Int J Clin Exp Pathol 2016;9(7):7140-7147
www.ijcep.com /ISSN:1936-2625/IJCEP0027224

Original Article

Pulmonary sclerosing hemangioma: frozen section diagnosis based on an analysis of the varied appearances in a series of thirteen cases from a single institution

Ling Zhao[1], Binglin Zhang[1], Jie Luo[1], Jie Tong[1], Emine Bozkurtlar[2], Eugene J Mark[3*], Jiping Da[1*]

[1]Department of Pathology, China-Japan Friendship Hospital, Beijing, China; [2]Department of Pathology, Marmara University, Istanbul, Turkey; [3]Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, USA. [*]Co-senior authors.

Received March 3, 2016; Accepted May 23, 2016; Epub July 1, 2016; Published July 15, 2016

Abstract: Pulmonary sclerosing hemangioma is a rare neoplasm with polymorphic histological features. The frozen section diagnosis of sclerosing hemangioma can be difficult, as it can be confused for malignancy, creating intraoperative dilemmas for pathologists. To identify the histopathologic features that may be of value in making a correct diagnosis on frozen sections, we retrospectively analyzed thirteen cases of pulmonary sclerosing hemangioma diagnosed on frozen sections in China-Japan Friendship Hospital from 2009 to 2014. We characterized the predominant patterns: solid, papillary, hemorrhagic or sclerotic. Two or more patterns were identified in twelve cases. One case exhibited only papillary pattern. A frozen section diagnosis of 'sclerosing hemangioma' was reported in ten cases, and 'benign lesion' was given in one case. Because of technical artifact and the uncommon morphology, the diagnosis was deferred in two cases. Significant cytological atypia was present in one case. Because sclerosing hemangioma is a benign tumor, accurate frozen diagnosis may avoid unnecessarily excessive surgery. Awareness of its varied patterns and distinctive cytological features, together with careful gross examination and sampling may help to avoid a diagnosis of malignancy and lead to conservative management.

Keywords: Sclerosing hemangioma, frozen section diagnosis, lung

Introduction

Pulmonary sclerosing hemangioma, recently renamed as sclerosing pneumocytoma, is a rare lung tumor, which was first described in 1956 by Liebow and Hubbell [1]. It predominantly affects middle-aged adults with a marked female predilection [2]. Generally the tumors are solitary and peripheral. Multifocal sclerosing hemangiomas have been reported rarely [3, 4]. Although metastases to regional lymph nodes have been observed [5], the biologic behavior is almost always benign. Sclerosing hemangiomas are listed under the group of 'Adenomas' in 2015 WHO classifications [6]. Histologically, sclerosing hemangioma has as a cardinal feature of variegated histology including solid, hemorrhagic, papillary and sclerotic areas. Two types of tumor cells occur: 1) round stromal cells and 2) surface cells [7]. Since larger sclerosing hemangiomas may have increasing F-18 FDG PET uptake [8], clinical and radiological characteristic of sclerosing hemangioma are not specific enough to diagnose the condition preoperatively. It also cannot be accurately diagnosed by transbronchial or needle biopsies, because an intrinsic facet of the histology is the multiplicity of patterns. The frozen section diagnosis is of great importance, because the cellular proliferation within fibrosis can suggest invasion by adenocarcinoma and lead to unnecessary lobectomy. Although problems with frozen section diagnosis of sclerosing hemangioma are encountered in routine pathology practice, a limited number of studies addressing this issue have appeared in the literature [9].

Table 1. Clinicopathological features of pulmonary sclerosing hemangiomas

Case NO.	Gender	Age (yrs)	Location	Size (cm)	Visible nucleoli	Mitosis	Necrosis	Surgery	Follow-up (months)
1	F	68	LUL	3.5	No	0	0	Lobectomy	56
2	F	27	LUL	2	No	0	0	Enucleation	36
3	F	57	RLL	2.5	No	0	0	Enucleation	26
4	F	59	LLL	4	No	0	0	Lobectomy	35
5	M	25	RLL	3.7	No	0	0	Wedge excision	26
6	F	25	The fissure of the left lung	4.5	No	0	0	Enucleation	75
7	F	47	RLL	2.5	No	0	0	Enucleation	10
8	F	57	RML	1	No	0	0	Wedge excision	10
9	F	62	Right hilus	3	No	0	0	Enucleation	13
10	M	43	LLL	4	No	0	0	Lobectomy	15
11	F	47	RLL	2; 2.2	No	0	0	Wedge excision	16
12	F	24	RUL	2	Yes	0	0	Enucleation	16
13	F	80	RLL	1.5	No	0	0	Wedge excision	21

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

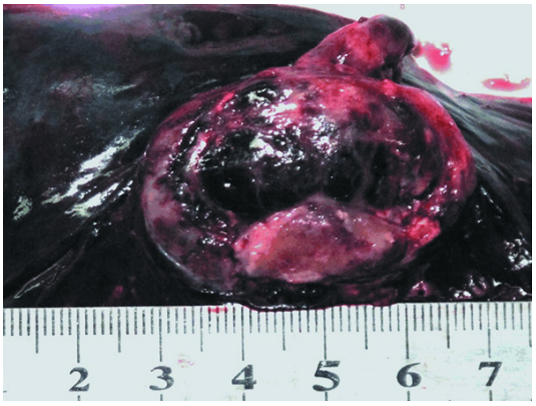

Figure 1. Macroscopy of sclerosing hemangioma (Case 4). The tumor was solid, tan, with hemorrhage and shelled out from the surrounding parenchyma.

We report thirteen cases of pulmonary sclerosing hemangioma with intraoperative consultations and identify salient diagnostic features on frozen sections.

Materials and methods

We reviewed thirteen cases of pulmonary sclerosing hemangioma where intraoperative frozen section diagnosis had been requested between 2009 and 2014 at the Department of Pathology, China-Japan Friendship Hospital (Beijing, China). All were surgical resection specimens. The pathology reports of all cases were reviewed, and the frozen sections were compared with the paraffin sections. This study was approved by the institutional review board of China-Japan Friendship Hospital.

The tissue were embedded and frozen within optimal cutting tissue (OCT) medium (Tissue-Tek OCT, Sakura Finetek-USA) and cooled to at least -25°C in a Leica CM3050S Cryostat device (Leica Biosystems, Wetzlar, Germany). It was cut into sections measuring 5 to 6 μm in thickness. The sections were treated with 95% alcoholic formalin, and subsequently stained with hematoxylin-eosin. The rest specimens were fixed in 10% neutral formalin for permanent histological evaluation.

Immunohistochemical stains were applied to paraffin sections with a Polink-1 HRP detection system (Golden Bridge International Inc, Mukilteo, WA). The following mouse monoclonal antibodies were used: AE1/AE3, TTF-1, Napsin A, and EMA. The staining procedure followed manufacturer's instruction.

Results

Clinical features

Table 1 showed a marked female predominance, with a female to male ratio of 11:2. The patients ranged in age from 24 to 80 years (mean age, 48 years). All patients were non-smokers except for Case 10 with smoking index of 20. Six patients were asymptomatic and seven presented with cough. Multiple, bilateral

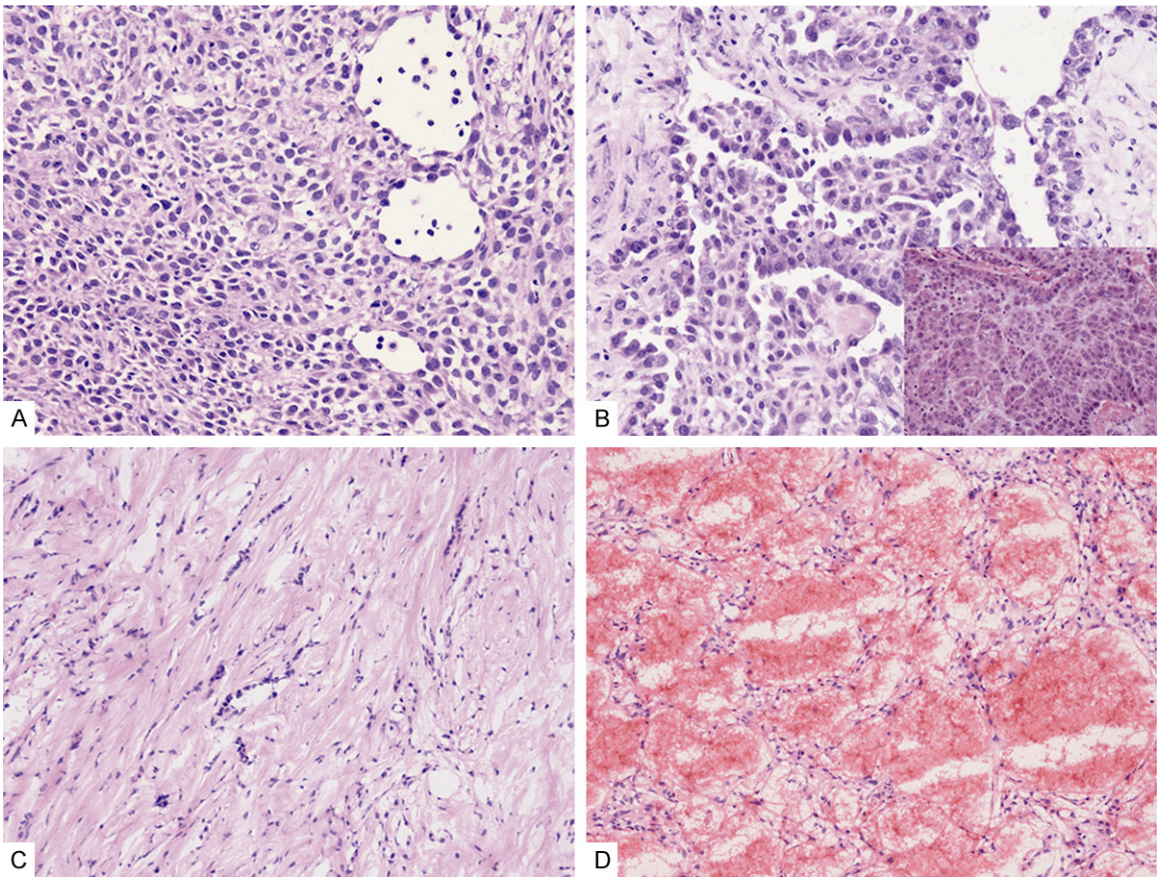

Figure 2. Variegated histological patterns of sclerosing hemangioma (frozen sections): A. Solid pattern (Case 5). B. Papillary pattern (Case 2); Insert: papillary adenocarcinoma. C. Sclerotic pattern (Case 4). D. Hemorrhagic pattern (Case 4).

nodules were found in Case 13, with only one nodule for wedge excision. One patient (Case 11) had two nodules in the right lower lobe, all other lesions were solitary. Six patients underwent enucleation and four underwent wedge excision. Three patients had a lobectomy, because the lesions were close to main pulmonary vessels. All the patients are alive and well (mean follow-up, 22 months; range, 10 to 75 months).

Gross features

Tumors ranged in size from 1 to 4.5 cm, with an average of 3.3 cm. In ten cases, the tumors were round, well circumscribed, nonencapsulated lesions, while in Case 1, Case 3 and Case 9, the specimens were fragmented yellow tissues when received. Cut surfaces were solid, grey to yellow to tan, with foci of hemorrhage and calcification (**Figure 1**).

Intraoperative frozen sections

At the time of frozen section, ten cases were diagnosed as 'sclerosing hemangioma', one case was interpreted as 'benign, sclerosing hemangioma cannot be completely excluded', and the diagnosis was deferred in Case 1 and Case 13.

Two or more patterns with varying proportions were present in twelve cases (**Figure 2**). Case 3 showed only papillary growth (**Figure 3A** and **3B**).

The papillary pattern predominated in Case 3 was characterized by fronds which were covered by cuboidal to hobnail cells with round or oval nuclei and eosinophilic cytoplasm (**Figure 3C**). Intranuclear inclusions and multinucleation were seen occasionally. The surface cells exhibited modest variation in nuclear size and pleomorphism. Mitotic figures were rare (**Figure**

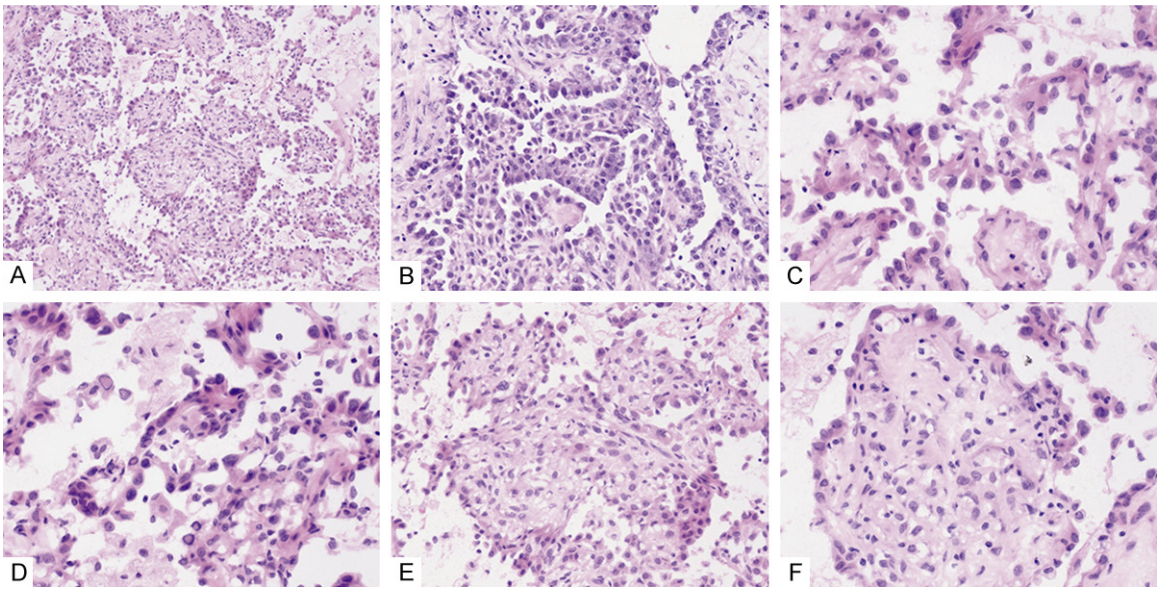

Figure 3. Papillary pattern of sclerosing hemangioma (Case 3, frozen sections). A. Complex papillae covered by cuboidal surface cells. B. A lepidic growth pattern, mimicking bronchioloalveolar carcinoma. C, D. The surface cells display moderate to marked nuclear atypia. Note the prominent hobnail cells and the intranuclear inclusions. E. The stalks of the papillae contain the round cells. F. Round cells with a signet ring appearance.

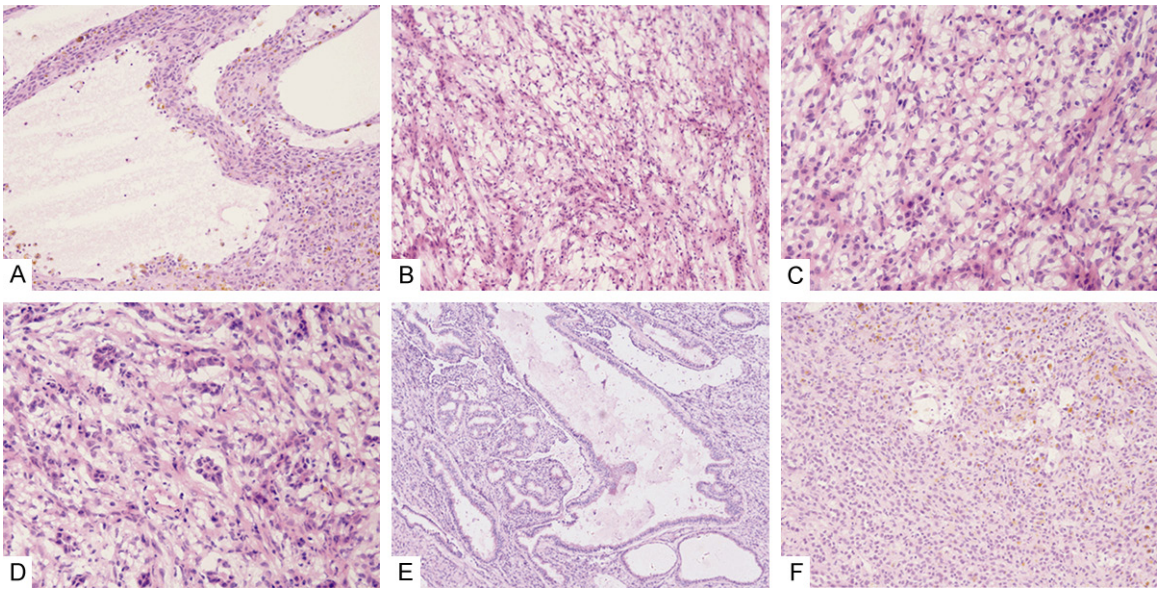

Figure 4. A. Variable blood-containing spaces lined by flat epithelial cells. Note the diffuse growth of round stromal cells (Case 1, frozen section). B. A solid proliferation of bland spindle cells and clear cells (Case 1, frozen section). C. Round cells with a signet ring appearance contain clear cytoplasm and eccentric nuclei (Case 13, frozen section). D. The cells forming glandular or tubular structures are large, hyperchromatic and atypical (Case 13, frozen section). E. The presence of the mucinous cystic space lined by ciliated bronchiolar epithelium (Case 4, frozen section). F. Polygonal cells with bland, centrally located nuclei admixed with histiocytes (Case 1, frozen section).

3D). The stalks of the papillae were acellular or contained round stromal cells which sometimes had a signet appearance (**Figure 3E** and **3F**). Histiocytes lay in the spaces between the papillae. In one case (Case 2), the papillae had sclerotic cores covered by columnar cells.

The hemorrhagic pattern was characterized by the presence of large, dilated spaces filled with red blood cells. The cystic spaces of varying sizes were lined by a single layer of cytologically bland fattened cells, which resembled a true hemangioma (**Figure 2D**). The dense groups of round cells were found in the interstitium between the blood-filled spaces (**Figure 4A**).

The solid pattern was characterized by sheets of the round stromal cells. The cells were uniform and bland-appearing, with round-to-oval nuclei, fine chromatin, and inconspicuous nucleoli. The cytoplasmic border was indistinct (**Figure 4B**). Because of the histological artifact, the round cells showed eccentric nuclei with clear cytoplasm and resembled signet-ring cells (**Figure 4C**). Mitoses were absent. Irregular spaces lined by cuboidal cells represented entrapped alveolar pneumocytes (**Figure 4D**). Numerous mucinous cystic spaces were lined by ciliated epithelium in one case (**Figure 4E**). Occasionally, interspersed histocytes caused a picture that mimicked inflammatory myofibroblastic tumor (**Figure 4F**).

In the sclerotic pattern, there was dense collagen within the solid areas, within the papillary stalks, or around the hemorrhagic areas. Irregularly shaped gland-like spaces were present within a hyaline stroma. Calcifications were also encountered (**Figure 2C**).

In Case 13, the lesion is a well circumscribed but unencapsulated nodule with central calcification. Cords of round to spindle cells with clear to eosinophilic cytoplasm were embedded in the abundant sclerotic stroma in the center. Sheets of monotonous round to polygonal cells with small, bland nuclei and eosinophilic cytoplasm were present at the peripheral. These merged with cords and poorly developed glandular or tubular structures of large, hyperchromatic polygonal cells, some with atypia.

Immunohistochemical finding

Nuclei of the round cells stained for TTF-1, as did many of the surface lining tumor cells. Both types of tumor cells expressed EMA, while only the surface lining cells expressed AE1/AE3 and Napsin A.

Discussion

Intraoperative frozen section diagnosis is a challenging area for diagnostic surgical pathology [10]. The diagnostic clues of sclerosing hemangioma on frozen sections are similar to those of permanent sections. The diagnosis is evident when one observes the mixture of the four major histological patterns (solid, papillary, sclerotic, and hemorrhagic) and the distinctive cellular components (surface cells and round stromal cells) within the single tumor [7, 11]. Difficult situations may arise in tumors with one pattern predominant [12, 13]. Intraoperative consultation may be complicated by frozen section artifact as well.

A papillary pattern with moderate to marked cytological atypia can lead to misdiagnosis as malignancy. The differential diagnosis can include papillary adenoma, bronchioloalveolar carcinoma, papillary adenocarcinoma, and metastatic thyroid carcinoma. Sclerosing hemangioma may be confused with papillary adenoma when cytologically bland cuboidal to columnar cells line the surface of a fibrovascular stroma [14, 15]. Varied architectural growth pattern favors a diagnosis of sclerosing hemangioma rather than papillary adenoma. Cuboidal to columnar shaped cells may grow along alveolar walls in a lepidic fashion and may resemble bronchioloalveolar carcinoma. If obviously malignant nuclear features are observed, a sclerosing hemangioma can be excluded. However, the cells of a bronchioloalveolar carcinoma usually are bland, and may mimic normal or atypical respiratory epithelium. Infiltration into surrounding lung parenchyma and the severe nuclear atypia cause concern for papillary adenocarcinoma, which is the most deceiving condition. Frozen section slides or reactive pneumocytes frequently look disturbing. The presence of uniform small nucleoli, homogenous chromatin, lack of hyperchromasia, and low nucleus-to cytoplasm (N/C) ratio are more suggestive of reactive change rather than atypical pneumocytes [10]. If the papillary pattern predominates, the differential diagnosis of metastatic papillary thyroid carcinoma is also well considered. However, the typical nuclear features of papillary thyroid carcinoma are not seen in sclerosing hemangioma. Recognition of nuclear clearing, enlargement, overlapping, intranuclear grooves and pseudoinclusions provides sufficient evidence for diagnosis of papillary thyroid carcinoma.

The solid pattern of sclerosing hemangioma that presents with regular cells may simulate

carcinoid tumor. Carcinoid tumors may have a mixed pattern, including solid, organoid, trabecular and papillary as well as spindle cells [16]. Not only frozen section but permanent section may resemble carcinoid tumor, and occasionally immunohistochemistry is the decisive test.

The diagnosis was deferred in Case 1 which was composed mainly of hemorrhagic and solid patterns. Due to the artifact which modifies the architecture, two slides showed slightly atypical spindle cells admixed with clear cells, but the mitotic figures were rarely evident. The characteristic stromal cells could not be easily recognized. Although the clear cells raised a consideration of clear cell tumor, the thin-walled sinusoidal vessels were absent [17]. In another slide, histocytes were scattered throughout sheets of cytologically bland spindle cells that gave this lesion a fibroxanthomatous appearance. Inflammatory myofibroblastic tumor should be separated from sclerosing hemangioma, but it is usually composed of myoblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils [18]. Identification of varied patterns would argue strongly against inflammatory myofibroblastic tumor. It was hard to make a precise diagnosis of an uncommon tumor at the time of frozen section. The characteristic histological morphology of sclerosing hemangioma was better appreciated on paraffin sections. The diagnosis was further confirmed by immunohistochemical stains. The spindle cells and the clear cells showed an immunohistochemical profile consistent with the round stromal cells: TTF-1+EMA+AE1/AE3-Napsin A-.

In Case 4, the areas showing the hemorrhagic pattern were composed of large blood-filled spaces lined by epithelial cells. But the spaces separated by septa of the round tumor cells were not always observed, the tumor was reminiscent of an alveolar adenoma [19, 20]. Sclerotic areas and foci of stromal cells provide evidence to exclude the diagnosis of alveolar adenoma. Moreover, the single architecture growth pattern and large ectatic spaces lacking blood distinguish alveolar adenoma from sclerosing hemangioma.

The clear cells of Case 13 showed a signet pattern and were devoid of significant cytological atypia. The clinical presentation of multiple, bilateral small nodules in an old woman should raise the suspicion of epithelioid hemangioendothelioma and metastatic tumors. One of the clues to the diagnosis of epithelioid hemangioendothelioma is the presence of cytoplasmic vacuoles consistent with intracytoplasmic vascular lumen formation, which are the hallmarks of the lesion [21]. But it was not observed in this case. The clinical history and immunohistochemistry are necessary to distinguish metastatic tumors from sclerosing hemangioma. Another important differential diagnosis when dealing with sheets of bland cells in the lung is the need to rule out the possibility of carcinoid tumors. The identification of a characteristic delicate and highly vascular stroma is helpful in establishing the diagnosis of carcinoid tumors [16]. Definitive diagnosis of this case may be impossible, because it's not feasible to appreciate the admixture of the various patterns. It's more appropriate to require deferral of the frozen section diagnosis in such instances.

Case 3 which had a single pattern emphasizes that only one pattern predominant can lead to diagnostic misinterpretation, particularly on frozen sections. In the rest cases, two or more patterns are present. So it is not difficult to make an accurate diagnosis. In eight cases, one additional histological pattern not revealed on frozen section was identified on paraffin sections after additional sampling. Thus in order to avoid the possibility of a wrong diagnosis, careful and thorough gross examination is a critical component of intraoperative pathological consultation. In the gross evaluation, heterogeneity of gross appearance, circumscription and the color of the tumor are all helpful features.

Conclusion

Pathologists need to be aware that sclerosing hemangioma can be difficult to diagnose on frozen sections, especially when the characteristic variegated pattern is not evident. Recognition of the varied patterns and dual type cells should allow one to arrive at the correct diagnosis. The peculiar bland cytological feature can be helpful in confirming a diagnosis of sclerosing hemangioma in equivocal cases. Adequate biopsy/sampling is also important to improve the diagnostic accuracy of sclerosing hemangioma on frozen section. The differential diagnosis is very difficult when only a single pattern is identified

or when there is significant cytological atypia, and pathologists should defer the definitive diagnosis.

Sclerosing hemangioma has been termed the lawyers' favorite tumor, because of the possibility of unnecessary resection for a benign lesion. If the pathologist cannot be confident of the diagnosis on frozen section, this uncertainty including the possibility of benign sclerosing hemangioma should be conveyed to the surgeon, so that this will be taken into consideration when the decision is to perform a completion lobectomy.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Eugene J Mark, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA. Tel: 617-726-889; Fax: 617-573-3389; E-mail: emark@partners.org; Dr. Jiping Da, Department of Pathology, China-Japan Friendship Hospital, 2 Yinghua Dongjie, Hepingli, Beijing 100029, China. Tel: 86-10-84205191; Fax: 86-10-84205191; E-mail: djp02@sina.com

References

[1] Liebow AA, Hubbell DS. Sclerosing hemangioma (histiocytoma, xanthoma) of the lung. Cancer 1956; 9: 53-75.

[2] Katzenstein AL, Gmelich JT, Carrington CB. Sclerosing hemangioma of the lung: a clinicopathologic study of 51 cases. Am J Surg Pathol 1980; 4: 343-356.

[3] Lee ST, Lee YC, Hsu CY, Lin CC. Bilateral multiple sclerosing hemangiomas of the lung. Chest 1992; 101: 572-573.

[4] Noguchi M, Kodama T, Morinaga S, Shimosato Y, Saito T, Tsuboi E. Multiple sclerosing hemangiomas of the lung. Am J Surg Pathol 1986; 10: 429-435.

[5] Miyagawa-Hayashino A, Tazelaar HD, Langel DJ, Colby TV. Pulmonary sclerosing hemangioma with lymph node metastases: report of 4 cases. Arch Pathol Lab Med 2003; 127: 321-325.

[6] Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JH, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I; WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances since the 2004 Classification. J Thorac Oncol 2015; 10: 1243-1260.

[7] Devouassoux-Shisheboran M, Hayashi T, Linnoila RI, Koss MN, Travis WD. A clinicopathologic study of 100 cases of pulmonary sclerosing hemangioma with immunohistochemical studies: TTF-1 is expressed in both round and surface cells, suggesting an origin from primitive respiratory epithelium. Am J Surg Pathol 2000; 24: 906-916.

[8] Lin KH, Chang CP, Liu RS, Wang SJ. F-18 FDG PET/CT in evaluation of pulmonary sclerosing hemangioma. Clin Nucl Med 2011; 36: 341-343.

[9] Chan AC, Chan JK. Can pulmonary sclerosing haemangioma be accurately diagnosed by intra-operative frozen section? Histopathology 2002; 41: 392-403.

[10] Sienko A, Allen TC, Zander DS, Cagle PT. Frozen section of lung specimens. Arch Pathol Lab Med 2005; 129: 1602-1609.

[11] Leong AS, Chan KW, Seneviratne HS. A morphological and immunohistochemical study of 25 cases of so-called sclerosing haemangioma of the lung. Histopathology 1995; 27: 121-128.

[12] Khoury JD, Shephard MN, Moran CA. Cystic sclerosing haemangioma of the lung. Histopathology 2003; 43: 239-243.

[13] Nicholson AG, Magkou C, Snead D, Vohra HA, Sheppard MN, Goldstraw P, Beddow E, Hansell DM, Travis WD, Corrin B. Unusual sclerosing haemangiomas and sclerosing haemangioma-like lesions, and the value of TTF-1 in making the diagnosis. Histopathology 2002; 41: 404-413.

[14] Hegg CA, Flint A, Singh G. Papillary adenoma of the lung. Am J Clin Pathol 1992; 97: 393-397.

[15] Fukuda T, Ohnishi Y, Kanai I, Emura I, Watanabe T, Kitazawa M, Okamura A. Papillary adenoma of the lung. Histological and ultrastructural findings in two cases. Acta Pathol Jpn 1992; 42: 56-61.

[16] Gupta R, Dastane A, McKenna RJ Jr, Marchevsky AM. What can we learn from the errors in the frozen section diagnosis of pulmonary carcinoid tumors? An evidence-based approach. Hum Pathol 2009; 40: 1-9.

[17] Gaffey MJ, Mills SE, Askin FB, Ross GW, Sale GE, Kulander BG, Visscher DW, Yousem SA, Colby TV. Clear cell tumor of the lung. A clinicopathologic, immunohistochemical, and ultrastructural study of eight cases. Am J Surg Pathol 1990; 14: 248-259.

[18] Hammas N, Chbani L, Rami M, Boubbou M, Benmiloud S, Bouabdellah Y, Tizniti S, Hida M, Amarti A. A rare tumor of the lung: inflamma-

tory myofibroblastic tumor. Diagn Pathol 2012; 7: 83.
[19] Halldorsson A, Dissanaike S, Kaye KS. Alveolar adenoma of the lung: a clinicopathological description of a case of this very unusual tumour. J Clin Pathol 2005; 58: 1211-1214.
[20] Burke LM, Rush WI, Khoor A, Mackay B, Oliveira P, Whitsett JA, Singh G, Turnicky R, Fleming MV, Koss MN, Travis WD. Alveolar adenoma: a histochemical, immunohistochemical, and ultrastructural analysis of 17 cases. Hum Pathol 1999; 30: 1581-67.
[21] Hristova EN, Krishnamurthy S, Ro JY, Ayala AG. Pulmonary epithelioid hemangioendothelioma with prominent signet ring cell features mimicking metastatic adenocarcinoma. Ann Diagn Pathol 2003; 7: 160-164.