Radiology Case Reports 15 (2020) 502–506

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Pulmonary adenomyoma presenting as a right cardiophrenic angle mass

Osigbemhe Iyalomhe, MD, PhD[a,*], *Sam Sadigh, MD*[b], *Charuhas Deshpande, MD*[b], *Leslie Litzky, MD*[b], *Anna Moran*[b], *Scott Simpson, DO*[a]

[a] *Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA*

[b] *Department of Pathology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA*

ARTICLE INFO

Article history:
Received 15 August 2019
Revised 25 December 2019
Accepted 28 December 2019

Keywords:
Pulmonary adenomyoma
Harmatoma
Adenofibroma
Solitary fibrous tumor
Myasthenia gravis
Thymoma

ABSTRACT

Pulmonary adenomyomas are rare adenomyomatous hamartomas. In the few cases described in the literature, these benign tumors are encapsulated by lung parenchyma. We describe a case of a 59 year-old woman with acetylcholine receptor antibody-negative myasthenia gravis and a right cardiophrenic mass initially thought to be a thymoma. Histopathology surprisingly revealed a pulmonary adenomyoma which involved the mediastinal fat at the cardiophrenic angle.

Introduction

The location of a mass in the mediastinum is an important consideration in the differential diagnoses [1]. In some instances, cross-sectional imaging can narrow the possibilities; and when imaging findings are considered in combination with clinical observations, a single diagnosis can at times be rendered. On occasion, however, direct tissue sampling or surgical excision is necessary for definitive diagnosis.

We discuss a case of a mass in the cardiophrenic space in a patient with myasthenia gravis, with clinical and imaging observations suggesting a thymoma. However, surgical excision and histopathologic analysis led to the unexpected diagnosis of a pulmonary adenomyoma at the right cardiophrenic space.

Case report

Clinical history

A 59-year-old woman with a productive cough was found to have a mediastinal mass on chest x-ray in 2016. She also

Conflict of interest: None.

* Corresponding author.
E-mail address: osiyal@gmail.com (O. Iyalomhe).

https://doi.org/10.1016/j.radcr.2019.12.025

complained of progressive dysphagia and proximal muscle weakness which prompted molecular testing when she presented for formal evaluation 2 years later. Acetylcholine receptor antibody testing and a barium esophagram were unrevealing. However, given her clinical history and symptoms, a diagnosis of myasthenia gravis was made after neurology consultation. She reported significant improvement after treatment with intravenous immunoglobulins, an event consistent with myasthenia gravis. Given age, symptomatology, clinical evaluation, and response to intravenous immunoglobulin treatment, the right cardiophrenic mass was thought to be a thymoma. Computed tomography (CT) of the chest was previously performed in 2016 and follow-up preoperative chest CT (2 years later) again demonstrated a right cardiophrenic mass with minimal change in size, compatible with an indolent biology.

CT imaging and histopathologic findings

CT imaging showed a heterogeneous and mildly lobulated mass measuring $5.2 \times 4.4 \times 4.5$ cm containing a tiny punctate calcification and small foci of cystic change, and abutting the right pericardiac fat, pericardium of the right atrium, and parietal pleura of the adjacent right lung (Fig. 1, *top and middle rows*). There were no definitive imaging findings to support extension into the lung parenchyma, local invasion or distant metastasis.

Enbloc resection of the cardiophrenic mass along with wedge resection of the right middle lobe of the lung showed that it was adherent to lung only peripherally. Of note, follow-up imaging 8 months later did not show tumor recurrence (Fig. 1, *bottom row*). Histopathologic sections of the mass (Fig. 2) revealed a relatively well-circumscribed neoplasm that was predominantly extrapulmonary with a fibrous capsule, though portions of the lesion appeared to connect with lung parenchyma. The lesion was composed of 2 cell populations: epithelial cuboidal lining cells with minimal atypia and a variably cellular underlying stromal cell population. The cells were arranged in a papillary configuration with some large pseudopapillae and solid areas. Mitotic activity was not increased and there was no necrosis. Regional lymph nodes were negative for neoplasm.

Immunohistochemical stains were performed on representative formalin-fixed paraffin-embedded sections with adequate controls (Fig. 3). Lining epithelial cells were positive for Cam5.2, CK7, and EMA (markers of epithelioid differentiation) [2–4], as well as Napsin-A, a cytoplasmic proteinase that can be seen in lung parenchyma [5]. TTF-1, a transcription factor in pneumocytes but which can also be seen in thyroid tissue [5,6], strongly stained in the lining cells and was also very weakly positive in the underlying stromal cells. The stromal cells were strongly positive for smooth muscle actin and desmin (see Discussion section). There was scattered PAX-8 positivity, a nonspecific finding. CK5/6 (epithelial markers), WT-1 (a marker for mesothelioma) [7,8], D2-40 [9], calretinin [10], p40 [11], estrogen receptor (see Discussion section), progesterone receptor (PR), STAT-6 (see Discussion section), Ckit [12], ERG [13], and CD1a [14] stains were negative in the lesional cells. Markers for melanoma (HMB45, Melan-A, and S100 [15,16]) were negative. Ki-67 proliferation index was low (<1%), suggesting low cellular proliferation. The overall morphologic appearance and immunohistochemical profile led to a diagnosis of pulmonary adenomyoma being rendered. A thymectomy was also performed for a presumptive presurgical diagnosis of thymoma; histologic evaluation revealed normal thymic tissue.

Discussion

Differential diagnosis for masses in the right cardiophrenic space is broad [17]. These include fat containing lesions such as prominent pericardial fat, lipoma, and liposarcoma. Cystic lesions include pericardial and thymic cysts. Thymic neoplasms, germ cell tumors, Morgagni hernias, lymphadenopathy, and varices from prominent pericardiophrenic veins are other entities that can be found at the cardiophrenic angles. Together with the clinical history, presentation and laboratory data, cross-sectional imaging using CT or magnetic resonance imaging (MRI) can help narrow the differential diagnoses. In the present case, the clinical history of myasthenia gravis, CT features of a relatively unchanged well-circumscribed right cardiophrenic mass, as well as known association of thymoma and myasthenia gravis [18], all initially suggested that the mass was probably a thymoma situated within the mediastinal fat at the cardiophrenic angle. Although thymic neoplasms are typically located in the anterior mediastinum [17], on rare occasions they can demonstrate ectopic positioning, such as in the cervical region or visceral pleura of the lung [19,20], indicating that communication with the anterior mediastinum is not an inviolable criterion.

Histopathology in the current case showed that the right cardiophrenic angle lesion contained epithelial cuboidal cells lining cystic spaces and surrounding cellular stroma which stained positive for actin and desmin confirming a smooth muscle stroma. Malignancy was unlikely given the absence of necrosis, lack of atypia, low Ki-67 index, and low mitotic activity. The overall findings were compatible with an adenomyomatous pulmonary hamartoma which involved the fat at the cardiophrenic angle. It is relevant to note that the imaging appearance is insufficient to make a definitive diagnosis, and biopsy or surgical resection is most likely necessary as was done here. In addition, stability and absence of radiotracer activity on positron emission tomography imaging may suggest a nonfat containing hamartomatous lesion such as a pulmonary adenomyoma.

While representing only 8% of solitary lung nodules, pulmonary hamartomas are among the most common benign lesions in the adult lung (75%) and are defined by abnormal growth of native tissue such as fat, muscle, epithelium, and cartilage, or an abnormal admixture of different tissue types [21,22]. Classification of pulmonary hamartomas by their cellular composition includes recognized categories such as chrondromas, leiomyomas, adenomyomas, and adenofibromas [23]. In very exceptional cases, for example as in mesenchymal cystic hamartomas, malignant transformation can occur [24].

The differential diagnosis of a “hamartomatous” lung lesion composed of cellular stroma surrounding cystic spaces

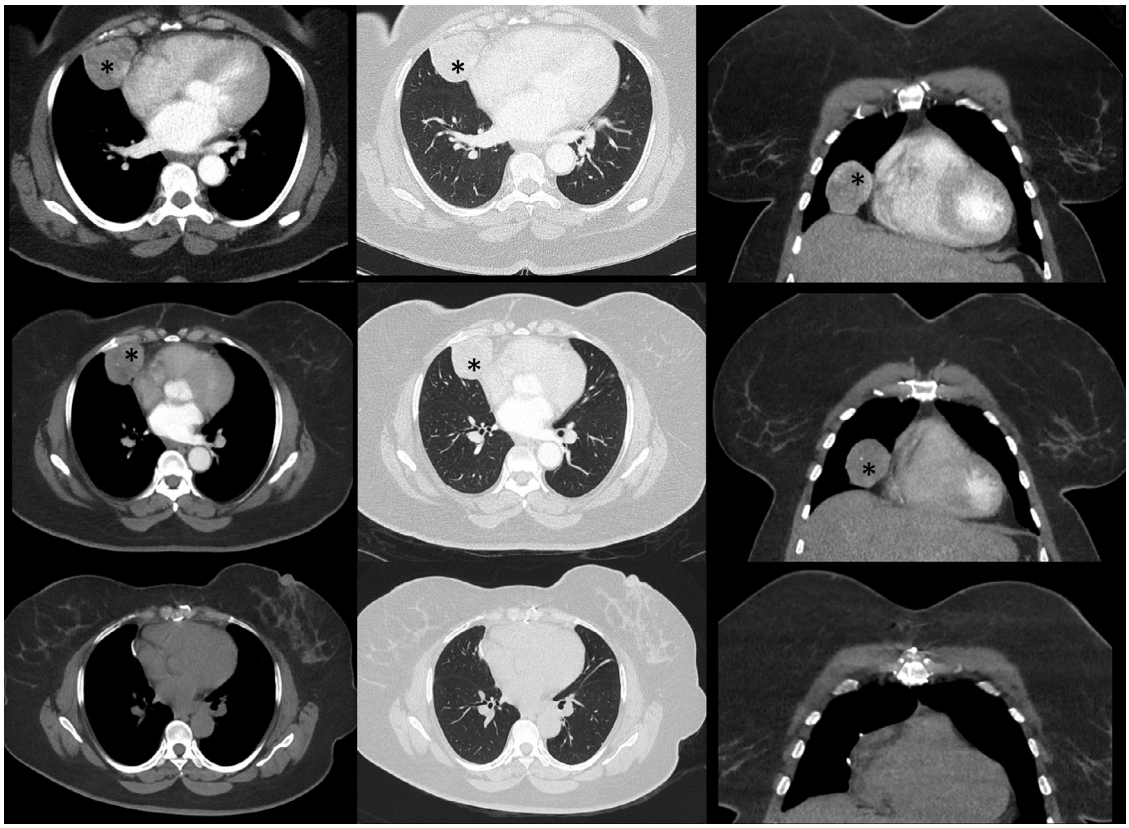

Fig. 1 – Top row: Preoperative contrast-enhanced CT of the chest obtained 2 years before surgery in axial soft tissue window (left), lung window (middle), and coronal soft tissue (right) reconstructions. An asterisk (*) denotes the right cardiophrenic pulmonary adenomyoma.
Middle row: Preoperative contrast-enhanced CT of the chest obtained just before surgery (2 years after the images shown in "Top row"). Images are provided in axial soft tissue window (left), lung window (middle), and coronal soft tissue (right) reconstructions. An asterisk (*) denotes the right cardiophrenic pulmonary adenomyoma.
Bottom row: Postoperative noncontrast CT of the chest in axial soft tissue window (left), lung window (middle), and coronal soft tissue (right) reconstructions. Hyperdense material at the right cardiophrenic space are surgical clips/sutures from wedge resection of the right middle lobe.

lined by simple cuboidal to columnar epithelium includes consideration of other possibilities such as adenofibroma and solitary fibrous tumor. Adenofibromas and solitary fibrous tumors variably stain positive for ER, BCL-2, and CD34 [25] and would not be expected to stain for smooth muscle markers such as actin and desmin. A recent report [26] documented desmin staining in a muscle-deficient lesion described as a pulmonary adenofibroma. This unusual characteristic of a pulmonary adenofibroma suggests that this lesion represents a variant with stromal spindle cells expressing desmin, or alternatively, an adenofibroma with a small, histologically undetectable smooth muscle component. The distinction from an adenofibroma and solitary fibrous tumor is further cemented by using immunohistochemistry for STAT6, a surrogate for the *NAB2-STAT6* gene fusion characteristic of these lesions [25]. The cardiophrenic angle mass in our described case did not stain for STAT6, CD34, or estrogen receptor, making an adenofibroma or solitary fibrous tumor unlikely. The histologic appearance of the mass was also similar to the appearance described for a pulmonary adenomyoma with a comparable immunohistochemical profile [27]. In addition, the patient did not have any known history of an extrathoracic tumor or uterine fibroid, the latter which may cause a metastasizing leiomyoma [28].

One unusual feature in the current case is the largely extrapulmonary location of the adenomyoma. In other cases in the literature, the lesion is typically encapsulated totally by lung parenchyma [27,29]. This indicates that these tumors may not necessarily be confined to lung tissue, an observation that may hold implications for the cellular origin and evolution of pulmonary adenomyomas.

Finally, it is unclear whether the cardiophrenic adenomyoma was related to the patient's myasthenia gravis. On review of the literature, there are no reports documenting an association between myasthenia gravis and adenomyomas. Given negative laboratory data, it is likely that the patient had idiopathic myasthenia gravis. Moreover, histopathologic review of the resected thymus revealed normal tissue without thymoma. If future reports document a temporal association between adenomyomas and neuromuscular disease,

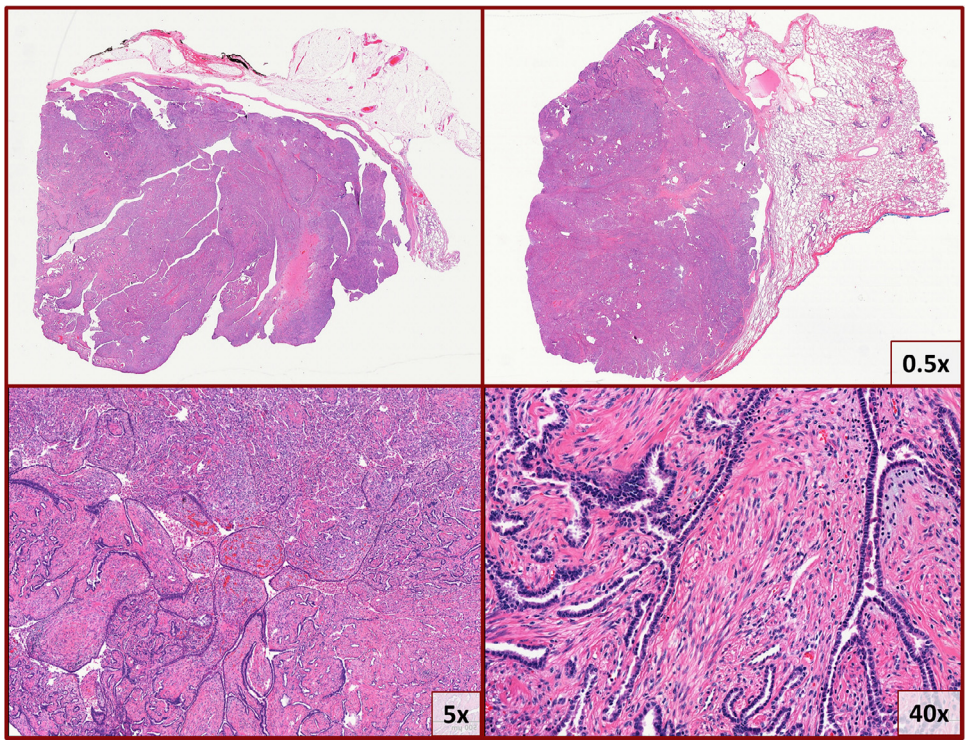

Fig. 2 – Low magnification (top panels) photomicrographs of H&E stained sections show a well-circumscribed mass that is predominantly extrapulmonary with a fibrous capsule, and focally appears connected with lung parenchyma. On high magnification (bottom panels) a biphasic histology with 2 cell populations is evident: epithelial cuboidal lining cells with minimal atypia and a variably cellular underlying stromal population. There is a papillary configuration with some large pseudopapillae and solid areas.

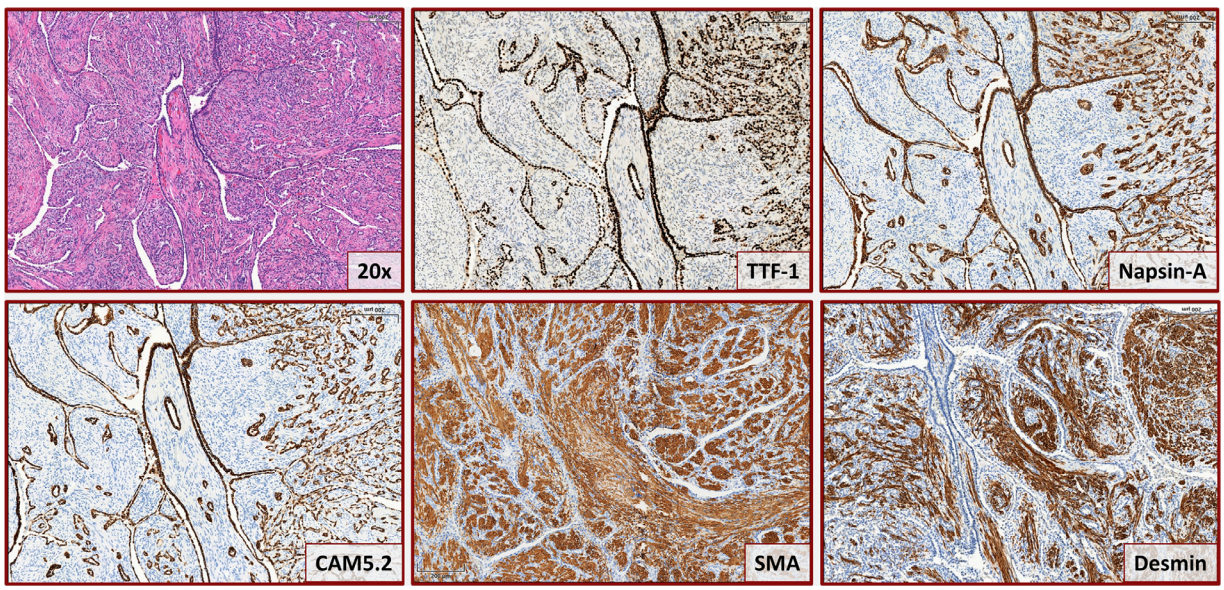

Fig. 3 – A panel of immunohistochemical stains show that the lining epithelial cells are positive for Cam5.2 (cytokeratin), TTF-1, and Napsin-A. The stromal cells are positive for smooth muscle actin (SMA) and desmin.

it is possible that adenomyomas may cause paraneoplastic phenomena.

REFERENCES

[1] Carter BW, Benveniste MF, Madan R, Godoy MC, de Groot PM, Truong MT, et al. ITMIG classification of mediastinal compartments and multidisciplinary approach to mediastinal masses. Radiographics 2017;37(2):413–36. doi:10.1148/rg.2017160095.

[2] He S, Peng J, Li L, Xu Y, Wu X, Yu J, et al. High expression of cytokeratin CAM5.2 in esophageal squamous cell carcinoma is associated with poor prognosis. Medicine (Baltimore) 2019;98(37):e17104. doi:10.1097/MD.0000000000017104.

[3] Kummar S, Fogarasi M, Canova A, Mota A, Ciesielski T. Cytokeratin 7 and 20 staining for the diagnosis of lung and colorectal adenocarcinoma. Br J Cancer 2002;86(12):1884–7. doi:10.1038/sj.bjc.6600326.

[4] Pinkus GS, Kurtin PJ. Epithelial membrane antigen—a diagnostic discriminant in surgical pathology: immunohistochemical profile in epithelial, mesenchymal, and hematopoietic neoplasms using paraffin sections and monoclonal antibodies. Hum Pathol 1985;16(9):929–40. doi:10.1016/s0046-8177(85)80132-5.

[5] Turner BM, Cagle PT, Sainz IM, Fukuoka J, Shen SS, Jagirdar J. Napsin A, a new marker for lung adenocarcinoma, is complementary and more sensitive and specific than thyroid transcription factor 1 in the differential diagnosis of primary pulmonary carcinoma: evaluation of 1674 cases by tissue microarray. Arch Pathol Lab Med 2012;136(2):163–71. doi:10.5858/arpa.2011-0320-OA.

[6] Lau SK, Luthringer DJ, Eisen RN. Thyroid transcription factor-1: a review. Appl Immunohistochem Mol Morphol 2002;10(2):97–102. doi:10.1097/00129039-200206000-00001.

[7] Foster MR, Johnson JE, Olson SJ, Allred DC. Immunohistochemical analysis of nuclear versus cytoplasmic staining of WT1 in malignant mesotheliomas and primary pulmonary adenocarcinomas. Arch Pathol Lab Med 2001;125(10):1316–20. doi:10.1043/0003-9985(2001)125⟨1316:IAONVC⟩2.0.CO;2.

[8] Park S, Schalling M, Bernard A, Maheswaran S, Shipley GC, Roberts D, et al. The Wilms tumour gene WT1 is expressed in murine mesoderm-derived tissues and mutated in a human mesothelioma. Nat Genet 1993;4(4):415–20. doi:10.1038/ng0893-415.

[9] He C, Wang B, Wan C, Yang T, Shen Y. Diagnostic value of D2-40 immunostaining for malignant mesothelioma: a meta-analysis. Oncotarget 2017;8(38):64407–16. doi:10.18632/oncotarget.19041.

[10] Chhieng DC, Yee H, Schaefer D, Cangiarella JF, Jagirdar J, Chiriboga LA, et al. Calretinin staining pattern aids in the differentiation of mesothelioma from adenocarcinoma in serous effusions. Cancer 2000;90(3):194–200. doi:10.1002/1097-0142(20000625)90:3⟨194::aid-cncr8⟩3.0.co;2-k.

[11] Affandi KA, Tizen NMS, Mustangin M, Zin R. p40 immunohistochemistry is an excellent marker in primary lung squamous cell carcinoma. J Pathol Transl Med 2018;52(5):283–9. doi:10.4132/jptm.2018.08.14.

[12] Ashman LK. The biology of stem cell factor and its receptor C-kit. Int J Biochem Cell Biol 1999;31(10):1037–51. doi:10.1016/s1357-2725(99)00076-x.

[13] Sullivan HC, Edgar MA, Cohen C, Kovach CK, HooKim K, Reid MD. The utility of ERG, CD31 and CD34 in the cytological diagnosis of angiosarcoma: an analysis of 25 cases. J Clin Pathol 2015;68(1):44–50. doi:10.1136/jclinpath-2014-202629.

[14] Mizumoto N, Takashima A. CD1a and langerin: acting as more than Langerhans cell markers. J Clin Invest 2004;113(5):658–60. doi:10.1172/JCI21140.

[15] Mahmood MN, Lee MW, Linden MD, Nathanson SD, Hornyak TJ, Zarbo RJ. Diagnostic value of HMB-45 and anti-Melan A staining of sentinel lymph nodes with isolated positive cells. Mod Pathol 2002;15(12):1288–93. doi:10.1097/01.MP.0000037313.33138.DF.

[16] Shinohara MM, Deubner H, Argenyi ZB. S100, HMB-45, and Melan-A negative primary melanoma. Dermatol Online J 2009;15(9):7.

[17] Pineda V, Andreu J, Caceres J, Merino X, Varona D, Dominguez-Oronoz R. Lesions of the cardiophrenic space: findings at cross-sectional imaging. Radiographics 2007;27(1):19–32. doi:10.1148/rg.271065089.

[18] Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. Cancer 1987;60(11):2727–43.

[19] Nagasawa K, Takahashi K, Hayashi T, Aburano T. Ectopic cervical thymoma: MRI findings. AJR Am J Roentgenol 2004;182(1):262–3. doi:10.2214/ajr.182.1.1820262a.

[20] Skoutelis K, Nikolopoulos DD, Markopoulos K, Chabipi K, Stoungioti S, Papastamatiou M. Ectopic thymoma of the lung; a rare case report and review of the literature. Cases J 2009;2:9149. doi:10.1186/1757-1626-2-9149.

[21] Madewell JE, Feigin DS. Benign tumors of the lung. Semin Roentgenol 1977;12(3):175–86.

[22] De Cicco C, Bellomi M, Bartolomei M, Carbone G, Pelosi G, Veronesi G, et al. Imaging of lung hamartomas by multidetector computed tomography and positron emission tomography. Ann Thorac Surg 2008;86(6):1769–72. doi:10.1016/j.athoracsur.2008.08.033.

[23] Narita T, Takahashi H. Unusual cystadenomatous hamartoma of the lung. Histopathology 1996;28(3):285–7.

[24] Hedlund GL, Bisset GS 3rd, Bove KE. Malignant neoplasms arising in cystic hamartomas of the lung in childhood. Radiology 1989;173(1):77–9. doi:10.1148/radiology.173.1.2781034.

[25] Fusco N, Guerini-Rocco E, Augello C, Terrasi A, Ercoli G, Fumagalli C, et al. Recurrent NAB2-STAT6 gene fusions and oestrogen receptor-alpha expression in pulmonary adenofibromas. Histopathology 2017;70(6):906–17. doi:10.1111/his.13165.

[26] Hao J, Zhang C, Cao Q, Zou J, Wang C. Pulmonary adenofibroma: report of a case with multiple masses. Ann Clin Lab Sci 2016;46(6):691–5.

[27] Takeshima Y, Furukawa K, Inai K. 'Adenomyomatous' hamartoma of the lung. Pathol Int 2000;50(12):984–6.

[28] Miller J, Shoni M, Siegert C, Lebenthal A, Godleski J, McNamee C. Benign metastasizing leiomyomas to the lungs: an institutional case series and a review of the recent literature. Ann Thorac Surg 2016;101(1):253–8. doi:10.1016/j.athoracsur.2015.05.107.

[29] Jin MS, Ha HJ, Baek HJ, Lee JC, Koh JS. Adenomyomatous hamartoma of lung mimicking benign mucinous tumor in fine needle aspiration biopsy: a case report. Acta Cytol 2008;52(3):357–60. doi:10.1159/000325523.