Respiratory Medicine Case Reports 25 (2018) 318–322

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

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

Case report

An unusual case of chylothorax

Lauryn A. Benninger[a], Julia A. Ross[b], Marino E. Leon[b], Raju Reddy[a,*]

[a] Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, College of Medicine, Gainesville, FL, United States
[b] Department of Pathology, Immunology and Laboratory Medicine, University of Florida, College of Medicine, Gainesville, FL, United States

ARTICLE INFO

Keywords:
Chylous pleural effusion
Chylothorax
Malignant mesothelioma
Epithelioid type
Reactive mesothelial cells

ABSTRACT

Pleural effusions occur in up to 70% of cases of malignant pleural mesothelioma (MPM). However, MPM rarely presents as a chylous effusion making it a diagnostic challenge. There are only six reported cases to date. Most cases of chylothoraces due to malignancy are due to lymphoma or bronchogenic carcinoma. We report an interesting case of MPM in a 75-year-old man who presented with recurrent chylothorax. He reported a four-month history of dyspnea and chest discomfort. Chest x-ray revealed a pleural effusion. Pleural fluid analysis was consistent with a chylothorax. Pleural fluid cytology was negative for malignancy. Computed tomography of the chest showed pleural calcifications, mediastinal adenopathy and left lung infiltrate. A fine needle aspirate of the lymph node and transbronchial biopsy specimen (TBBX) of the left lung infiltrate showed extensive reactive appearing mesothelial cells but none that appeared malignant. A video assisted thoracoscopic surgery was suggested but the patient declined. He returned 3 months later with recurrent pleural effusion and worsening airspace disease. Thoracentesis revealed a chylothorax again. Repeat analysis of TBBX and lymph node specimens showed extensive reactive appearing mesothelial cells. Due to concern for MPM, ancillary testing was obtained - loss of BRCA1 associated protein (BAP-1) and *CDKN2A/p16* gene deletion. BAP1 staining was lost in the mesothelial cells supporting MPM. This case highlights a rare cause of MPM presenting as a chylous effusion. In a patient with an unknown etiology of chylothorax, MPM must remain in the differential.

1. Introduction

Chylous pleural effusions or chylothorax is a type of pleural effusion that is characterized by the presence of chyle in the pleural space. Chylous pleural effusions occur as a result of both traumatic and non-traumatic causes [1]. Traumatic etiologies include thoracic surgeries such as esophagectomy, coronary artery bypass grafting and congenital heart surgeries. Non-traumatic causes include malignancy such as lymphoma and bronchogenic carcinoma as well as non-malignant causes such as lymphangioleiomyomatosis and yellow nail syndrome. Idiopathic cases occur in about 6–14% of chylothoraces. Pleural effusions in malignant pleural mesothelioma (MPM) can be seen in up to 70% of the cases; however, chylous effusions are a rare manifestation of the disease. Here, we describe a patient who was diagnosed with MPM after presenting with recurrent chylous pleural effusions.

2. Case report

A 75-year-old Caucasian male with a past medical history of coronary artery disease status post coronary artery bypass grafting 11 years prior, congestive heart failure with an ejection fraction of 25%, atrial fibrillation, hypertension, and hyperlipidemia presented to the hospital with dyspnea and chest pain. He has no history of tobacco use. He worked as a lawyer all his life and had no occupational exposures. On exam, the patient had diminished breath sounds over the left lung. Chest x-ray revealed a large left-sided pleural effusion (Fig. 1). Of note, he had previously been evaluated by his primary care doctor four months prior with similar symptoms and was found to have a left-sided pleural effusion. At that time, he underwent a thoracentesis at an outside facility with unknown pleural fluid analysis (PFA).

He was admitted to the hospital for further evaluation and underwent both a diagnostic and therapeutic thoracentesis (Fig. 2). PFA revealed a lymphocytic predominant, exudative effusion with total triglyceride level of 1406mg/dL consistent with a chylous effusion.

Abbreviations: MPM, Malignant pleural mesothelioma; PFA, pleural fluid analysis; EBUS-FNA, endobronchial ultrasound guided fine needle aspiration; TBBX, transbronchial biopsy; BAP-1, BRCA1 associated protein; FISH, fluorescent in situ hybridization

* Corresponding author. University of Florida, Division of Pulmonary, Critical Care and Sleep Medicine, 1600 SW Archer Road, M452, PO Box 100225, Gainesville, FL, 32610, United States.
E-mail address: raju.reddy@medicine.ufl.edu (R. Reddy).

https://doi.org/10.1016/j.rmcr.2018.10.020
Received 7 September 2018; Received in revised form 22 October 2018; Accepted 22 October 2018

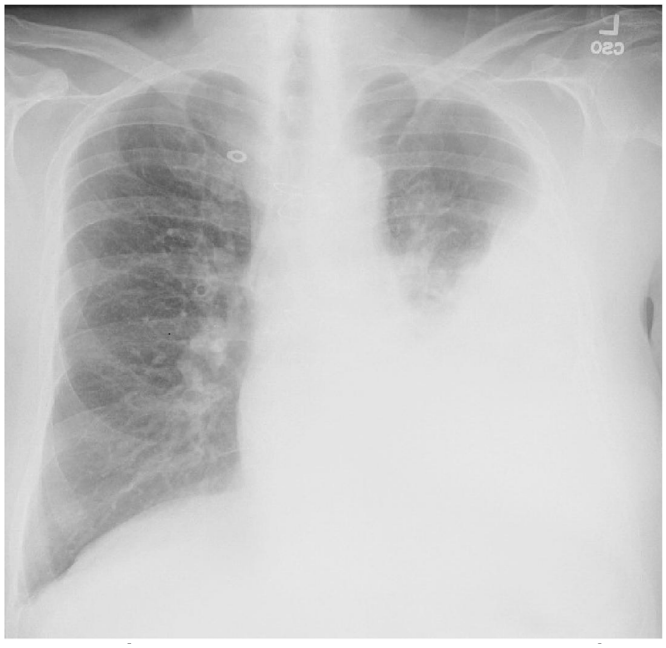

Fig. 1. On admission, chest x-ray showed a large left sided pleural effusion.

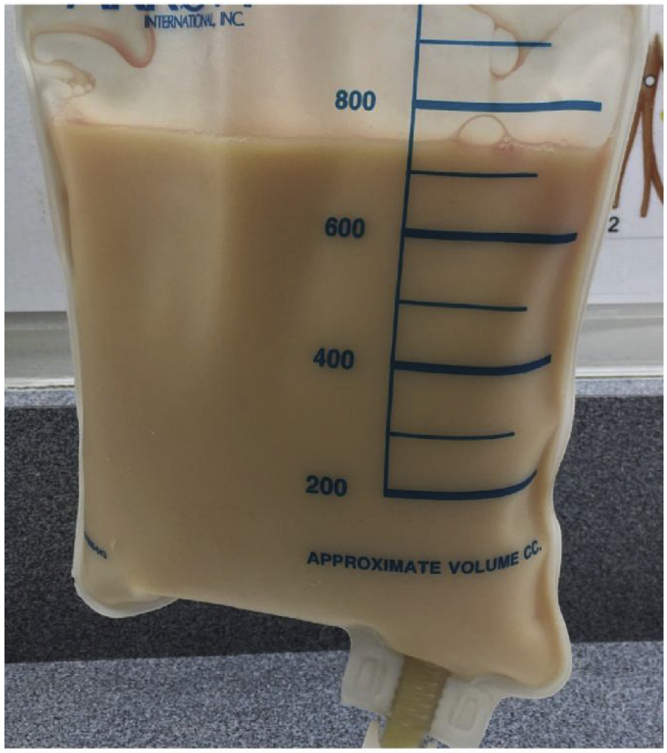

Fig. 2. Approximately 700 ml of milky colored fluid was obtained on thoracentesis.

Microbiology was negative. Cytology of the pleural fluid revealed reactive appearing mesothelial cells as evidenced by positive calretinin and Wilms tumor-1 (WT-1) immunohistochemical (IHC) stains. Adenocarcinoma was ruled out by negative BerEP4 and MOC-31 IHC stains (Fig. 3).

Computed tomography (CT) of the chest after the thoracentesis was performed revealing left lung airspace disease, pleural calcifications and mediastinal adenopathy (Fig. 4). Due to concern for a possible malignancy, he underwent an endobronchial ultrasound guided fine needle aspiration (EBUS-FNA) biopsy of station 7 lymph node and transbronchial biopsy (TBBX) of the left lung infiltrate. Cytology of the EBUS-FNA lymph node specimen revealed abundant bland mesothelial cells with minimal amounts of lymphoid tissue. Interestingly, histologic examination of the concomitant TBBX specimen showed only rare atypical epithelioid cells floating within lymphatic spaces that stained with mesothelial markers. These findings were suspicious for a malignant process; however, limited sampling precluded a definitive diagnosis. A thoracoscopy was performed but an additional specimen could not be obtained due to extensive adhesions. A lymphangiogram was also performed. The contrast injected into the femoral vein did not progress to the level of the cisterna chyli suggesting an obstructive process in the lymph nodes. Due to concern for malignancy, the patient was offered a video-assisted thoracoscopic surgery, but he declined.

He returned to the hospital 3 months later with progressive dyspnea. CT chest revealed progression of the left lung infiltrate, a new right-sided pleural effusion and persistent mediastinal adenopathy (Fig. 5). Thoracentesis on the right sided revealed a chylothorax. He underwent another EBUS-FNA biopsy of station 7 lymph node and a TBBX of the left lung infiltrate. Cytologic examination of the lymph node FNA specimen again showed abundant bland mesothelial cells in the lymphatic spaces. Given the concern for MPM, the lymph node specimen was sent for additional ancillary testing - BRCA1 associated protein (BAP-1) IHC stain and *CDKN2A/p16* homozygous deletion by fluorescent in situ hybridization (FISH). BAP-1 staining was lost in the mesothelial cells supporting MPM; the *CDKN2A/p16* FISH study did not show a homozygous deletion. A third TBBX specimen of the left lung infiltrate was obtained which confirmed the diagnosis of MPM, epithelioid subtype.

Due to the patient's poor functional status, no treatment was offered. An indwelling pleural catheter was placed for palliative measures. Four months after his diagnosis, the patient presented with worsening dyspnea. He expired during that hospitalization. Autopsy examination demonstrated diffusely thickened pleura bilaterally, concentrated mostly of the left side, and measuring up to 1cm thick. Histologic sections confirmed the presence of dyscohesive malignant mesothelial cells, epithelioid subtype, with bland appearance throughout the pleura. The malignant mesothelial cells invaded the lung parenchyma minimally. While MPM is known to invade the lung parenchyma, in our case, tumor cells were present predominately within lymphatics in lung sections [2]. Furthermore, metastatic tumor cells were evident in multiple mediastinal lymph nodes (Fig. 6).

3. Discussion

Chylothorax is a rare presentation of MPM. To our knowledge, there have been 6 reported cases in the literature to date [3–7]. Most cases of MPM occur due to asbestos exposure; however, other etiologies include erionite (a mineral found in the rocks of Turkey), chest wall radiation and simian virus 40[8]. The majority of patients with MPM present with chest pain and dyspnea. Pleural effusions occur in up to 70% of patients [8]. The mechanism of chylous pleural effusion in MPM is likely due to the following reasons: 1) direct invasion of malignant mesothelial cells into lymph nodes causing a mass effect resulting in secondary obstruction of the thoracic duct and it's tributaries and 2) a large tumor burden around the pleura causing a direct mechanical compressive effect on the intercostal trunks, which empty into the thoracic duct. In our case, the patient's lymphangiogram suggested an obstructive process in the lymph nodes.

A pathologic diagnosis of MPM can be difficult to make. There are three main mesothelioma histologic subtypes – epithelioid, sarcomatoid, and biphasic [9]. Benign, reactive mesothelial cell proliferations can resemble epithelioid MPM. Both can have a significant amount of cellularity, many mitotic figures, necrosis and cytologic atypia. Stromal invasion is a key finding differentiating between reactive mesothelial cell proliferation and MPM, which can be difficult to assess on cytology.

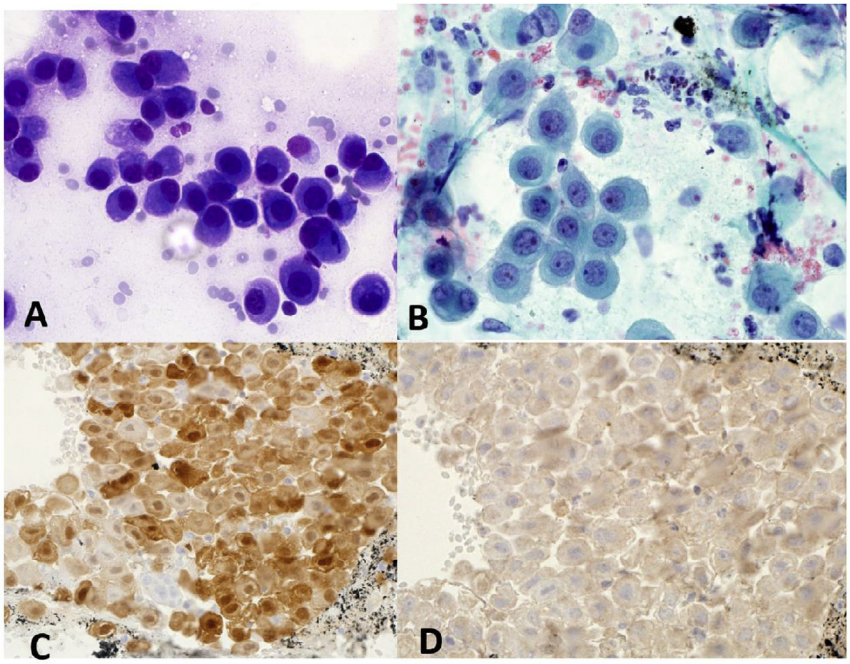

Fig. 3. The patient's pleural fluid cytology specimen showing **(A)** non-clustered, bland appearing mesothelial cells on Diff Quik stain, 600X **(B)** non-clustered, bland appearing mesothelial cells on Papanicolaou stain, 600X **(C)** positive calretinin IHC stain highlighting and supporting mesothelial origin, 400X, and **(D)** negative MOC-31 IHC stain, 400X ruling out carcinoma and lending further supporting to the mesothelial origin.

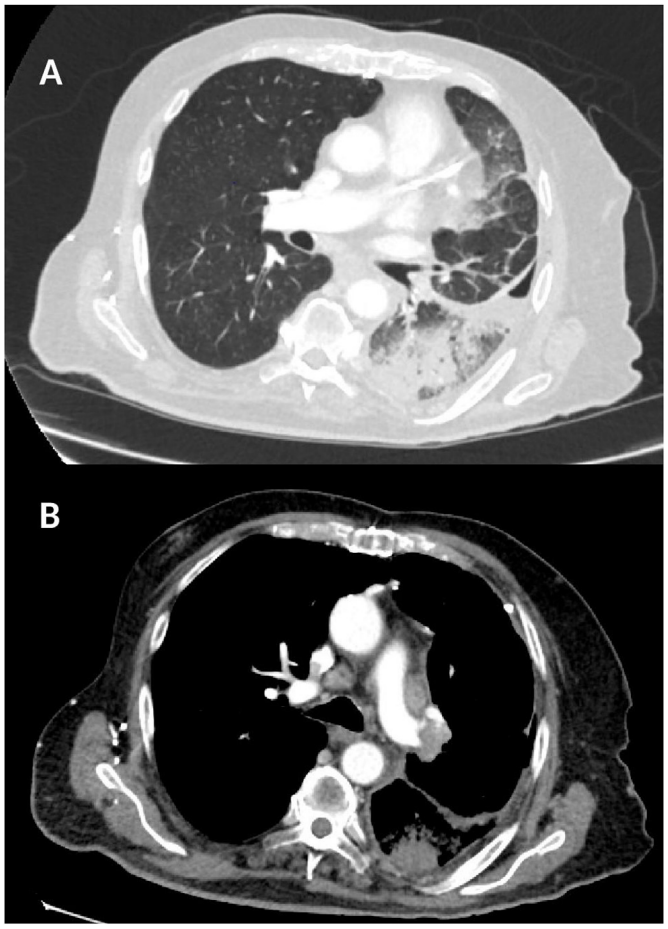

Fig. 4. On admission, computed tomography of the chest showed (A) left lung infiltrate, and (B) pleural calcifications and mediastinal adenopathy. Lung window settings: thickness 1mm, width 1600.

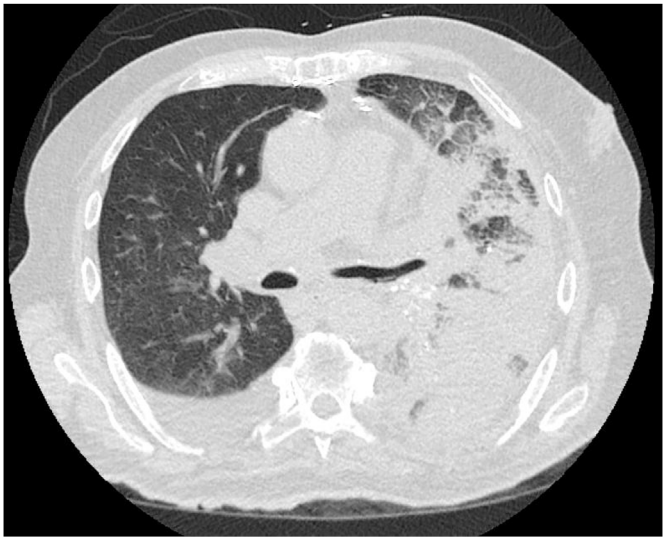

Fig. 5. Computed tomography of the chest 3 months after initial admission showed worsening left lung infiltrate and a new right sided pleural effusion. Lung window settings: thickness 1mm, width 1600.

Occasionally, on surgical biopsy specimens, reactive mesothelial cells can become entrapped within fibrotic tissue mimicking invasion thus making the diagnosis challenging [9]. As described previously, our patient underwent an autopsy, which revealed the presence of dyscohesive malignant mesothelial cells with bland appearance in the pleura, lymphatics and mediastinal lymph nodes. These bland dyscohesive tumor cells almost replaced entire lymph nodes; hence the difficulty of identifying them as cells from a malignant mesothelioma metastatic to lymph nodes.

Another method to diagnose MPM is PFA. However, the diagnostic yield of pleural fluid cytology is only 32% [10]. Routine IHC stains are unable to reliably distinguish between benign mesothelial proliferations and malignant mesothelioma, particularly epithelioid subtype. For example, calretinin and WT-1 are found on benign and malignant mesothelial cells. If there is a strong suspicion for MPM, ancillary studies such as homozygous deletion of *CDKN2A/p16* by FISH or the loss of

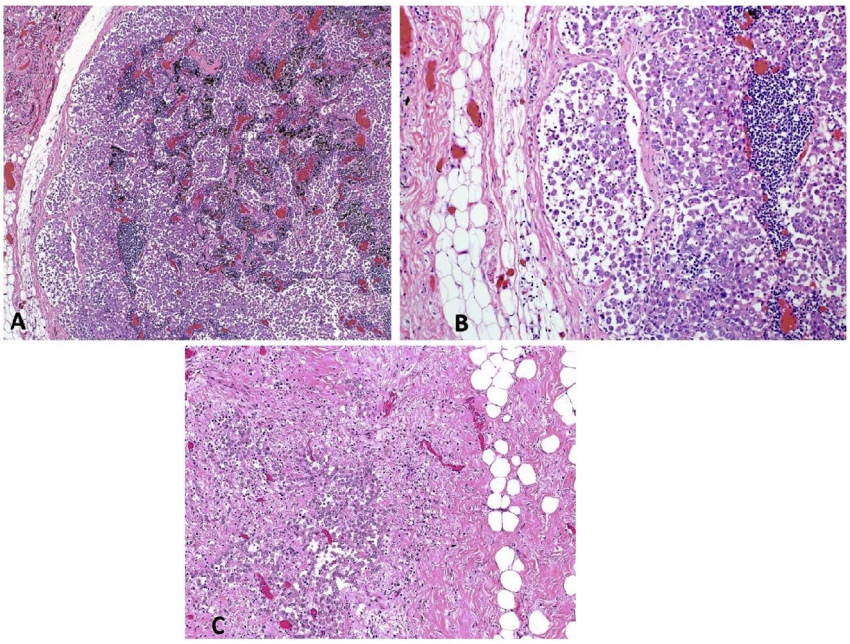

Fig. 6. Autopsy specimen images showing abundant non-clustered, bland-appearing epithelioid mesothelial cells replacing the lymph node (**A**- low magnification, 40X & **B**- high magnification, 100X) and **(C)** invading connective tissue on Hematoxylin & Eosin stain, 100X.

BAP1 by IHC stain can further point toward a diagnosis of MPM. In one study of 70 cytological tumor samples, loss of BAP1 was seen in 66% of cases of MPM and the presence of BAP1 was seen in 100% of benign reactive mesothelial cells [11]. Our patient had loss of BAP1 staining in mesothelial cells from lymph node EBUS guided cytology specimen. *CDKN2A/p16* deletion was not found in our patient possibly because *CDKN2A/p16* deletion is more frequently associated with the sarcomatoid variant rather than the epithelioid variant of MPM [12]. Loss of BAP1 and *CDKN2A/p16* can also be checked in pleural fluid cytologic specimens. In a study of 11 pleural fluid specimens, loss of BAP1 was seen in 67% of cases and CDKN2A/p16 deletion was seen in 73% of cases [13]. Presently, there is no role for biomarkers in diagnosis of MPM.

Prognosis in MPM is poor. The median survival is 8–14 months from the time of diagnosis. The sarcomatoid variant has the worst outcomes with median survival of 4 months while the epithelioid variant has a more favorable prognosis with median survival of 13.1 months [8]. Poor prognostic factors include age > 75 years, lactate dehydrogenase > 500 IU/L and poor performance status at the time of diagnosis. Treatment options are limited in MPM. The mainstay of therapy is pemetrexed and cisplatin but the number of treatment cycles and the role of maintenance therapy remain unknown. Surgical therapy defined as extended pleurectomy with decortication is an option for selected patients. More recently, trimodality therapy, defined as radiotherapy therapy followed by extrapleural pneumonectomy and subsequent chemotherapy has been shown to extend median survival to 36 months, particularly in patients with the epithelioid subtype [14]. Since 70% of patients with MPM develop pleural effusions, placement of an indwelling pleural catheter is a reasonable option for management of symptoms.

Given than MPM is a complex disease, early referral and management at a specialized center is imperative. Our case highlights that MPM must remain in the differential of a chylothorax, albeit rare.

Declarations of interest

None.

Conflicts of interest statement

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank Dr. Nada Al Qaysi and Dr. Wendy Stroh with the Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, United States.

References

[1] C.H. Doerr, M.S. Allen, F.C.R.J. Nichols, Etiology of chylothorax in 203 patients, Mayo Clin. Proc. 80 (7) (2005) 867–870.
[2] B.T.1 Larsen, J.R. Klein, H. Hornychová, R. Nuti, S. Thirumala, K.O. Leslie, T.V.T.H. Colby, Diffuse intrapulmonary malignant mesothelioma masquerading as interstitial lung disease: a distinctive variant of mesothelioma, Am. J. Surg. Pathol. 37 (10) (2013) 1555–1564.
[3] N. Shimizudani, T. Morisako, Y. Miyao, et al., A Case of Diffuse Malignant Mesothelioma of the Pleura with Bilateral Chylothorax, Nihon Kokyuki Gakkai Zasshi, 2002.
[4] E. Kurtipek, M.İ. Eren Karanis, N. Düzgün, H. Esme, M. Çaycı, A cause of bilateral chylothorax: a case of mesothelioma without pleural involvement during initial diagnosis, Case Rep. Pulmonol. (2015), https://doi.org/10.1155/2015/962504.
[5] S. Ito, Y. Takashima, T. Sano, et al., Chylothorax as the Initial Manifestation of Malignant Pleural Mesothelioma–a Case Report, Nihon Kokyuki Gakkai Zasshi, 2001.
[6] S. Kostiainen, H. Meurala, S.A.P. Mattila, Chylothorax. Clinical experience in nine cases, Scand. J. Thorac. Cardiovasc. Surg. 17 (1) (1983) 79–83.
[7] D.R. Darley, E. Granger, A.R. Glanville, Chest pain and recurrent chylothorax: an unusual presentation of malignant pleural mesothelioma, Respirol. Case Rep. 5 (5) (2017) 1–3, https://doi.org/10.1002/rcr2.250.
[8] A.C. Bibby, S. Tsim, N. Kanellakis, et al., Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment, Eur. Respir. Rev. 25 (142) (2016) 472–486, https://doi.org/10.1183/16000617.0063-2016.
[9] A.N. Husain, T.V. Colby, N.G. Ordóñez, et al., Guidelines for pathologic diagnosis of malignant mesothelioma: 2017 update of the consensus statement from the international mesothelioma interest group, Arch. Pathol. Lab Med. 142 (1) (2018) 89–108, https://doi.org/10.5858/arpa.2017-0124-RA.
[10] E.A. Rakha, S. Patil, K. Abdulla, M. Abdulkader, Z. Chaudry, I.N. Soomro, The sensitivity of cytologic evaluation of pleural fluid in the diagnosis of malignant mesothelioma, Diagn. Cytopathol. (2010), https://doi.org/10.1002/dc.21303.
[11] M. Cigognetti, S. Lonardi, S. Fisogni, et al., BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations, Mod. Pathol. 28 (8) (2015) 1043–1057, https://doi.org/10.1038/modpathol.2015.65.

[12] D. Wu, K. Hiroshima, S. Matsumoto, et al., Diagnostic usefulness of p16/CDKN2A FISH in distinguishing between sarcomatoid mesothelioma and fibrous pleuritis, Am. J. Clin. Pathol. 139 (1) (2013) 39–46, https://doi.org/10.1309/AJCPT94JVWIHBKRD.

[13] H.C.1 Hwang, B.S. Sheffield, S. Rodriguez, K. Thompson, C.H. Tse, A.M.C.A. Gown, BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations, Mod Pathol. 2015, Am. J. Surg. Pathol. 40 (1) (2016) 120–126.

[14] M. De Perrot, R. Feld, N.B. Leighl, et al., Accelerated hemithoracic radiation followed by extrapleural pneumonectomy for malignant pleural mesothelioma read at the 95th annual meeting of the american association for thoracic surgery, Seattle, Washington, april 25-29, 2015, J. Thorac. Cardiovasc. Surg. 151 (2) (2016) 468–473, https://doi.org/10.1016/j.jtcvs.2015.09.129.