Case Report

An unexpected cause of recurrent pneumothorax

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Summary

The thoracic district is the most frequent visceral location of synovial sarcoma, generally involving lung and pleura as a large solid mass. We present herein a 57-year-old man with recurrent pneumothorax and a localized bulla at the lingula. The lesion was excised by a Video-Assisted-Thoracoscopic-Surgery (VATS) wedge resection and surprisingly consisted of a unilocular cyst with fibrous wall intermingled by a longitudinal proliferation of bland-looking, dense, monomorphic spindle cells diffusely expressing EMA, CD99, CD56 and focally staining with cytokeratins. Fluorescent in situ hybridization demonstrated the presence of SYT rearrangement and a diagnosis of pulmonary cystic monophasic synovial sarcoma was made. Only few similar cases have been reported in literature, mainly occurring in young male adults. A meticulous examination of all resected tissue from pneumothorax is the prerequisite to suspect this extremely challenging condition, while immuno-molecular studies are mandatory to achieve the correct diagnosis.

Key words: cystic synovial sarcoma, lung, pneumothorax, surgery

Introduction

Surgical resections after recurrent pneumothorax are relatively common specimens with which pathologists face in routine practice [1]. Apart from the primary idiopathic form, secondary spontaneous pneumothorax can also occur in several conditions, such as an underlying airway disease, various infections, idiopathic and secondary interstitial lung diseases, genetic diseases, connective tissue diseases, endometriosis and even primary or metastatic neoplasms [2-6].

In particular, primary pleuropulmonary tumors presenting with pneumothorax rarely appear as localized bullous disease making impossible its suspicion at imaging studies [7,8]. We describe herein an exceedingly uncommon primary cystic synovial sarcoma of the lung unexpectedly discovered on bullectomy after recurrent episodes of pneumothorax. A detailed review of the literature with discussion of the differential diagnosis and identification of practical points to avoid a misdiagnosis are reported.

Case report

A 57-year-old man, former smoker, presented with recurrent left pneumothoraces. His medical history was unremarkable. At the chest Computed Tomography (CT), a localized bullous area of about 2 cm in maximum diameter was observed in the lingular region of the left upper lobe (Fig. 1). A Video-Assisted-Thoracoscopic-Surgery (VATS) wedge resection of the lesion was performed. The formalin-fixed surgical specimen was grossly examined evidencing a single cystic formation measuring about 2 cm in maximum diameter,

Figure 1. Chest CT showed a cystic lesion with thin wall of 2 cm in maximum diameter at the left upper lobe.
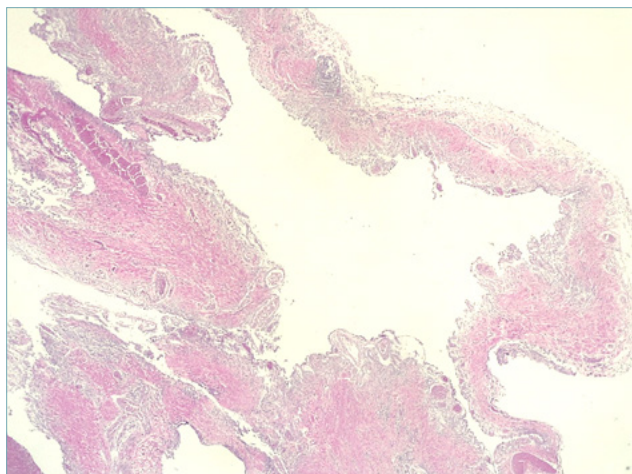

Figure 2. Low power histologic examination showed a cystic wall alternating dense acellular fibrosis and hypercellular zones.

surrounded by smooth and thickened, whitish visceral pleura. The sample was entirely included in a single paraffin-embedded block.

At histology, the cyst consisted of a dense fibrous wall of variable thickness (Fig. 2), externally lined by reactive mesothelium and internally lined by hyperplastic pneumocytes (Fig. 3). The fibrous tissue showed numerous dilated vessels and was dissected by a linear, longitudinal growth of bland-looking, monomorphic spindle cells. Immunohistochemical stains were performed using an automated immunostainer (ULTRA Benchmark, Ventana Medical Systems/Roche Diagnostics) and appropriate primary antibodies. The spindle cells showed strong positivity with EMA (clone E29), CD99 (clone O13) and CD56 (clone 123C3), partial expression of pan-cytokeratins (clones AE1/AE3 and MNF116) and CK7 (clone SP52) (Fig. 4), while negative staining was observed with desmin (clone DER-11), S100 (polyclonal), smooth-muscle actin (clone 1A4), CD31 (clone JC70), CD34 (clone QBEND10), anti-melanoma (clone HMB45), h-caldesmon (clone E99), myo-D1 (clone EP212), STAT6 (clone EP325). TTF-1 (clone 8G7G3/1) stained the pneumocytes, while podoplanin (clone D2-40), calretinin (SP65), WT-1 (clone 6F-H2) immunoreacted with the mesothelial cells. BAP1 (clone C4) was positive in spindle cell proliferation, as well as mesothelial cells and pneumocytes. Fluorescent in situ hybridization (FISH) (Vysis LSI SS18-18q11-dual break-apart rearrange-
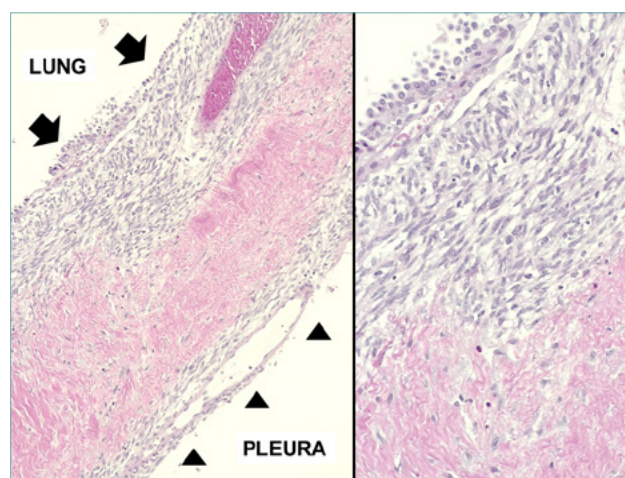

Figure 3. The cystic lesion showed dilated vessels and had and external and internal lining by reactive mesothelium and hyperplastic pneumocytes, respectively. The collagen-rich fibrous tissue was irregularly dissected by a cellular growth of bland-looking, monomorphic spindle cells.
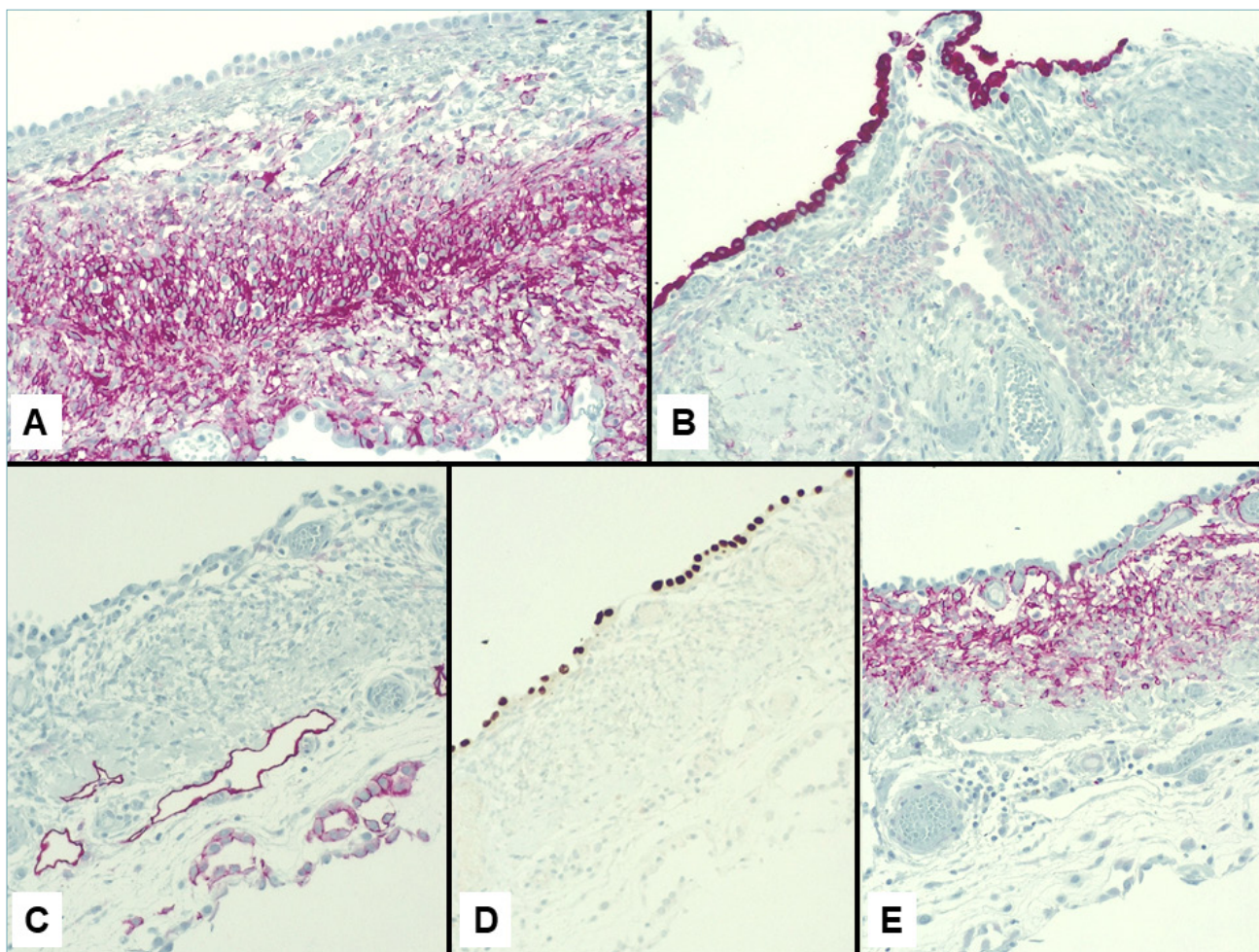
Figure 4. The spindled tumor cells expressed EMA (A) and focally stained with pan-cytokeratins (clones AE1/AE3, B). Podoplanin (clone D2-40, C) immunoreacted with mesothelial cells, while TTF-1 (clone 8G7G3/1, D) staining was restricted to the pneumocytes. A consistent expression was noted with CD56 (123C3, E).
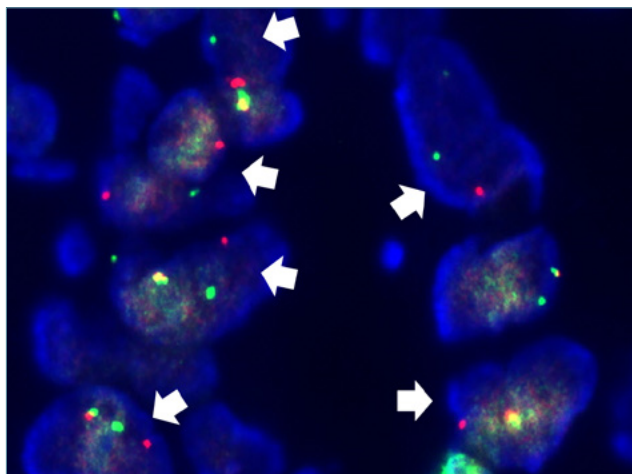
Figure 5. SS18 dual break apart probe at fluorescent in situ hybridization analysis demonstrated 18q11 rearranged tumor cells with splits of red and green signals (arrows).

ment probe, Abbott) evidenced about 40% of 18q11 rearranged tumor cells (Fig. 5).

A diagnosis of cystic monophasic synovial sarcoma was made. Subsequently, a total-body CT with fluorodeoxyglucose-positron-emission tomography (FDG-PET) did not reveal any other tumor site and the patient is alive and well with no disease at 4 months-follow-up with no further therapy.

Discussion

The case here described represents an exceedingly uncommon example of a pathologic condition characterized by recurrent pneumothorax secondary to an unexpected synovial sarcoma with prominent cystic pattern.

Although the thoracic region is considered the commonest visceral site of synovial sarcoma, the tumor generally presents as a large, solid pulmonary or pleura-based mass often associated with pleural effusion [9,10].

A careful search of the literature on cystic synovial sarcoma of the lung revealed 10 cases from seven studies, and a single case series of four cases [11-17].

The most relevant clinico-pathologic features were summarized in Table I. There were eight men and two women and the age at diagnosis ranged from 14-41 years, with a mean of 24.8 years. Smoking history was recorded in only one case. All the patients but one experienced recurrent pneumothorax. The lesions were equally distributed in the right and left lung, with a size ranging from 0.7 cm to 5 cm, although information was available only in half of cases. Outcome was extremely variable with four patients alive and well, one patient experiencing tumor recurrence after 23 years and 4 patients died of disease (from 3 to 75 months after the diagnosis). Chemotherapy was performed in seven cases, comprising all patients who had died. Given the heterogeneity of clinical outcomes, the lack of effective standardized therapy and the localized pulmonary involvement of disease, a conservative approach with imaging follow-up was decided in our case.

The main problem in correct recognition of this neoplasm is the prominent and unusual cystic appearance at imaging studies coupled with the subtle histologic features, likely leading to misdiagnosis.

In fact, the differential diagnosis of pulmonary cysts is very broad, including neoplastic and non-tumoral diseases (Tab. II) [18-23]. The spindle cell proliferation growing in the cystic wall of cystic monophasic synovial sarcoma may be confused with some benign diseases (e.g., endometriosis) or other neoplastic lesions showing cystic changes, as type 1 pleuropulmonary blastoma (PPB), lymphangioleiomyomatosis (LAM), benign metastasizing leiomyoma, cystic fibrohistiocytic tumor (CFHT), and metastatic low-grade sarcoma [18-23].

Some pathologies are related to patient gender and may be excluded in males, such as endometriosis, benign metastasizing leiomyoma and metastatic low-grade endometrial sarcoma [19,21]. In women, the timing of menstrual-related recurrent pneumothorax or the medical past of uterine nodules together with immunostains for hormonal receptors, smooth-muscle and CD10 appropriately lead to differential diagnosis. LAM is another cystic disease almost restricted to female gender with progressive and diffuse, bilateral pulmonary cysts consisting of proliferating myoid cells expressing melanosome markers (HMB45), smooth-muscle actin, hormonal receptors and cathepsin K [22,23]. Type 1 PPB is a childhood tumor, but it has been described in young adults. The identification of rhabdomyoblast proliferation staining with muscle-positive markers (e.g., desmin, myogenin, myo-D1) showing a cambium-layer arrangement and/or identification of *DICER1* mutation characterize type 1 PPB [22-24].

In their study, Cummings et al. [14] initially misdiagnosed 2 cases as type I PPB based on the pure cystic architecture, then underlying this challenging differ-

Table I. Main clinic-pathologic features of cystic synovial sarcoma of the lung reported in literature.

Author/State	Age/Gender	Symptoms	Size (cm)	Site	Outcome	Therapy
Argani, USA [11]	17/M	Recurrent pnx	0.7	RLL	AW (8 yrs)	WR + CT
Esaka, USA [12]	NA/F	Recurrent pnx	NA	LUL	DOD (13 months)	Pn + CT
Watzka, AT [13]	41/M	Asymptomatic	4	RLL	AW (11 months)	Segmentectomy
Cummings, Uk [14]	21/M	Recurrent pnx	1.5	RUL	AW (36 months)	Lobectomy
Cummings, UK [14]	25/M	Recurrent pnx	NA	NA	NA	Bullectomy
Cummings, UK [14]	14/F	Recurrent pnx	NA	RML	DOD (75 months)	Lobectomy + P + CT
Cummings, UK [14]	29/M	Recurrent pnx	NA	LUL	DOD (23 months)	WR + CT + P
Johnson, USA [16]	25/M	Recurrent pnx	1.1	LLL	AW (2 years)	WR + CT
van der Heijden, NL [15]	14/M	Recurrent pnx	5	LLL	AWD (23 years)	Lobectomy + CT
Guo, CN [17]	37/M	Recurrent pnx	NA	RUL	DOD (3 months)	Lobectomy + CT

Abbreviations: M, male; F, female; NA, not available; pnx, pneumothorax; RUL, right upper lobe; RML, right middle lobe; LUL, left upper lobe; LLL, left lower lobe; RLL, right lower lobe; AW, alive and well; DOD, died of disease; P, pleurectomy; CT, chemotherapy; WR, wedge resection; Pn, pneumonectomy.

Table II. A concise summary of the most relevant clinic-pathologic features characterizing the most common causes of pneumothorax due to cystic diseases of the lung.

Pathology	Gender	Distribution	Helpful diagnostic features
LCH	Male > Female	Upper lobes with bronchiolocentric nodules and cysts	Smokers CD1a and S100 immunostains (V600E/BRAF in a subset of cases)
Endometriosis	Female	Right lobe prevalence; tiny nodules, single or multiple or cysts	Recurrent pneumothorax during menstrual phase Endometriosis without glands and composed only of stromal spindle cell component is relatively frequent CD10 and hormonal receptors staining
Type 1 PPB	No prevalence; childhood	Thin-walled multilocular cysts	Cambium-layer change with rhabdomyoblasts; immunostains with muscle markers (desmin, myogenin, myoD1) DICER1 mutation
LAM	Female	Diffuse, bilateral	HMB45, hormonal receptors, SMA, cathepsin K IHC stains
Metastatic endometrial sarcoma	Female	Localized or multiple	History of uterine mass/hysterectomy Hormonal receptors, SMA, CD10
Benign metastizing leiomyoma	Female	Localized or multiple	History of uterine nodules/hysterectomy
Mesothelioma	Male > Female	Localized or diffuse, monolateral	Asbestos exposure Mesothelial markers (calretinin, D2-40, WT1, CK5/6, negative staining with BAP1, CEA, CD15 and claudin-4); no SYT rearrangement
Lung carcinoma	Male > Female	Localized	Smokers Epithelial markers (pan-CKs, TTF-1, p40); no SYT rearrangement

Abbreviations: LCH, Langerhans cell histiocytosis; PPB, pleuropulmonary blastoma; LAM, lympahngioleiomyomatosis; CK, cytokeratins; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor 1; SMA, smooth muscle actin.

ential diagnosis requiring a meticulous morphologic examination coupled to immunostains and molecular investigations.

CFHT is a controversial lesion possibly representing a metastatic deposit from a benign or low-grade fibro-histiocytic tumor of the skin (dermatofibroma/fibrous histiocytoma) [18]. Given the lack of specific features by immunohistochemistry or at the genetic level, this represents a diagnosis of exclusion.

Localized mesothelioma and lung cancer rarely present as bullous/cystic lesions leading to pneumothorax, particularly in aged patients [7,8]. However, immunostains and molecular features can rule out the possibility of a sarcomatoid mesothelioma or carcinoma.

Various types of sarcoma, including synovial sarcoma, may involve pleuropulmonary parenchyma leading to pneumothorax [20,23], but in our patient detailed post-operatory imaging studies excluded other tumor sites.

In conclusion, we present here an exceedingly uncommon case of occult cystic primary monophasic synovial sarcoma of the lung manifesting with recurrent pneumothorax and conservatively treated by pulmonary wedge resection of the left upper lobe. The diagnosis required demonstration of SYT rearrangement by FISH on paraffin-embedded specimen. A review of the literature confirmed the rarity of this occurrence with 10 similar cases described so far, 4 of which had a fatal outcome despite multimodal chemotherapy and major surgery [11-17].

The case underlines the need of a meticulous examination of all surgical specimens from recurrent pneumothorax that may insidiously hide neoplastic growth requiring ancillary techniques to achieve a correct unexpected diagnosis.

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