AMERICAN JOURNAL OF DIAGNOSTIC IMAGING, 2019
VOL 5, NO. 2, PAGES 22–28
10.5455/ajdi.20190311030045

ORIGINAL ARTICLE

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Diagnostic challenge between placental transmogrification and low-grade endometrial stromal sarcoma metastases in a patient with cavitary pulmonary nodules

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ABSTRACT

Cystic lung lesions have limited differential diagnosis, which includes pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis (LAM), lymphocytic interstitial pneumonitis, tracheobronchial papillomatosis, and Birt-Hogg-Dube syndrome. However, a few rare entities, such as pulmonary placental transmogrification (PPT) and metastatic endometrial stromal cell sarcoma can also present as cystic lung lesions and pose diagnostic challenges to both radiologists and pathologists. Clinical history is the key in such situations. Since the first description in the literature of these both entities, there have been very few cases reported. We present our case in a middle-aged female who was known to have cystic lung disease but treated as LAM and had a recurrent pneumothorax. Surgical pathology ruled out LAM and other interstitial cystic lung diseases, and provided a diagnosis of PPT on wedge resection. Subsequent recurrence of cystic lung nodules led to the re-examination of histopathology and immunohistochemistry, concluding a diagnosis of metastasis from remote but undiagnosed low-grade stromal cell sarcoma. We will discuss the clinical, imaging, and pathologic features of both of the diagnoses in this report. Institutional review board approval was not required since it was a single patient report.

ARTICLE HISTORY

Received March 11, 2019
Accepted June 23, 2019
Published July 19, 2019

KEYWORDS

Placental transmogrification; endometrial stromal cell sarcoma; stromal metastases; pulmonary cyst; cystic lung nodule

Introduction

Endometrial stromal cell sarcoma (ESS) metastases and pulmonary placental transmogrification, also known as placentoid bullous lesions of the lung, are rare causes of cystic lung lesions. ESS metastases have been reported in literature in fewer than 50 cases and PPT in fewer than 30 cases since PPT was first described by McChesney [1–9]. ESS are very rare tumors, accounting for 0.2% of all uterine malignancies and 15%–25% of all uterine sarcomas, of which low-grade ESS are the most common and carry favorable prognosis. These are common in women in their 50's and risk factors are similar to endometrial adenocarcinoma [10–17]. Recurrence of primary tumor is common, however, is usually limited to the pelvis. Distant metastases are rare and, when they occur, pulmonary metastases are the most common, followed by brain and liver metastases [10–12,18].

Low-grade sarcomas have been reported to metastasize even after long disease-free periods, which complicates diagnosis. Also, a majority of these patients are asymptomatic and incidentally detected although they can present with hemoptysis, cough, shortness of breath, or severe respiratory distress from spontaneous pneumothorax. Imaging findings could vary from large bulla to spontaneous pneumothorax or pulmonary nodule(s). Surgical excision is usually curative in these patients with excellent prognosis thereafter.

Case Report

A 49-year-old female, never-smoker, with a past medical history of asthma and cystic lung disease, with an empirical diagnosis of LAM at an outside hospital, was referred after she had a recurrent pneumothorax. She was admitted at the outside hospital

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for shortness of breath and cough with severe right pneumothorax. A chest tube was placed with re-expansion of the lung. However, there was recurrent pneumothorax with attempts to remove the chest tube. Her Vascular endothelial growth factor-factor D (VEGF-D): SSA was 1.0 (normal < 1) and SSB <1.0 (negative) with quantitative VEGF-D being 299 pg/ml (normal is <600 pg/ml). She was then transferred to our hospital for further management. On admission, her chest radiograph (Fig. 1a and b) and CT chest showed large subpleural bullae in the right lower lung (Fig. 2a and b) and smaller bulla in right upper lobe which were unchanged from her prior examinations at the outside hospital, and a small right apical pneumothorax. She also had multiple cavitary micronodules in right upper lobe (Fig. 3a and b). She underwent right video-assisted thoracoscopic surgery with lobectomy and wedge resection of right middle lobe, and mechanical pleurodesis in view of her recurrent spontaneous pneumothorax.

Surgical pathology was reported as placental transmogrification of the lung (Fig. 4) with eosinophilic pleuritic and reactive mesothelial changes consistent with the history of pneumothorax. The

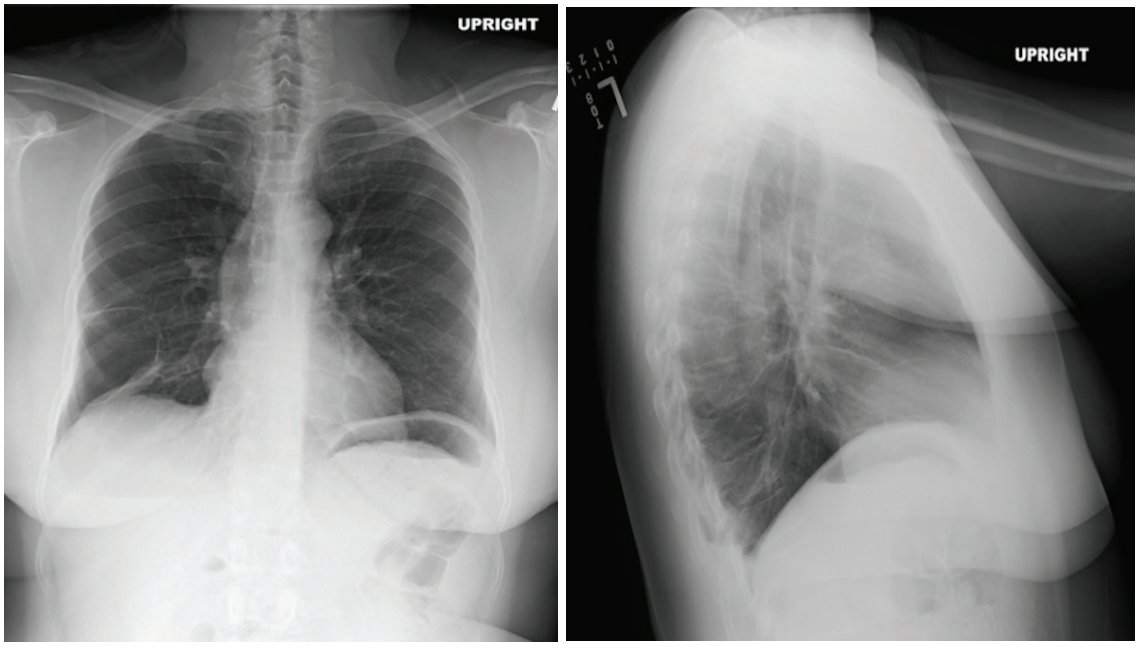


Figure 1. (a) Frontal and (b) lateral upright chest radiographs on admission to our hospital showed a right apical pneumothorax. Large thin walled cyst 5.4 × 4.9 cm in right lower lobe.

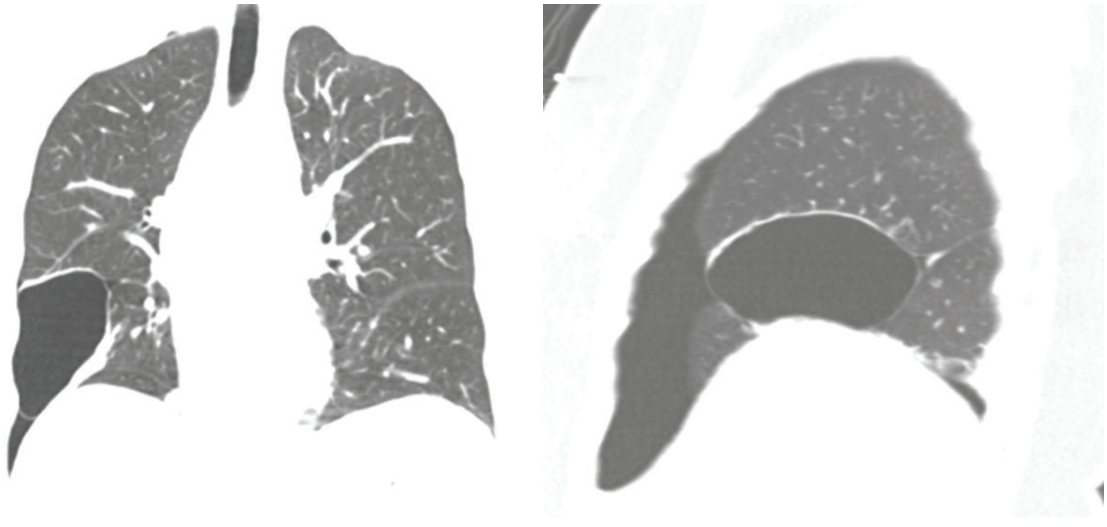


Figure 2. (a) Coronal and (b) sagittal reformatted CT chest in lung window setting shows the cyst in right middle lobe with variable wall thickness. Left lung is normal.

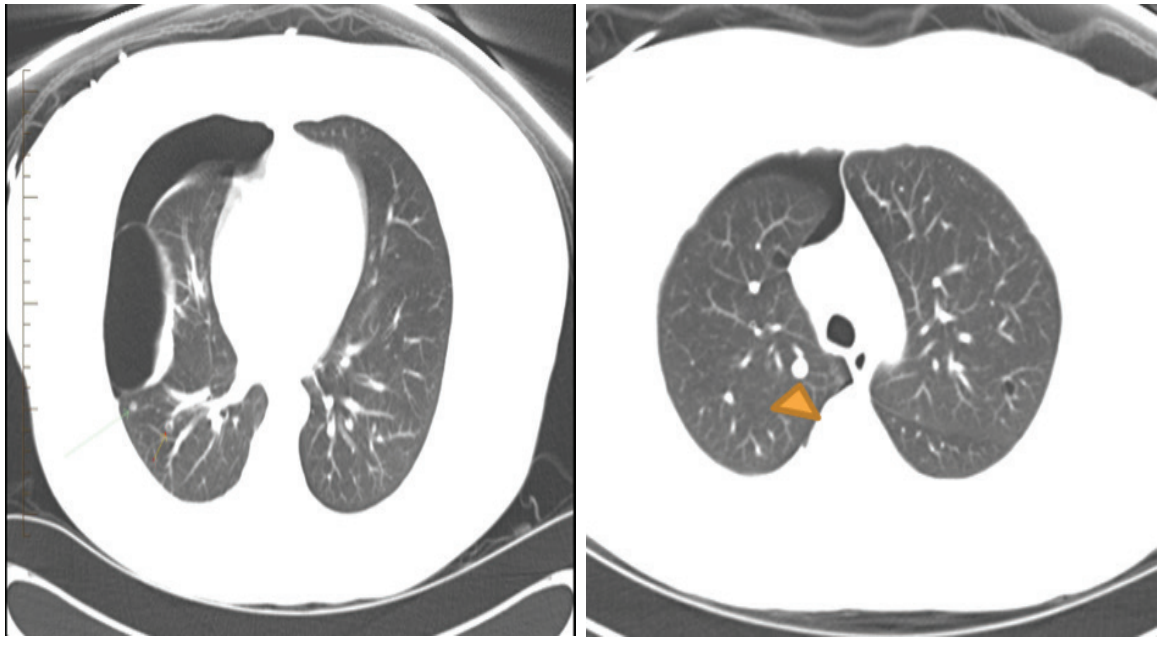


Figure 3. (a) Axial CT chest showing (a) the cavitary micronodules in the posterior segment of right upper lobe on (arrows) and (b) the 7 mm nodule (arrowhead).

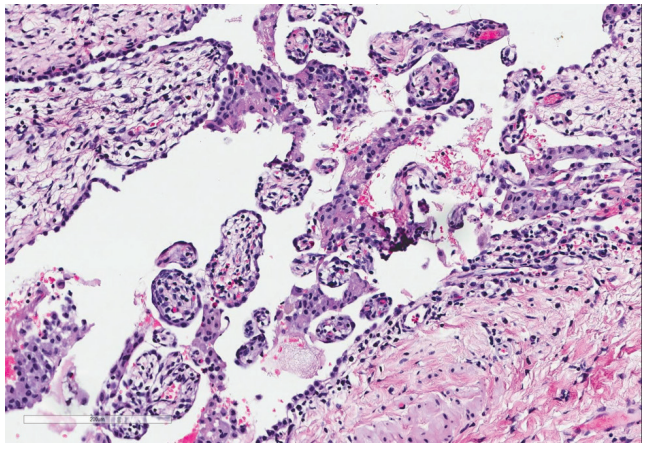


Figure 4. Histopathology showed saccular cysts with fibrovascular papillary cores lined by single layered cuboidal epithelium. The core comprised of loose edematous mesenchymal stroma with many blood vessels, focal clear cells, and few inflammatory cells. Adjoining lung parenchyma showed no evidence of interstitial lung disease.

pathology sections showed saccular cystic lesion with fibrovascular papillary cores lined by single layered cuboidal epithelium. The core comprised loose edematous mesenchymal stroma with many blood vessels, focal clear cells, and few inflammatory cells. In view of the clinical suspicion of LAM, immunostaining was performed. The lining epithelium was positive for thyroid transcription factor (TTF)-1. Stromal cells were positive for desmin, smooth muscle actin, progesterone receptor, and CD10. There was no morphologic or immunophenotypic evidence of LAM. Adjoining lung parenchyma showed no evidence of interstitial lung disease.

She was asymptomatic on follow up at 6 months with chest radiograph showing no new/recurrent pneumothorax and the spirometry showed no significant change in the mild restrictive lung disease which was also seen on spirometry performed in June 2015. Her pulmonary function test at initial presentation in 2015 was: forced vital capacity (FVC)—2.28 L (74% predicted), forced expiratory volume (FEV) 1—1.82 L (71% predicted), FEV1/FVC ratio—80, total lung capacity (TLC)—4.57 L. The pulmonary function test in 2016 was FVC—2.26 L (73% predicted), FEV1—1.74 L (68% predicted), FEV1/FVC ratio—77, TLC—4.12 L. Follow up CT chest at 1-year post-surgery showed multiple lung nodules raising the suspicion for an alternative diagnosis (Fig. 5a). There was a progressive increase in the size of multiple pulmonary nodules, ranging from 0.7 to 1.9 cm maximal diameter. Several of these nodules showed cavitation in CT chest from July 2016 (Fig. 5b). Positron emission tomography/computed tomography (PET-CT) was subsequently performed which demonstrated no hypermetabolic areas in any of the visualized pulmonary nodules. Review of her past medical history included hysterectomy for uterine fibroids in 1992 and no known history of gynecological malignancy.

The histopathology slides were sent to Cleveland Clinic and Johns Hopkins Hospital for independent

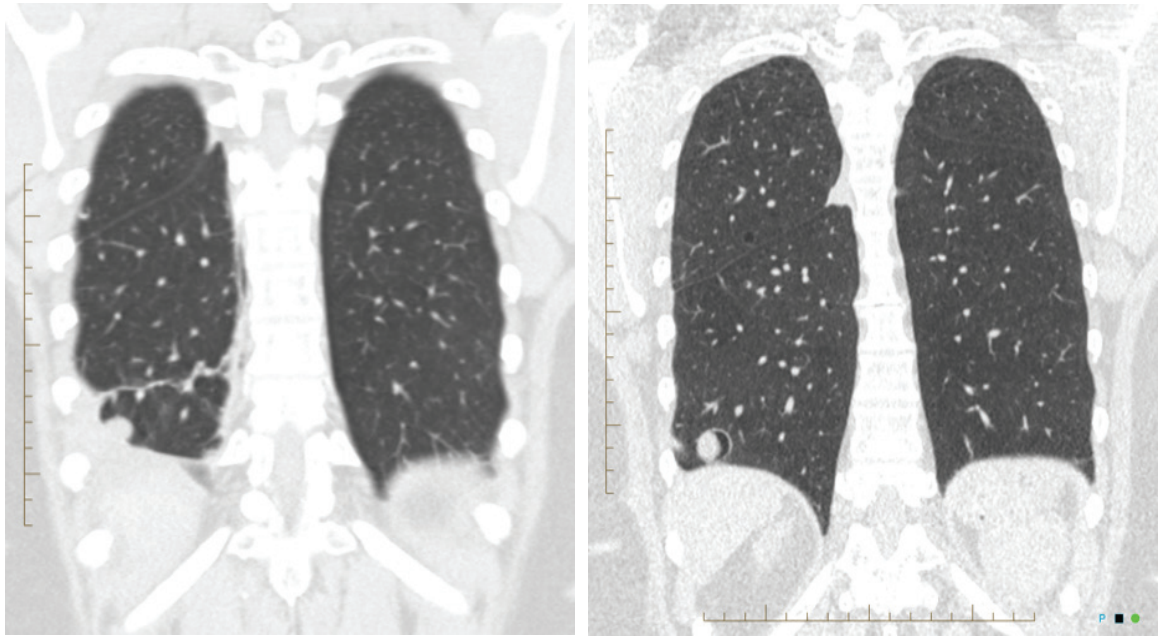


Figure 5. (a) Coronal image of CT chest in lung window settings show the right lower lobe lung nodule in 2015 and (b) cavitation of the lung nodule seen at 1 year follow up after wedge resection.

review. The reviewing pathologists concurred with previous report of pneumothorax, cystic lesions, and immunohistochemical workup. They further described portions of collapsed cystic lesions lined by TTF-1 positive entrapped lung epithelium with cyst walls containing atypical cellular stromal proliferation composed of short, cytologically bland spindle cells with scant cytoplasm and rare mitotic figures. Some of the morphologic features resembled mesenchymal cystic hamartoma, while other morphologic features and the staining pattern were suggestive of a neoplasm most consistent with a low-grade endometrial stromal cell sarcoma. Unfortunately, the patient's hysterectomy specimen was not available for comparison.

The patient was started on anastrozole, a hormone-based chemotherapy for management of low-grade stromal sarcoma metastasis. Her follow-up in 2018 showed the annual pulmonary function test with an increase in FVC from 2.02 to 2.48 L (90% predicted) without significant change in FEV1 at 1.76 L (80% predicted), FEV1/FVC ratio—71, and TLC—3.79 L.

Discussion

PPT is a benign disease, with the age of patients reported in literature ranging between the second and fifth decade and are more common in men [4,7,9,19–21]. PPT derives its name from its characteristic gross and microscopic appearance resembling placental chorionic villi of early pregnancy with papillary structures covered by epithelial cells; however, lacking the biological and biochemical properties of the placenta [2,5,6,9,19,22]. Pathogenesis of PPT remains inconclusive although literature exists describing its congenital origin versus secondary reactive changes to emphysema, lymphatic, or vascular abnormality [2,5–8,19,20,21,23,24]. However, similar interstitial proliferation with secondary cystic changes can also be seen in other conditions, such as cystic pleuropulmonary blastoma, endometrial stromal sarcoma with cystic metastasis, and dermatofibrosarcoma protuberans [23]. There have been case reports describing papillary adenocarcinoma arising from the epithelial components of PPT [2,22]. Rare associations with Swyer–James syndrome, pulmonary fibro chondromatous hamartomas, and pulmonary lipomatosis have been reported [2,6,24,25].

Clinical features of PPT can range from being asymptomatic to hemoptysis, chest pain, severe dyspnea or respiratory distress, primarily from pneumothorax [2,3,5,7,9,20,21,25], whereas patients with metastatic ESS are usually asymptomatic with an indolent clinical course. Distant metastasis of ESS is rare, with lung metastases reported in 7%–30% [10,11,16,17,26,27]. The metastatic pulmonary nodules or mass from ESS can appear between 3 months and 31 years, including after long disease-free period [10,11,13,27,28,29]. Takizawa et al described a large 3.5 cm suspicious lung mass in a 74-year-old female who had hysterectomy 31

years ago for low-grade endometrial stromal cell carcinoma [29].

Imaging findings of PPT could vary from bullous emphysema, pulmonary nodule, hilar mass, spontaneous, or tension pneumothorax [2,5,6,9,19,21]. ESS pulmonary metastasis is described as varying presentations including cystic lesions, solitary pulmonary nodule, multiple pulmonary nodules (most common presentation) or multiple intra alveolar micronodules, or spontaneous pneumothorax; however, quite similar to the imaging presentation of PPT [10,14,17,30]. Miyamoto et al. [12] described the pulmonary ESS metastatic nodules demonstrating increased FDG uptake on PET-CT with SUVmax up to 6.3 in one of their patients.

Diagnosis is primarily by surgical resection and histopathological examination, though CT and MRI can help in narrowing the differentials. The characteristic microscopic features of PPT are papillary structures filling the bulla that is lined by placental villi like appearing epithelial cells, papillary core containing proliferative blood vessels, mesenchymal elements, including fat, inflammatory cells, and calcifications rarely [2,5–7,19,20,22,23]. The stromal cells were described to have a pathognomonic appearance with clear cytoplasm and immature mesenchymal phenotype from its immunohistochemical staining pattern- positive stain for CD-10, and negative for desmin, actin, S-100 protein, HMB-45, MART-1, CD-68, CD-34, CD-117, TTF-1, estrogen, and progesterone receptors [9,23]. However, there are variable results with regard to immunohistochemical profile. In contrast, metastatic ESS presents histologically as characteristic small blood vessels resembling spiral arterioles with uniform small spindle- or oval-shaped nuclei, finely granular chromatin, and indistinct cell borders in a vaguely fascicular arrangement [13,14], and, on immunohistochemistry, they stain positive for CD10, estrogen, and progesterone receptors [10–12,28,31]. CD10 and CD44v3 positivity helps in differentiating ESS from other smooth muscle neoplasms like leiomyoma [10,12]. Apart from mitotic index which differentiates low-grade from high-grade ESS, low-grade is more likely to express estrogen and progesterone receptors which contributes to its responsiveness to hormonal therapy [12,14]. HMB45 immunohistochemical marker can be used to differentiate between the various cystic pulmonary lesions [14,30]. LAM is one disease with stains positive for HMB45 (antimelanoma antibody), and helps in differentiating it from ESS metastases [30]. Myogenic markers, actin and desmin, can be used to differentiate ESS metastases from mesenchymal cystic hamartoma [30].

The differential diagnosis for PPT includes congenital pulmonary airway malformation, intralobar pulmonary sequestration, bronchogenic cyst, mucinous cystic tumors of the lung, mucinous bronchoalveolar carcinoma arising from a cyst, hamartoma, sclerosing hemangioma, solitary fibrous tumor, alveolar adenoma, LAM, and lymphangiodysplasia [2,8,9,20]. The common differential diagnosis to metastatic ESS are benign metastasizing leiomyoma and other differentials included above for PPT [10,11,17].

Possible complications with PPT and metastatic ESS are tension pneumothorax, spontaneous pneumothorax, malignancy arising from epithelial components of the lesion, however, more common with PPT [2,19,22]. Treatment of PPT and metastatic ESS are similar which includes lobectomy or pneumonectomy and is usually curative [2–5,7–9,16,19,21,23]. Overall prognosis after surgical resection is excellent in both these subgroup of patients [2,5,11,13,16].

In conclusion, pulmonary placental transmogrification and low-grade stromal sarcoma metastasis are rare differentials to be considered in patients presenting with cystic lung nodules in the absence of underlying pulmonary pathology. Placental transmogrification should be considered in the differential of middle-aged patients presenting with unilateral spontaneous or recurrent pneumothorax irrespective of their smoking history. On the contrary, low-grade endometrial stromal sarcoma metastasis is considered in women presenting with cystic or solid lung nodules and a remote history of hysterectomy for uterine tumor or documented benign causes like leiomyoma. Microscopic histology and immunohistochemistry in these both diagnoses are classical and surgical excision is curative, yielding excellent prognosis with nearly symptom-free life thereafter. Also, it is important to have definitive diagnosis before instituting treatment as misdiagnosis can be disastrous. LAM misdiagnosis can result in lung transplantation with immunosuppression, which can be deleterious for a patient with metastatic endometrial stromal cell sarcoma.

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