

Primary pleural angiosarcoma: Case report and literature review

SAGE Open Medical Case Reports
Volume 8: 1–6
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/2050313X20904595
journals.sagepub.com/home/sco



Yub Raj Sedhai¹ , Soney Basnyat², Reshma Golamari³,
Ajay Koirala⁴ and Mengdan Yuan⁵

Abstract

Primary pleural angiosarcoma is an exceptionally rare malignancy of pleura originating from the vascular endothelial cells. Here, we present a 70-year-old African-American female who presented with 1-month history of dyspnea on exertion, loss of appetite, and loss of weight along with left-sided pleuritic chest pain. Evaluation revealed hemorrhagic pleural effusion in the left pleural cavity. Computed tomography of the chest performed after therapeutic thoracentesis revealed left upper lobe lung mass along with multiple nodules in right lung. Mass was biopsied at video-assisted thoracoscopy. Histopathology was consistent with high-grade angiosarcoma. Endothelial origin of the tumor cells was confirmed with positive immunohistochemical staining with CD31 antibodies. Our patient was diagnosed with primary pleural angiosarcoma metastatic to the lung. She opted for palliative care and had a rapidly declining clinical course and expired within 5 weeks of the diagnosis. Here, we present a case report and review the relevant literature.

Keywords

Oncology, angiosarcoma, pleural malignancy

Date received: 3 May 2019; accepted: 6 January 2020

Introduction

Angiosarcomas are uncommon malignancies of the vascular endothelial origin. It includes about 1% of all soft tissue malignancies and most commonly involves skin, soft tissue, liver, bone, breast, and spleen.¹ Primary pleural angiosarcoma (PPA) is a rare malignancy and literature is merely limited to anecdotal case reports. We performed an extensive literature search in Medline (via PubMed), Scopus, Cochrane library and Google Scholar and were able to identify 46 published cases^{1–31} since the first reported case in 1943.² In this article, we describe the clinical presentation of PPA and have reviewed the literature.

Case presentation

A 70-year-old African-American woman presented to the emergency room on account of worsening of dyspnea for 1 month. At baseline, she was able to walk 1–2 blocks of streets. However, over the past 1 month, dyspnea had worsened making her short of breath at rest and limiting her from performing activities of daily living. Symptoms also included minimally productive cough and bilateral pleuritic chest pain. It was

associated with progressive loss of appetite and 10 pounds of unintentional weight loss. Patient denied symptoms including orthopnea, paroxysmal nocturnal dyspnea, and swelling of lower extremities. She had history of chronic obstructive pulmonary disease with 70 pack-year history of smoking and was a social drinker denied use of illicit/narcotic drugs and asbestos or agent orange exposure. Our patient had never traveled to the tubercular endemic zone and did not have previous diagnosis or contact with tuberculosis. She did not have family history of cancer or other comorbidities. On initial evaluation, she had a respiratory rate of 28 breaths per minute and saturated 90% on room air, blood pressure of 100/70 mmHg, and a heart rate of 90 beats per minute in sinus rhythm. Examination

¹VCU School of Medicine, Richmond, VA, USA

²St. Mary Mercy Hospital, Livonia, MI, USA

³Mercy Catholic Medical Center, Darby, PA, USA

⁴Reading Hospital, Reading, PA, USA

⁵University of Michigan, Ann Arbor, MI, USA

Corresponding Author:

Yub Raj Sedhai, VCU School of Medicine, Richmond, VA 23298-0565, USA.

Email: dr.sedhai@gmail.com



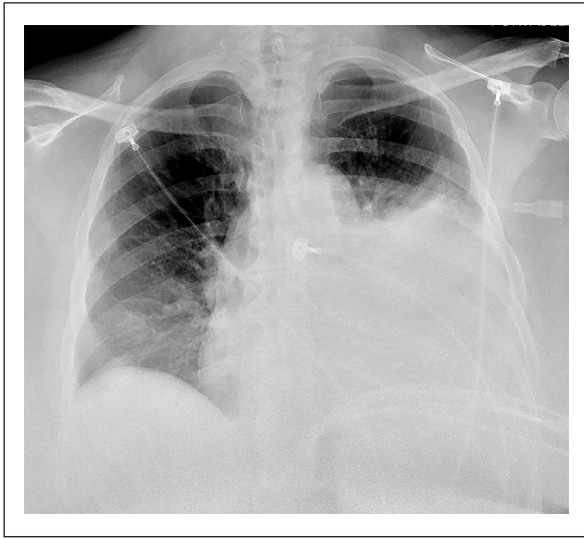


Figure 1. Chest X-ray anteroposterior view showing left-sided pleural effusion.

of the chest revealed diminished expansion of the left hemithorax. Left hemithorax was dull to percussion and breath sounds were of diminished intensity on auscultation. Trachea was pushed to the right and position of cardiac apex was difficult to localize on palpation. Heart sounds were diminished in intensity, and there was no audible murmur, bruit, rubs, or third and fourth heart sounds. Examination of the other systems including abdomen, neurology, head, neck, and extremities were essentially unremarkable.

Investigation, clinical course, and outcome

Point of care ultrasound (POCUS) revealed large left-sided pleural effusion. Laboratory parameters revealed hemoglobin of 11 g/dL, hematocrit of 42%, and white blood cell count of 11,000 cells/mcL with 74% neutrophils and 22% lymphocytes. Serum protein level was 4.8 g/dL, serum albumin was 3.5 g/dL, and serum LDH was 140 U/L. Metabolic parameters including serum creatinine of 1.1 mg/dL, blood glucose of 110 mg/dL, and other metabolic parameters were within normal limits. Coagulation parameters were remarkable with prothrombin time measuring 11 s, international normalized ratio (INR) 1.2, and d-dimer measured 0.12 μ g/mL.

Chest X-ray revealed a large left-sided pleural effusion pushing the mediastinum to the opposite side (Figure 1). Diagnostic thoracentesis revealed hemorrhagic pleural effusion on gross inspection. Laboratory analysis of pleural fluid revealed pH of 7.27, with 440,000 cells/mcL red blood cells and 14,000 cells/mcL white blood cells, and pleural fluid hematocrit was 31%. Pleural fluid protein was 2 g/dL, pleural fluid albumin was 1.8 g/dL, and pleural fluid LDH 100 U/L. Pleural fluid albumin to serum albumin ratio was more than 0.5, pleural fluid LDH to serum LDH ratio was more than 0.6, and pleural fluid LDH was more than two-third of the

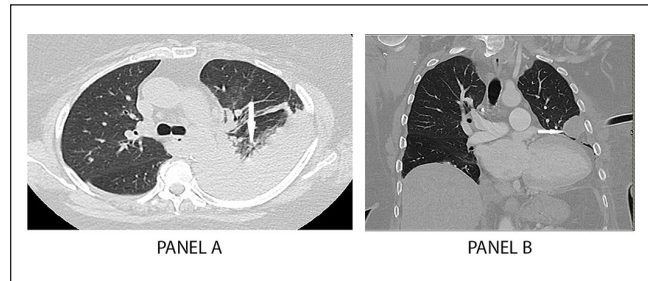


Figure 2. (Panel A) CT-chest with contrast axial view, showing left-sided pleural effusion, and (Panel B) CT chest coronal section performed after thoracentesis showing left upper lobe lung mass.

upper limit of serum LDH, and these findings were suggestive of exudative pleural effusion. More than hundred thousand red cells in pleural fluid were consistent with hemorrhagic pleural effusion. Patient underwent therapeutic thoracentesis and an intercostal drain was placed in the left pleural cavity given the concern for reaccumulation. Contrast-enhanced computed tomography (CT) of the chest was performed, and it revealed a lung mass involving left upper lobe with multiple pleuroparenchymal nodules in bilateral lung parenchyma and pleurae (Figure 2). She was further evaluated with video-assisted thoracoscopy (VATS), and wedge biopsy of left pleural nodule was performed.

Surgical specimen consisted of sections of lung with a pleural-based area of hemorrhage and necrosis with abundant fibrinous exudate. Located within the pleura and admixed with hemorrhage are scattered small islands of atypical cells containing enlarged hyperchromatic nuclei and ample eosinophilic cytoplasm. Few foci of atypical cells appear to be lining vessel-like spaces (Figure 3, Panels A and B). A panel of immunohistochemical stain was performed. It showed membranous and cytoplasmic positivity for CD31 antibody (Figure 3, Panel C) and WT1 antibody and focally positive for cytokeratin AE1/AE2. Stain for p63 was negative in atypical cells. Stain for Ki-67, a proliferation marker, showed nuclear positivity in >30% of atypical cells.

Histological appearance and distribution of the process and results of immunohistochemical stain were consistent with angiosarcoma. Positive cytokeratin staining suggested pleural origin of the cells. Pleural lesions had likely infiltrated the ipsilateral lung parenchyma and metastasized to the contralateral side. Further evaluation for staging with screening studies such as computed tomography of abdomen and pelvis, magnetic resonance imaging of the brain, and bone scan were negative. Our patient was diagnosed with primary pleural angiosarcoma metastatic to the contralateral lung. She opted for palliative care and had a rapidly declining clinical course. She passed away within 5 weeks of the diagnosis.

Discussion

Primary angiosarcoma of the chest wall and pleura is an extremely rare and aggressive malignancy. Angiosarcomas

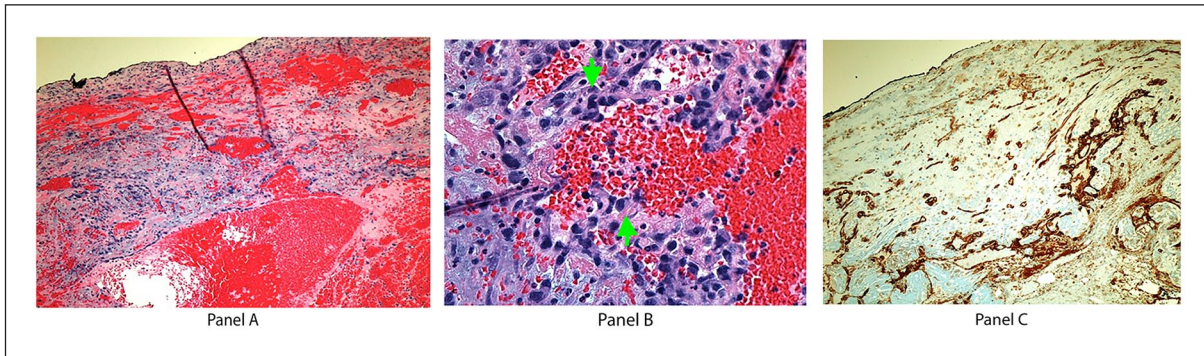


Figure 3. Histological sections of the left lung mass: (Panel A) Section of lung with areas of hemorrhage and necrosis. (Panel B) Atypical cells with hyperchromatic nuclei surrounding vascular spaces, marked with arrows. (Panel C) Positive nuclear and cytoplasmic activity with immunohistochemical staining with CD31.

Table 1. Cases of pleural angiosarcoma reported in English language in the literature.

| Case | Age (years)/sex | Presenting feature | Metastasis at diagnosis | Treatment | Survival after diagnosis (months) | Author |
|------|-----------------|----------------------------------|-------------------------|-----------|-----------------------------------|----------------------------|
| 1 | 57/F | Massive recurrent hemothorax | No | S, C, RT | 10 | Alexious ⁹ |
| 2 | 53/M | Pleural effusion | – | – | 6 | Zhang ¹¹ |
| 3 | 62/F | Pleural effusion, ascites | – | S | <1 | Zhang ¹¹ |
| 4 | 66/M | Pleural effusion | – | – | 6 | Zhang ¹¹ |
| 5 | 45/M | Recurrent pleural effusion | – | – | 6 | Zhang ¹¹ |
| 6 | 60/M | Bloody pleural effusion | – | – | 2 | Zhang ¹¹ |
| 7 | 34/F | Dyspnea, chest pain | No | S, C | A (5 months after surgery) | Roh ¹² |
| 8 | 57/M | Memory loss, headache | Brain | No | 2 | Kimura ¹⁵ |
| 9 | 55/M | Chest pain, cough, hemoptysis | – | S | – | Pramesh ²⁰ |
| 10 | 39/M | Chest pain, shortness of breath | No | S, C | 8 | Chen ¹⁷ |
| 11 | 61/M | Spontaneous hemothorax | Skin | – | 2 | Kurtz ¹⁸ |
| 12 | 62/M | Progressive dyspnea | No | No | <1 | Dainese ¹ |
| 13 | 68/M | Hoarseness | – | – | 10 | Miyazaki ²⁸ |
| 14 | 75/M | Chest pain | – | – | 10 | Baisi ³⁰ |
| 15 | 49/M | Chest pain | – | S, R, C | A (9 months after) | Kao ²⁷ |
| 16 | 77/M | Dyspnea | – | S | <1 | Lorentziadis ²⁹ |
| 17 | 58/F | Dyspnea, fever | No | C | 4 | Quesada ³¹ |
| 18 | 76/M | Cough | No | S | A (7 months after the surgery) | Zhang ²⁶ |
| 19 | 56/M | Chest pain, dyspnea, hemothorax | – | – | – | McCaughey ⁴ |
| 20 | 70/F | Chest pain, dyspnea, weight loss | Yes | – | 1 | Sedhai |

S: surgery; C: chemotherapy; R: radiotherapy; A: alive.

represent 1%–2% of all soft tissue tumors.^{1,32} It originates from the vascular endothelial cells of small blood vessels and affects retroperitoneum, subcutaneous tissue, liver, heart, spleen, and breast.³³ Primary angiosarcoma of the pleura and chest wall is rare. We performed an extensive literature search in Medline (via PubMed), Scopus, Google Scholar, and Cochrane Library and were able to identify 46 published cases^{1–31} ever reported in the literature since the first reported case in 1943² excluding the epithelioid hemangioendothelioma. Three cases^{23–25} in the literature are reported in conference abstracts only, and thus, we have not

included them in the literature review. Of the 46 cases identified in 28 manuscripts, we have summarized 20 cases of pleural angiosarcoma reported in the literature in English language excluding the pleuropulmonary angiosarcoma and the chest wall angiosarcomas listed in Table 1. We have performed narrative review of the inherent literature and constructed the Kaplan–Meier survival curve of the 20 cases of primary pleural angiosarcoma.

The most common presentation is pleuritic chest pain (47.5%), followed by shortness of breath (35%), hemoptysis (27.5%), cough (15%), and constitutional symptoms like

weight loss (10%). Radiologic evaluation usually shows unilateral or bilateral pleural effusion (70%) and focal or diffuse pleural thickening (40%), mimicking the presentation of mesothelioma.²⁷ Mass lesions are seen in about half of the reported cases^{2–10,14,20–22,26} similar to the one observed in our patient with a left upper lobe mass. There are no distinct radiologic characteristics to differentiate from other metastatic and primary pleural tumors. The common metastatic sites reported in the literature are lymph nodes, bone, brain, liver, spleen, adrenals, skin, oral cavity, and spinal cord.^{2,3,5,15,18,19} Aozasa et al.⁵ reported adrenal as a preferential metastatic site with ($n=5$).

Pleural fluid is usually hemorrhagic. Pleural fluid cytology for atypical cells was performed in seven cases^{1,8,9,13,19,20,22} and is reported positive in one case.²⁰ Most patients were diagnosed at a surgical biopsy.^{3,5,7,9,12,15,17,18,20,26,27} PPA was reported as diagnosed at autopsy in seven case reports.^{2,4,5,8,21,22} Non-invasive biopsy and surgical biopsy obtained without direct vision or non-targeted biopsy were low yield and diagnostic only in small proportion of cases.^{1,5,6,14,16,19} Biopsy was non-diagnostic in six patients.^{8,9,13,19,21,22} Thus, in setting of refractory pleural effusion, exploration of the pleural cavity with video-assisted thoracoscopy and visually targeted biopsy may aid in making the diagnosis.

Histologic characteristics of the tumor show malignant cells with epithelioid neoplasm with vasoformative nature, such as vascular spaces lined by atypical tumor cells intracytoplasmic and vasoformative spaces containing red blood cells. There are other differential diagnoses of a biphasic pleural tumor which includes mesothelioma and sarcomatoid carcinoma. Mesothelioma is characterized by more monotonous arrangement of the tumor cells with less degree of cytologic atypia. Intracytoplasmic lumen can be present in both angiosarcoma and mesothelioma, but intraluminal RBCs are not seen in mesotheliomas.²⁷ Immunohistochemical stains are important in confirming the diagnosis, and at least one positive immunohistochemical marker (CD31, CD34, Factor VIII, or FLI-1) is essential to make the diagnosis of angiosarcoma. CD31 is the most sensitive and specific immunohistochemical marker.^{23,31} Epithelial markers are expressed in the epithelioid variant of angiosarcoma.²³ Positive cytokeratin^{1,5,11,14,15} and immunoreactivity to CAM5.2, CK7, CK8, or CK18 are reported positive in a few case reports.^{1,13,14} Cytokeratin is strongly positive in carcinoma along with mesothelioma and can be variably expressed from diffusely strong to focal and weak in distribution, thus making it less useful in the diagnosis of angiosarcoma.¹⁷ Cytokeratin is a marker of mesothelial/pleural origin of cells but cannot be used to differentiate pleural malignancies. Markers of mesothelial cells such as calretinin, CK5/6, HBME-1, and WT-1 can be useful in differentiating tumors of vascular origin from mesothelioma.

Given the rarity of PPA, etiopathology is not well studied. Case reports from Japan have studied the association with tuberculous pyothorax ($n=15$).^{5,15,21,24} Case reports from the Western world have reported association with asbestos exposure ($n=4$)^{7,10} and radiotherapy ($n=1$).¹¹ Aozasa et al.⁵ in a

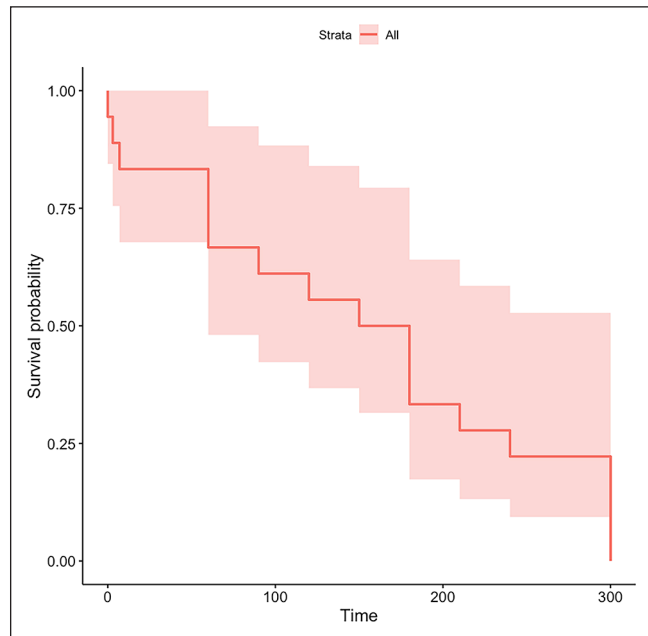


Figure 4. Survival length of 18 cases of pleural angiosarcoma reported in English language. Most patients died within the end of a year.

small case series of five cases postulated 3600-fold increased risk of pleural angiosarcoma in the presence of chronic tuberculous pyothorax, although that conclusion was drawn from a small case series ($n=5$). Hattori²⁵ reported that angiosarcoma associated with pyothorax manifesting as a chest wall tumor. Atanoos et al.¹⁰ reported three cases of pleural angiosarcoma, and two of the three reported cases had history of asbestos exposure and only one patient had asbestos fiber content by mineral analysis. One patient reported by Zhang et al.¹¹ had previous history of radiotherapy for ovarian carcinoma and developed simultaneous angiosarcomas in the pleura and peritoneum. Miyazaki et al.²⁸ reported angiosarcoma in setting of expanding hematoma-associated previous pneumonectomy. Our patient did not have history of tuberculous pyothorax, asbestos exposure, radiotherapy, prior thoracic surgery, or other risk factors. Thus, angiosarcoma in our patient can be described as de-novo pleural angiosarcoma.¹⁸

Treatment modalities for pleural angiosarcoma include surgery, radiotherapy, and/or chemotherapy. Surgery can be useful in the presence of localized tumor. Vascular embolization using endovascular techniques can be helpful in reducing tumor size and vascularity supporting perioperative hemostasis.^{18,29} Role of chemotherapy is limited but radiotherapy can be useful in adjuvant setting. With rare exceptions, clinical course of the disease is rapidly progressive and usually fatal within few months of the diagnosis. We constructed a Kaplan–Meier curve for cases of pleural angiosarcoma ($n=20$) reported in English language in the literature, as summarized in Table 1. The mean survival after the diagnosis was less than 1 year (Figure 4).

Conclusion

Primary pleural angiosarcoma is an extremely rare and an aggressive malignancy. Patients usually have a rapidly declining clinical course and have a dismal prognosis with rare exceptions. Clinical and radiologic presentation can be similar to mesothelioma and use of immunohistochemical staining can aid in the diagnosis.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article. A written consent is obtained from the patient's next of kin by the corresponding author. It can be presented to the journal at request.

ORCID iD

Yub Raj Sedhai  <https://orcid.org/0000-0002-1755-5489>

References

- Dainese E, Pozzi B, Milani M, et al. Primary pleural epithelioid angiosarcoma. A case report and review of the literature. *Pathol Res Pract* 2010; 206(6): 415–419.
- Stout AP. Hemangio-endothelioma: a tumor of blood vessels featuring vascular endothelial cells. *Ann Surg* 1943; 118(3): 445–464.
- Ximenes M 3rd and Miziara HL. Hemangioendothelioma of the lung and pleura: report of three cases. *Int Surg* 1981; 66(1): 67–70.
- McCaughey WT, Dardick I and Barr JR. Angiosarcoma of serous membranes. *Arch Pathol Lab Med* 1983; 107(6): 304–307.
- Aozasa K, Naka N, Tomita Y, et al. Angiosarcoma developing from chronic pyothorax. *Mod Pathol* 1994; 7(9): 906–911.
- Nappi O, Swanson PE and Wick MR. Pseudovascular adenoid squamous cell carcinoma of the lung: clinicopathologic study of three cases and comparison with true pleuropulmonary angiosarcoma. *Hum Pathol* 1994; 25(4): 373–378.
- Lin BTY, Colby T, Gown AM, et al. Malignant vascular tumors of the serous membranes mimicking mesothelioma: a report of 14 cases. *Am J Surg Pathol* 1996; 20(12): 1431–1439.
- Falconieri G, Bussani R, Mirra M, et al. Pseudomesotheliomatous angiosarcoma: a pleuropulmonary lesion simulating malignant pleural mesothelioma. *Histopathology* 1997; 30(5): 419–424.
- Alexiou C, Clelland CA, Robinson D, et al. Primary angiosarcomas of the chest wall and pleura. *Eur J Cardiothorac Surg* 1998; 14(5): 523–526.
- Attanoos RL, Suvarna SK, Rhead E, et al. Malignant vascular tumours of the pleura in “asbestos” workers and endothelial differentiation in malignant mesothelioma. *Thorax* 2000; 55(10): 860–863.
- Zhang PJ, Livolsi VA and Brooks JJ. Malignant epithelioid vascular tumors of the pleura: report of a series and literature review. *Hum Pathol* 2000; 31(1): 29–34.
- Roh MS, Seo JY and Hong SH. Epithelioid angiosarcoma of the pleura: a case report. *J Korean Med Sci* 2001; 16(6): 792.
- Liu SF, Wu CC, Lai YF, et al. Massive hemoptysis and hemothorax caused by pleuropulmonary angiosarcoma. *Am J Emerg Med* 2002; 20(4): 374–375.
- Del Frate C, Mortelet K, Zanardi R, et al. Pseudomesotheliomatous angiosarcoma of the chest wall and pleura. *J Thorac Imaging* 2003; 18(3): 200–203.
- Kimura M, Ito H, Furuta T, et al. Pyothorax-associated angiosarcoma of the pleura with metastasis to the brain. *Pathol Int* 2003; 53(8): 547–551.
- Varsano S, Edelstein E, Gendel B, et al. Bilateral and unilateral spontaneous massive hemothorax as a presenting manifestation of rare tumors. *Respiration* 2003; 70(2): 214–218.
- Chen L, Shih HJ, Seguerra E Jr, et al. Pathologic quiz case: a 39-year-old man with diffuse pleural thickening and massive hemothorax. *Arch Pathol Lab Med* 2004; 128(11): 1299–1300.
- Kurtz JE, Serra S, Duclos B, et al. Diffuse primary angiosarcoma of the pleura: a case report and review of the literature. *Sarcoma* 2004; 8(4): 103–106.
- Maglaras GC, Katsenos S, Kakadelis J, et al. Primary angiosarcoma of the lung and pleura. *Monaldi Arch Chest Dis* 2004; 61(4): 234–236.
- Pramesh CS, Madur BP, Raina S, et al. Angiosarcoma of the pleura. *Ann Thorac Cardiovas Surg* 2004; 10(3): 187–190.
- Kusano N, Nishikawa M, Ito M, et al. An autopsy case of chronic empyema-associated angiosarcoma that presented with a rapidly growing chest wall mass. *Nihon Kokyuki Gakkai Zasshi* 2008; 46(3): 248–252.
- Saitou M and Niitsuma K. A case of pyothorax-associated pleural angiosarcoma diagnosed by autopsy. *Kekkaku* 2009; 84(7): 531–534.
- Rose A, Sears CR and Onofrei C. Pleuro-pulmonary angiosarcoma presenting as spontaneous hemothorax and bilateral pulmonary nodules. *Am J Respir Crit Care Med* 2017; 195: A6695.
- Tabbara R, Craig-McQuaide A, Arya A, et al. Malignancy unmasked: a rare primary pleural angiosarcoma presenting as a complex empyema. *Am J Respir Crit Care Med* 2016; 193: A3312.
- Hattori H. Epithelioid angiosarcoma arising in the tuberculous pyothorax: report of an autopsy case. *Arch Pathol Lab Med* 2001; 125(11): 1477–1479.
- Zhang S, Zheng Y, Liu W, et al. Primary epithelioid angiosarcoma of the pleura: a case report and review of literature. *Int J Clin Exp Pathol* 2015; 8(2): 2153–2158.
- Kao YC, Chow JM, Wang KM, et al. Primary pleural angiosarcoma as a mimicker of mesothelioma: a case report. *Diagn Pathol* 2011; 6: 130.

28. Miyazaki H, Goto A, Hino R, et al. Pleural cavity angiosarcoma arising in chronic expanding hematoma after pneumonectomy. *Human Pathol* 2011; 42(10): 1576–1579.
29. Lorentziadis M and Sourlas A. Primary de novo angiosarcoma of the pleura. *Ann Thorac Surg* 2012; 93(3): 996–998.
30. Baisi A, Raveglia F, De Simone M, et al. Primary multifocal angiosarcoma of the pleura. *Interact Cardiovasc Thorac Surg* 2011; 12(6): 1069–1070.
31. Quesada A, Quesada J, Khalil K, et al. Morphoproteomic study of primary pleural angiosarcoma of lymphoendothelial lineage: a case report. *Ann Clin Lab Sci* 2013; 43(3): 317–322.
32. Boulay V, Jeanfaivre T, Enon B, et al. Angiosarcoma of the thoracic wall revealed by hemothorax. *Rev Pneumol Clin* 1998; 54(5): 259–262.
33. Young RJ, Brown NJ, Reed MW, et al. Angiosarcoma. *Lancet Oncol* 2010; 11(10): 983–991.