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Case report

Malignant mesothelioma presenting as recurrent hydro-pneumothorax: An atypical case presentation and literature review☆

Nadia Sattar[a], Richard Durrance[a,*], Ahmed Khan[a], Nilesh Patel[a], Maximo Mora[b], Artur Shalonov[c]

[a] Department of Internal Medicine, Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica NY 11420, United States
[b] Department of Pathology, Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica NY 11420, United States
[c] Department of Pulmonology, Jamaica Hospital Medical Center, 8900 Van Wyck Expressway, Jamaica NY 11420, United States

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ABSTRACT

Malignant Pleural Mesothelioma (MPM) is a rare pleural malignancy, with a vague presentation complicated by a decades-long latency period between environmental exposure and clinical manifestations. Spontaneous hydro-pneumothorax is a rare presentation of MPM, most often requiring invasive tissue biopsy to confirm the etiologic diagnosis. We present the case of 79-year-old male smoker with no documented history of asbestos exposure, who was found to have MPM after presenting with dyspnea and subsequently found to have recurrent hydro-pneumothorax. On Literature review of the limited documented cases of MPM with hydro-pneumothorax, we found an exclusively male population with a significant smoking history, a marked right sided pathology predominance, and a generally poor prognosis. While this corresponds with the examined case, and suggests that the presence of hydro-pneumothorax implies a high-grade tumor and significant tissue invasion, and therefore poor prognosis similar to that of stage 4 disease, it differs from more generalized case reviews of MPM, most importantly in their anatomical descriptions, prognostic indicators, and epidemiologic tendencies.

1. Introduction

Malignant pleural mesothelioma (MPM) is a rare pleural malignancy with an annual incidence of 2500 persons in the United States [1], and is largely occupational asbestos exposure related [1,2]. Presentation is typically vague, with nondescript symptoms of chest pain, dyspnea and cough, and is complicated by a latency period of up to 40 years between exposure and onset of symptoms [3]. Diagnosis may be strongly suggested by effusion cytology. While immunohistochemistry (IHC) is recommended to support the diagnosis [2], a histopathological confirmation of malignant pleural mesothelioma is required for definitive diagnosis [2], and in unclear cases may require multiple tissue sample biopsies.

Mean survival of MPM is 6–12 months with < 5% of patients surviving > 5 years [4]. Staging of mesothelioma is largely based on the presence of mediastinal lymph node and chest wall involvement following the TNM characterization [3], and does not consider the presence or absence of pleural effusion (in difference to NSCLC). Unless distant metastasis is detected, trimodal therapy involving chemotherapy, radiation therapy, and surgical resection is recommended, if the patient is amendable to such intervention [3]. However, because of the vague symptoms and typically late presentation, MPM is usually diagnosed in advanced stages with limited therapeutic options.

The presence of hydro-pneumothorax not only implies a chronic inflammatory process in the pleural tissue resulting in the effusion, but also the existence of a patent and persistent broncho-pleural communication [5]. Large scale and minimally symptomatic progressive hydro-pneumothorax carries a wide range of differentials, and malignant mesothelioma is an obscure diagnosis which requires a high index of suspicion and extensive occupational history investigation on the part of the clinician. Spontaneous hydro-pneumothorax is a rare presentation of MPM, with a literature review of PubMed (search criteria: Mesothelioma, pneumothorax, hydro-pneumothorax) revealing 9 total case reports [6–12]. We present a case of a MPM without documented asbestos exposure, presenting as recurrent right-sided hydro-pneumothorax.

2. Case presentation

A 79-year-old male with PMH of Hypertension and Diabetes presented to the ED after developing progressively worsening shortness of breath and mid sternal pleuritic chest pain during a *trans*-continental

☆ The patient has given informed consent for the use of the images and clinical history in the preparation of this manuscript.

* Corresponding author.
E-mail address: jessedurrance@gmail.com (R. Durrance).

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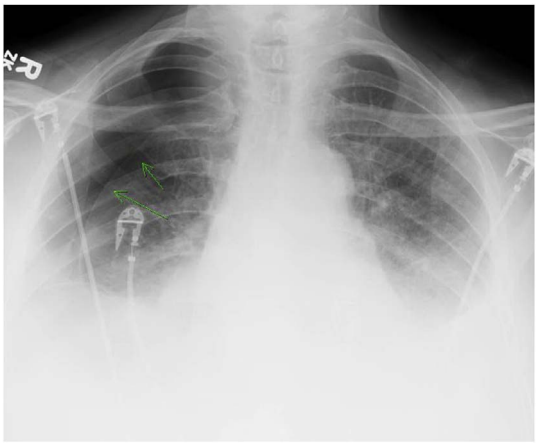

Fig. 1. AP Chest X-ray of the patient on admission, remarkable for images suggesting bilateral pleural effusions and right sided pneumothorax (marked by arrows).

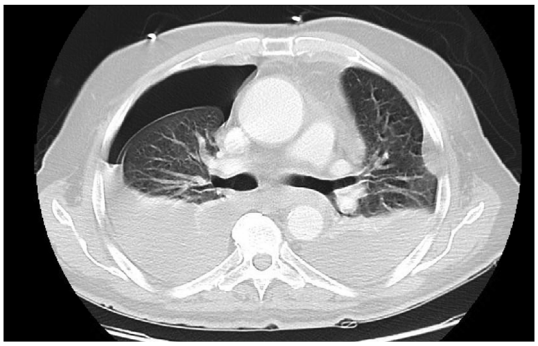

Fig. 2. CT Chest sagittal view showing bilateral pleural effusions and right sided pneumothorax.

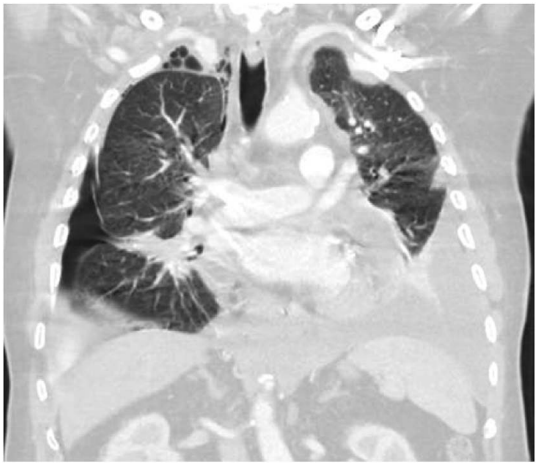

Fig. 3. CT Chest coronal view showing right sided hydro-pneumothorax and left sided pleural effusion.

flight, and was in mild respiratory distress by the time EMS evaluation occurred. In the ER chest x-ray suggested a large right hydro pneumothorax with moderate left sided pleural effusion (Fig. 1), which was confirmed by chest CT (Figs. 2 and 3).

Both large-bore and small-bore chest tubes were placed, which resulted in symptomatic improvement. Due to the unclear etiology, the patient was started on broad spectrum IV antibiotics for suspected pneumonia. Pleural fluid analysis was remarkable for an exudative pattern that was negative for malignant cells (Table 1). When infections etiologies as well as a Tuberculosis etiology were ruled out, antibiotics were discontinued. The small-bore catheter was eventually removed, however the chest tube remained due to the recurrence of pneumothorax on imaging studies.

While the patient initially experienced clinical improvement requiring only minimal supplemental oxygen, he soon developed recurrence of bilateral pleural effusions with clinical deterioration. This pattern persisted, and serial pleural cytology samples were remarkable for bloody fluid with elevated cellularity, proteins and LDH, but were negative for malignant cells. As infectious and inflammatory etiologies were ruled out as the cause of recurrent hydro-pneumothorax, video-assisted thoracoscopy (VATS) and pleural biopsy confirmed the diagnosis of malignant pleural mesothelioma-epithelioid variant-in the context of histologic findings (Figs. 4 and 5) and imunohistochemical markers positive for calretinin, CK 5/6, mesothelin and focal Glut-1 and negative for EpCam, CEA, Napsin A, TTF-1, and BerEP4. Interestingly, mesothelial plaques were restricted to the parietal pleural surface without invasion of the chest wall or extension into the contralateral pleura.

Given the imaging and tissue staging, chemotherapy was recommended, however prognosis remained reserved due to the patient's poor functional status. Ultimately, this patient opted not to pursue aggressive measures, and was discharged home with provisions for comfort care, and expired 3 months later.

3. Discussion

In this case, we identified an individual with no known exposure to asbestos, whose diagnosis of malignant pleural mesothelioma was confirmed only after extensive workup for multiple more probable causes of hydro-pneumothorax. When this case is compared to a literature review of cases of hydro-pneumothorax in the context of mesothelioma only two other cases were described in which hydro-pneumothorax was appreciated on presentation, highlighting the rarity of this finding. As a result of this review, a total of 9 cases were identified, and three main tendencies in the anatomical, prognostic, and epidemiological aspects of MPM were identified, and are exemplified by this case (Table 1).

Anatomically, a marked right sided predominance of hydro-pneumothorax is observed. The presence of right-sided pathology was ubiquitously described, while the presence of bilateral pathology was seldom appreciated, and there was an absence of exclusively left-sided pathology. This tendency correlates with the bilateral pleural effusions but exclusively right sided hydro-pneumothorax observed in the present case, however no explanation for said tendency could be found.

Prognostically, the presence of hydro-pneumothorax was observed to be associated with poor survivability as much in the reviewed cases as in the present case, with a mean survival of 16 months. More specifically, the question arises of whether or not the presence of a hydro-pneumothorax implies invasive mesothelial tissue in the creation of a patent and persistent broncho-pleural fistula. This point is of particular interest given that plaquar and lepidic extension is typically described while direct tissue invasion is not. Direct tissue invasion was not appreciated in any of the biopsy samples of the present case, and therefore cannot be assumed. However, the possibility of pulmonary invasion by malignant pleural tissue suggests not only a potentially important independent prognostic marker, but also an area for further investigation.

Epidemiologically, the exclusivity of MPM with hydro-pneumothorax and its relation to asbestos exposure is questioned here, given the lack of documented exposure in our case as well as several of the reviewed cases. While asbestos exposure is the most commonly considered risk factor for the development of MPM, the absence of known environmental exposure does not exclude the diagnosis, and this case as well as this literature review reaffirms this point. Additionally, the elevated coincidence between tobacco use (more-so than documented asbestos exposure) and hydro-pneumothorax gives rise to the question of whether or not concomitant tobacco use predispose to MPM variants

Table 1
Summary of literature review of case reports of MPM with hydro-pneumothorax since 2000. Average age: 67 years old; 100% male predominance; marked tobacco history; ubiquitous right thorax involvement; and epithelioid tissue subtype was ubiquitously described [6–12].

Case Report	Age	Sex	Environmental Exposure	Tobacco Exposure	Chief Complaint	Chest Roentograph	Cytology	Biopsy	Subtype of MPM
DeLapp et al. [12]	67	M	Asbestos	Yes	Cough, Dyspnea	Right hydropneumothorax	Negative	VATS- Biopsy +	Epithelioid
Fayed et al. [11]	69	M	Asbestos	No	Cough, Dyspnea	Bilateral hydropneumothorax	Negative	VATS- Biopsy +	Not clarified
Saleh et al. [10]	71	M	Asbestos	Yes	Chest Pain, Dyspnea	Right hydropneumothorax	Negative	VATS- Biopsy +	Epithelioid
Saleh et al. [10]	70	M	Unclear	Yes	Chest Pain, Dyspnea	Right hydropneumothorax	Not Declared	Open Thoracotom	Epithelioid
Wu et al. [9]	69	M	Asbestos	Yes	Dyspnea	Right hydropneumothorax	Positive	VATS- Biopsy +	Not clarified
Guha et al. [8]	73	M	Coal particles	Yes	Chest Pain, Dyspnea	Right hydropneumothorax	Not Declared	VATS- Biopsy +	Epithelioid
Mitsui et al. [7]	63	M	Industrial Factory	Yes	Cough	Right hydropneumothorax	Negative	VATS- Biopsy +	Epithelioid
Mitsui et al. [7]	57	M	No	Yes	Dyspnea	Right hydropneumothorax	Negative	VATS- Biopsy +	Epithelioid
Prasad et al. [6]	69	M	Asbestos	Yes	Dyspnea	Right hydropneumothorax	Positive	Open Thoracotomy	Epithelioid

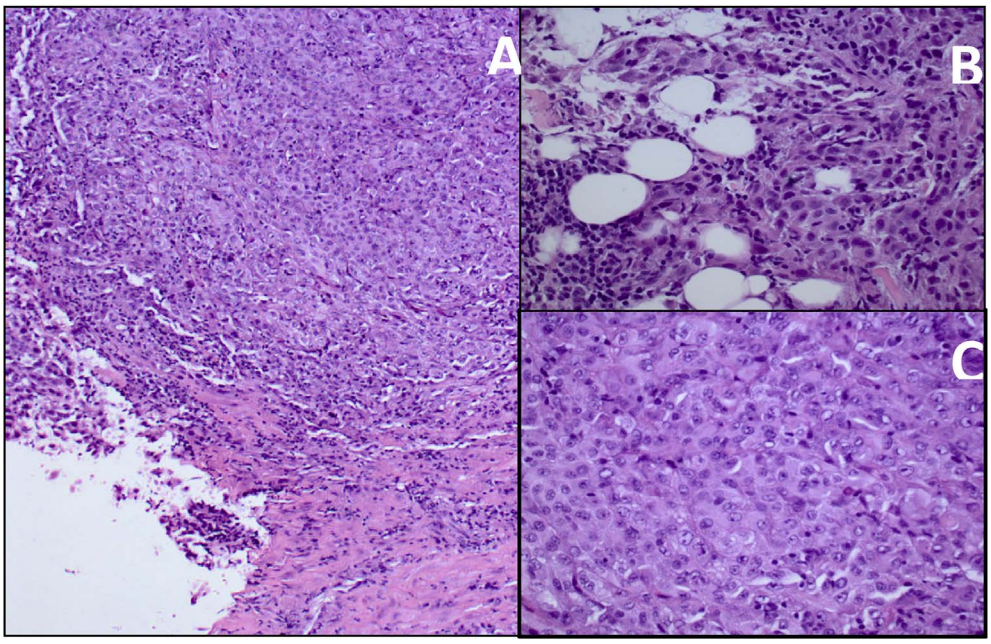

Fig. 4. Pathology slides of the patient showing malignant mesothelioma. Low (A), medium (B) and high (C) power magnification of pleural biopsy specimen with hematoxylin-eosin staining. A) Low (40x) magnification view agglomeration of tumor cells are appreciated, forming part of the mesothelial plaque by sheets of malignant mesothelial cells. B) Medium (100x) powered magnification of polygonal epithelioid cells arranged in sheets, and involving isolated adipocytes, compatible with parietal pleural tissue source. C: High (400x) power magnification showing polygonal epithelioid morphology of mesothelial cells. No direct invasion of pulmonary tissue was identified in biopsy samples.

in which hydro-pneumothorax are present, predispose to more severe cases, or to a more invasive nature of the cancerous tissue.

In review of a large retrospective analysis of patients diagnosed with different stages of MPM by Abakay et al. [13], there were similarities with our patient and literature review, however certain details stood out within the population complicated by hydro-pneumothorax. While Abakay et al. described a population with a mild tendency towards male predominance (59%), we observed a pathology exclusively reported in the male population. The same investigators reported a mild right-thorax predominant tendency, while our patient and group of reviewed cases showed an obligatory involvement of the right hemithorax with exceptional concomitant involvement of the left hemithorax. The patients presenting with hydro-pneumothorax were all found to have the epithelioid tissue variant of MPM while this was found to be the case in only 29% of the reviewed population by Abakay et al. The universal prognosis reported by Abakay et al. showed an overall average survival after diagnosis of 12.3 months, while the reported prognosis in the present case ranged from 3 to 36 months with an average of 16 months.

These results and observations suggest that clinical and radiologic presentation, male gender, and tobacco use could be independent risk factors for a prognosis with in the population suffering MPM, and should potentially carry greater weight in considering the diagnosis and evaluating the prognosis of this population. More specifically, these observations suggest that clinical and radiologic signs and symptoms may carry greater prognostic weight than the histopathologic subtype of tissue reported at biopsy (epithelioid vs other). Overall, the diagnosis of MPM continues to carry a grave prognosis, however these observations suggest that a re-evaluation of prognostic markers-more heavily weighted on clinical and radiologic indicators rather than tissue indicators, may more realistically predict the natural progression of the disease.

4. Conclusions

Malignant pleural mesothelioma presenting as hydro-pneumothorax is a very rare phenomenon, and upon review of all known published cases of MPM with documented hydro-pneumothorax, a clear pattern of right sided predominance on chest pathology and a clear pattern of males with significant tobacco history being affected most. Prognosis is also observed to be poor, with a maximum reported survival of less than 2 years. Given the universally poor prognosis observed, the presence of hydro-pneumothorax secondary to MPM seems to suggest a higher-grade tumor than previously appreciated. It also opens the more in-depth pathological question of whether or not hydro-pneumothorax implies not only parietal pleural invasion but visceral pleural and

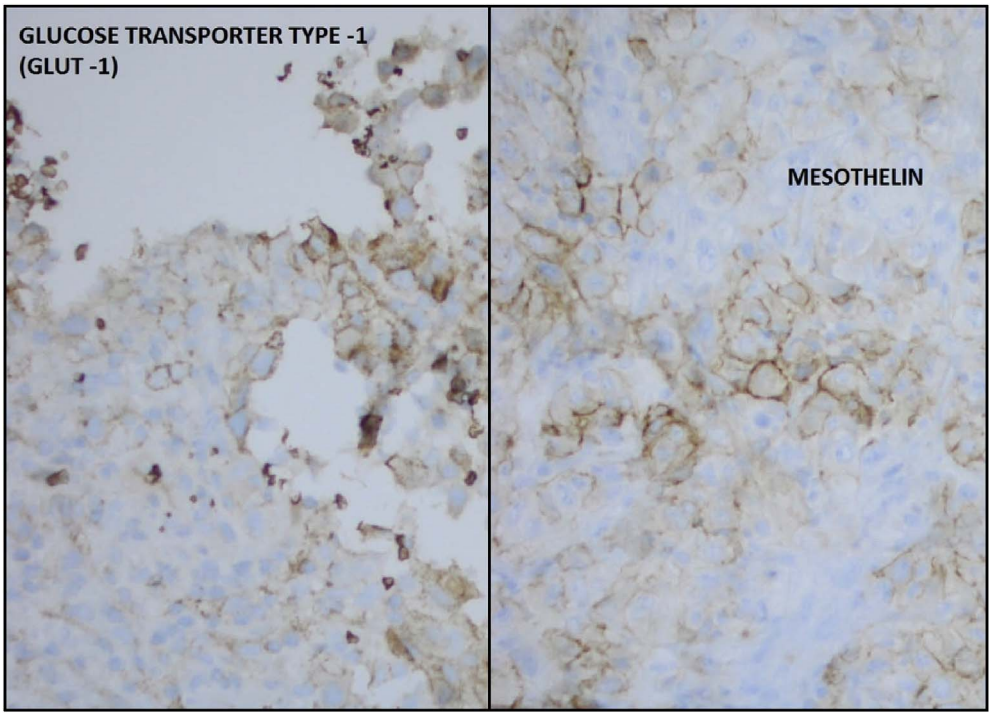

Fig. 5. Immunohistochemistry slides of the patient staining positive for GLUT-1 (a) and mesothelin (b) on pleural biopsy.

potentially pulmonary parenchymal invasion-thereby suggesting a much more aggressive and malignant clinical picture.

Conflicts of interest

The authors declare no conflicts of interest in the preparation of this manuscript.

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