuboidal, TTF-1 positive cells similar to smaller airways; such dichotomy is not mutually exclusive, and the histologic features do not always correspond to their anatomic location. While BA/CMPTs are generally considered indolent, they can

mimic invasive lesions on imaging studies[23] and pose a diagnostic challenge in intraoperative diagnosis.[24] The continuous basal cell lining can be a clue to avoid misinterpretation in frozen sections, and the diagnosis can be confirmed by immunohistochemical staining with p63, p40, or CK 5/6. Most BA/CMPTs demonstrate characteristic molecular alterations involving *BRAF*, *KRAS*, *EGFR*, and *HRAS* genes.[25]

SMARCA4-deficient undifferentiated tumor (SMARCA4-UT)

SMARCA4-UT is a newly added entity in the 2021 WHO classification. These tumors have a characteristic loss of expression of BRG1 caused by an inactivating mutation in the *SMARCA4* gene. BRG1 is a key member of the BAF chromatin-remodeling complex.[26] Morphologically, these tumors consist of diffuse sheets of monotonous, high-grade, discohesive, round to epithelioid cells with prominent nucleoli (Fig. 5). Areas of rhabdoid differentiation can be appreciated. Originally termed "*SMARCA4*-deficient thoracic sarcoma",[27–29] this entity was renamed due to its smoking-associated genomic signature, clinicopathologic characteristics, and immunohistochemical profile, which suggested that these tumors are undifferentiated/de-differentiated carcinomas.[30] Since a small proportion of conventional NSCLCs show *SMARCA4* mutation,[31] BRG1 immunohistochemical stains should be performed only in cases with appropriate clinical suspicion (i.e. high-grade, monotonous undifferentiated malignancies). SMARCA4-UTs lack the histologic (glandular formation) or immunohistochemical (keratin expression) features of carcinoma. Although SMARCA2, CD34, Sox2, SALL4, and p53 expression can be seen in SMARCA4-UTs,[27] none of these markers is entirely sensitive or specific. SMARCA4-UTs tend to affect younger patients with an aggressive clinical course; median survival ranges from 4 to 7 months.[27–30] Preliminary
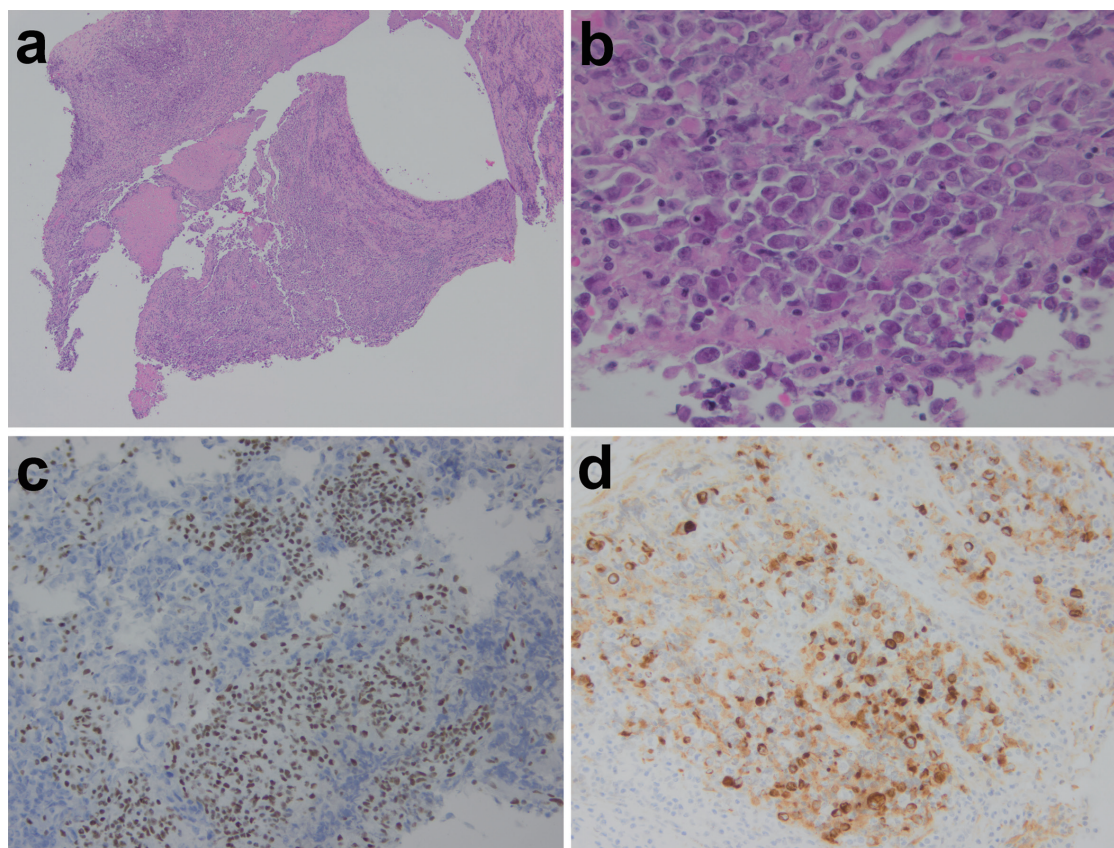
Fig. 5. SMARCA4-UT. (a) SMARCA4-UTs typically show solid sheets of monotonous epithelioid cells (×5). Areas of necrosis can be appreciated. (b) On high power (×40), tumor cell nuclei show vesicular chromatin and prominent nucleoli, with focal rhabdoid differentiation. The overall features share similarities with pediatric malignant rhabdoid tumors. (c) Tumor cells show loss of expression of SMARCA4 (BRG1). The background stromal cells and lymphocytes noticeably show retained expression for internal control (×20). (d) Tumor cells show focal reactivity for CAM5.2 (×20).

studies have shown improved clinical outcomes in patients treated with immune checkpoint inhibitors.[32]

Primary pulmonary hyalinizing clear cell carcinoma (HCCC)

HCCC is listed under the category of salivary gland-type tumors in the 2021 WHO classification. Originally described as a low-grade malignant neoplasm commonly involving the head and neck, roughly a dozen cases of primary pulmonary HCCC have been reported.[33] These tumors are usually found in the submucosa of a large airway. Small to medium sized bland epithelioid cells with ample clear to eosinophilic cytoplasm are typically arranged in nests, cords, sheets, and thin trabeculae, in a background of extensively hyalinized stroma.[33–36] Most cases lack high-grade features, such as necrosis, increased mitosis, and nuclear pleomorphism. The neoplastic cells express cytokeratin 7 and keratin AE1/AE3, the vast majority of which are positive for p63 and p40, and some cells are positive for cytoplastic mucin. Similar to their counterpart in the head and neck regions, primary pulmonary HCCC typically show *EWSR1* gene rearrangement.

Highlights of New WHO Classification of Pleural Mesothelioma

Mesothelioma *in situ* (MIS)

The new 2021 WHO Classification of Tumors of the Pleura and Pericardium included MIS as a distinct entity. MIS is the precursor to invasive mesothelioma, and tumor cells typically are single-layered, bland, cuboidal cells with inconspicuous nucleoli. Occasional simple papillary structures might be identified. Ancillary tests to support the diagnosis of MIS include loss of BAP1 or MTAP by immunohistochemistry or homozygous deletion of *CDKN2A* by FISH in the mesothelial cells positive for markers including calretinin, WT-1, CD5/6, and D2-40. Any complex structures, including multi-layered cells with significant atypia or prominent nucleoli and exophytic or branching papillary architectures, would raise the suspicion for invasive mesothelioma rather than MIS.

Grading of malignant epithelioid mesothelioma

The 2021 WHO classification introduced a two-tier grading system incorporating nuclear atypia, mitoses, and necrosis in both biopsy and resection specimens. Nuclear atypia is scored as mild-score 1; moderate-score 2; and severe-score 3. A similar three-tier scoring system is also applied for mitosis: within a 2 mm^2 area of highest-grade tumor, mitotic count is scored as: 0~1-score 1; 2~4-score 2; and greater than 4-score 3. Combining these two scores, a nuclear grade is assigned, and grading is dichotomized as low- or high-grade depending on the presence of necrosis.[37] The prognosis for the four groups are: grade I, 29 months; grade I with necrosis or grade II without necrosis, 16 months; grade II with necrosis, 10 months; and nuclear grade III, 8 months. In epithelioid mesothelioma, histologic features with
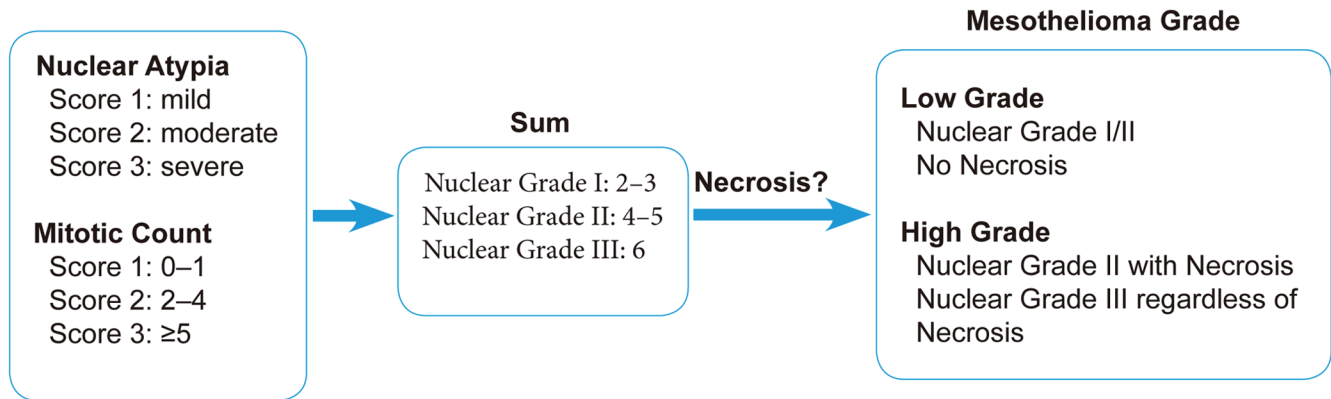
Mesothelioma Grade

Nuclear Atypia
  Score 1: mild
  Score 2: moderate
  Score 3: severe

Mitotic Count
  Score 1: 0–1
  Score 2: 2–4
  Score 3: ≥5

Sum

Nuclear Grade I: 2–3
Nuclear Grade II: 4–5
Nuclear Grade III: 6

Necrosis?

Low Grade
  Nuclear Grade I/II
  No Necrosis

High Grade
  Nuclear Grade II with Necrosis
  Nuclear Grade III regardless of
  Necrosis

Fig. 6. **Histologic grading algorithm of mesothelioma.**[40,41]

favorable prognosis include myxoid/microcystic, tubulopapillary, trabecular, and adenomatoid patterns.[38,39] Findings with worse prognosis include micropapillary and solid growth patterns. The histologic grading algorithm[40,41] is shown in Figure 6. Of note, mesotheliomas with nuclear grade I and tumor necrosis are not discussed in this algorithm (Fig. 6).

Perspective and future work

While the broad definitions of most tumors remain unchanged, the 2021 WHO classification refined the diagnostic guidelines with significant details on grading and molecular characteristics. These updates provide further data to improve diagnostic accuracy and reproducibility for pathologists and develop prognostic tools and novel therapeutic strategies for clinicians and scientists. Directions for future work include: (1) refining the diagnostic criteria of neuroendocrine tumors, especially for tumor with carcinoid morphology with >10 mitoses in a 2 mm^2 and/or high Ki67 (greater than 20%) region;[20,21] especially if the lung subclassification system can be paralleled with the current WHO classification of gastrointestinal and pancreatic neuroendocrine tumor (Grade 3 NET);[42,43] (2) exploring the clinicopathologic correlation of large cell neuroendocrine carcinomas based on their histologic and molecular features and providing potential strategies for treatment of this aggressive tumor; (3) elucidate molecular features for additional tumor types to improve the prognostic value and provide guidance for targeted therapy.

Conclusions

This review provides an overview on the key updates in diagnosing thoracic tumors, with recommendations for small diagnostic samples from the lung, the revised grading system for lung adenocarcinoma, and molecular features of large cell neuroendocrine carcinoma. Rare neoplasms including BA/CMPT, SMARCA4-UT, and primary pulmonary HCCC are discussed, and a new diagnostic algorithm for malignant epithelioid mesothelioma is briefly discussed. This review serves as a concise reference for general anatomic pathologists, residents, fellows, and clinicians for the diagnosis of thoracic tumors.

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Conflict of interest

The manuscript was submitted during Dr. Haodong Xu's term from May 2021 to May 2023 serving as an editorial board member of the *Journal of Clinical and Translational Pathology*. The authors have no other conflict of interests to declare.

Author contributions

Drafting of the manuscript (LL, HX), histology figures (LL, HX), critical revision and supervision (HX). All authors have made a significant contribution to this study and have approved the final manuscript.

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