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Review Article

Revisiting localized malignant mesothelioma

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ABSTRACT

Malignant Mesothelioma is an uncommon tumor that usually presents with diffuse pleural involvement and carries a dismal prognosis. Rarely, however, it can present as a localized, circumscribed mass or focal pleural lesion without evidence of diffuse spread. We found four such cases in our database. Three patients had localized epithelioid malignant mesothelioma and one had localized sarcomatoid mesothelioma. These localized tumors are a potential diagnostic pitfall for the pathologists as well as radiologists, especially those practicing in a community setting. Herein we discuss the clinicopathologic features of our cases along with a review of literature.

1. Introduction

Malignant mesothelioma is the most common primary tumor of the pleura as well as other serosal membranes. The usual growth pattern for this tumor is that of a diffuse involvement with multiple tumor nodules; however, a small proportion of cases demonstrate localized growth. These tumors are designated “localized malignant mesothelioma” and they have essentially the same morphologic and immunohistochemical features to their diffuse counterpart [1,2]. The incidence of these lesions is extremely low with only limited data available in literature [1-7]. Therefore these lesions can potentially pose a diagnostic challenge, especially in a community practice setting. We describe a series of four cases of this lesion with emphasis on clinical and pathologic features.

2. Case presentation

2.1. Case 1

A 71-year-old male was found to have a pleural based lung nodule in the left upper lung lobe while being evaluated after a fall (Fig. 1). The patient did not have any respiratory symptom. The lesion was solitary and hypermetabolic on a PET-CT scan. A fine needle biopsy was performed and a diagnosis of epithelioid malignant mesothelioma was established. Subsequently, the patient underwent a left upper lobectomy. Grossly, the tumor was well circumscribed and measured 2.2 cm in greatest dimension. Microscopy revealed sheets of epithelioid tumor cells with abundant eosinophilic cytoplasm. The surgical margins were free of tumor. Surgery was followed by Pemetrexed/Carboplatin for 6 months with follow up scans every 3 months. The patient responded well and went into complete remission. Thirty-five months after initial presentation patient had a relapse in the left pleura.

2.2. Case 2

A 65-year-old male was found to have a hypermetabolic nodule in the upper lobe of right lung while being evaluated for pneumonia. A biopsy was performed and a diagnosis of malignant epithelioid mesothelioma was made. Subsequently, a right upper lobe wedge resection was performed on which a 1.7 cm well-circumscribed nodule involving the visceral pleura and lung parenchyma was identified (Figs. 2–3). The final diagnosis for this nodule was epithelioid malignant mesothelioma and the surgical margins were free of tumor. Twenty-one months after initial presentation, the disease relapsed for which he received four cycles of cisplatin and pemetrexed, followed by a right extra pleural pneumonectomy and adjuvant radiation therapy. However, the disease progressed and the patient died of disease 39 months after initial presentation.

2.3. Case 3

A 42-year-old female with a known history of chondrosarcoma of the right iliac bone with pulmonary metastasis and was being evaluated for additional pulmonary involvement. A CT scan of the chest revealed a pleural based mass in the right lung apex. A wedge resection was

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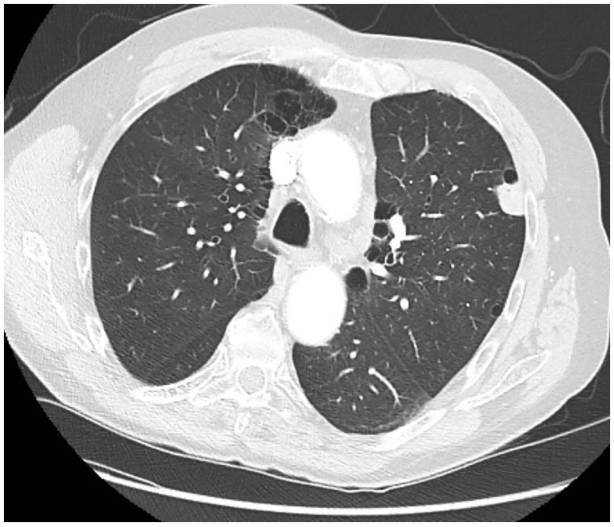

Fig. 1. CT-Scan demonstrating pleural based solitary nodule in first patient.

performed that showed the pleural nodule to be a sarcomatoid mesothelioma involving the visceral pleura and lung parenchyma (Fig. 4). Although suspected to be an additional metastasis from her known chodrosarcoma there was no chondroid differentiation identified within the new pleural mass and comparison to her prior chondrosarcoma showed a histologically different tumor with a distinct immunohistochemical profile. Surgical margins of the pleural tumor were negative. The patient lost follow up after 2 months, at which point she was disease free.

2.4. Case 4

A 78-year-old female was evaluated for chest discomfort and was found to have an anterior mediastinal mass. A biopsy was performed and a well-differentiated neuroendocrine tumor was identified. A left lower lobe wedge resection was performed and a carcinoid tumor forming a 1.1 cm mass was confirmed. Adjacent to the carcinoid tumor was an incidental, flat epithelioid lesion which turned out to be malignant epithelioid mesothelioma involving the pleura. This lesion was not recognized radiologically prior to surgery. The margins were free of tumor and the patient did not receive additional radiation or chemotherapy. She has had a recurrence of her neuroendocrine tumor; however, there was no evidence of recurrence of the malignant mesothelioma, 84 months after initial presentation.

All patients were either diagnosed incidentally or with non-specific complaints. Two patients were male (50%) and two were female (50%). All patients were non-smokers and had no history of asbestos exposure. Overall, the mean age of the patients was 64 years (range, 42–78). In three cases the imaging studies demonstrated a well circumscribed pleural based mass. In one case the mesothelioma involving the pleura was identified incidentally on a resection specimen of a well-differentiated neuroendocrine tumor. All lesions involved lung parenchyma, but did not involve chest wall, diaphragm or other organs. The demographic data and clinicopathologic features are summarized in Tables 1 and 2.

Three of the tumors had epithelioid histology composed of polygonal cells and one had sarcomatoid histology with spindle cells arranged in short fascicles. Immunohistochemical studies were performed in all cases to confirm the diagnosis. Calretinin stain highlighted the tumor cells in all four cases.

3. Discussion

Localized malignant pleural mesothelioma is a rare and distinct

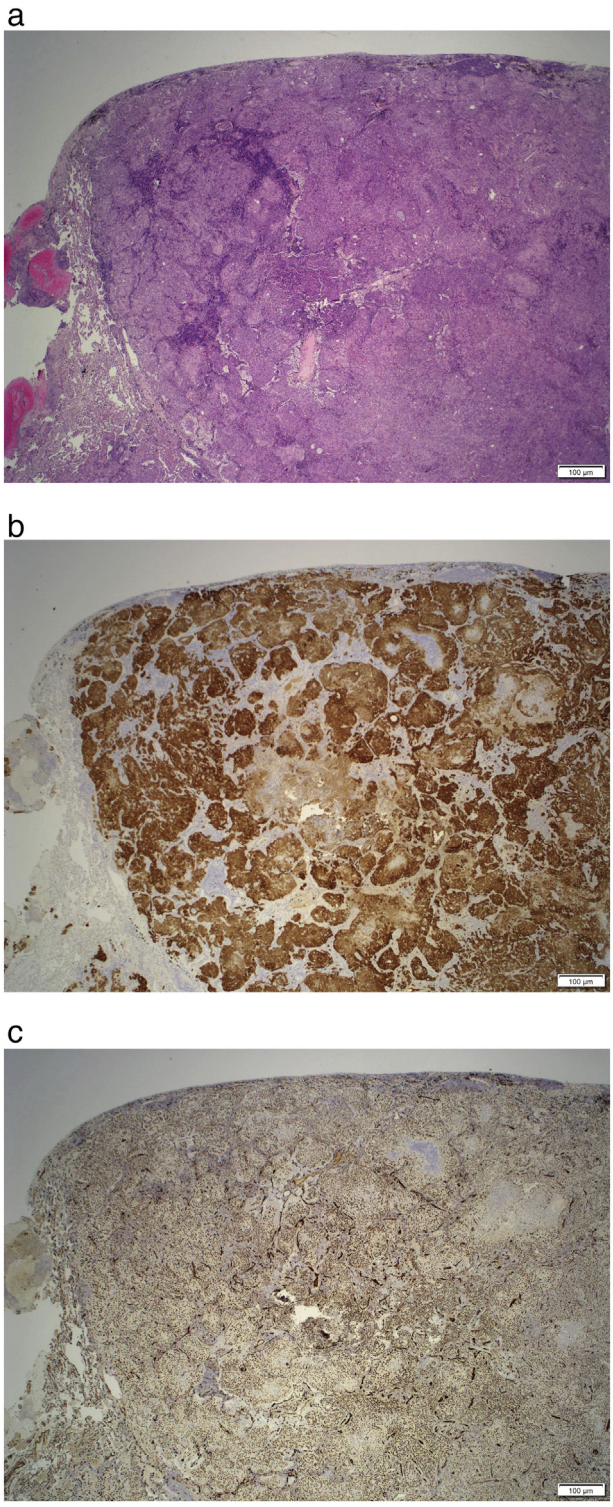

Fig. 2. Low power photomicrographs demonstrating a pleural based lesion (A: H&E 20×; B: Calretinin 20×; C: WT-1 20×).

entity with different biological behavior than diffuse pleural mesothelioma. It is speculated that the localized type arises from submesothlial layers [8].

Most affected patients are elderly males; however, females and middle aged individuals are also affected [1,6]. The mean age of patients in the largest reported series of cases was 62 years (range, 37–83 years) [1]. Localized pleural malignant mesotheliomas are most often discovered incidentally in asymptomatic patients. Unlike diffuse

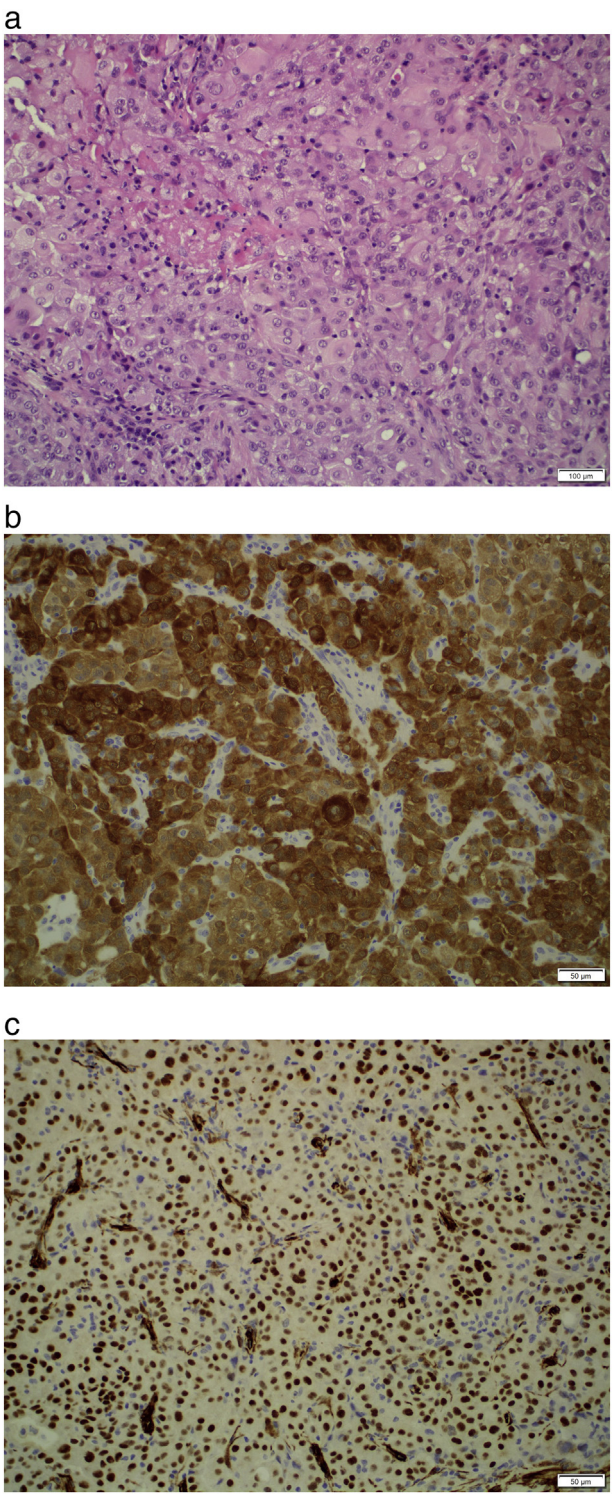

Fig. 3. Photomicrographs demonstrating epithelioid tumor cells with abundant eosinophilic cytoplasm (A: H&E 200×, B: Calretinin 200×; C: WT-1200×).

mesothelioma, the localized tumors rarely cause respiratory symptoms and rarely result in pleural effusion. Similar to diffuse malignant mesothelioma, a history of asbestos exposure can be elicited; however, much less frequently [1].

Among our cases the male to female ratio was 1:1, the mean age was 64 years (range, 42–78) and none of the patients had specific respiratory symptoms or history of asbestos exposure.

On imaging studies localized malignant mesothelioma most often appears as a pleural based smooth, lobulated mass [9,10]. Three of our

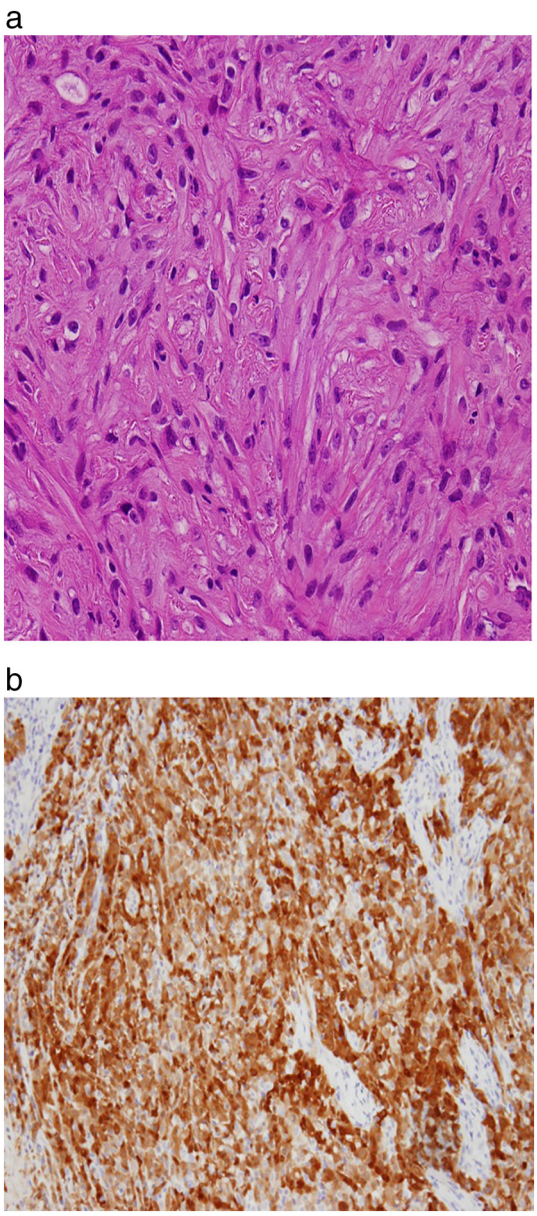

Fig. 4. Photomicrograph demonstrating spindled tumor cells forming short fascicles in the patient with sarcomatoid mesothelioma (A: H&E, 200×; B: Calretinin 200×).

cases depicted this radiologic characteristic while the fourth case was an incidental finding only on microscopic evaluation.

From a pathologic standpoint, grossly localized pleural malignant mesothelioma are well circumscribed, pleural-based masses that can either be peduncalated or sessile. They can vary in size from less than a centimeter to as large as 15 cm [1]; however, do not demonstrate a diffuse spread or invasion into adjacent organs.

Localized malignant mesothelioma histologically may present as epithelioid or sarcomatoid type. The epithelioid histologic type is considered to be a positive prognostic indicator over the sarcomatoid or biphasic type in the diffuse malignant mesothelioma, but several studies have shown it, not to be a definitive factor correlating to survival benefit in localized malignant mesothelioma [1,2] The isolated lesion is usually pleural based mass or flat lesion, but can be attached to the pericardium or peritoneum. One female patient was 42 years of age, which is significantly younger than the predominant age group of 70–79 years. One large study performed by Taioli et al. found that women in the age group of 18–49 years made up 2% of the patients

Table 1
Clinical features.

Case	Age (years)	Gender	Smoking history	Present complaints	Follow up
Case 1	70 years	Male	Non-Smoker	Incidental	Relapse 35 months after initial presentation
Case 2	65 years	Male	Non-Smoker	Cough, fever	Died of disease 39 months after initial presentation.
Case 3	42 years	Female	Non-Smoker	Incidental	Lost follow up after 2 months
Case 4	78 years	Female	Non-Smoker	Chest discomfort	Disease free 84 months after initial presentation

Table 2
Pathologic features.

Case	Site	Gross size	Microscopic morphology
Case 1	Lingula	2.2 cm	Epithelioid
Case 2	Right upper lobe	1.7 cm	Epithelioid
Case 3	Right upper lobe	2.6 cm	Sarcomatoid
Case 4	Left lower lobe	Incidental microscopic focus	Epithelioid

diagnosed with malignant mesothelioma while women in the 70–79 years age group comprised 6.5% of that population [11]. The differential diagnosis of localized malignant mesothelioma is broad, including mesothelial cell hyperplasia as well as primary and metastatic neoplastic conditions involving lung and pleura. Adequate patient medical history and correlations with imaging findings are crucial in arriving at a correct diagnosis. Immunohistochemical studies are immensely helpful in ruling out differential diagnoses. A panel of immunohistochemical stains is usually employed that consist of at least two mesothelial markers as well as several non-mesothelial markers [12-14]. Mesothelial markers most commonly used in practice include calretinin, WT-1, high molecular weight cytokeratin and podoplanin, while a variety of markers are used to rule out epithelial and mesenchymal tumors that are entertained in the differential diagnosis.

Because of the localized nature of the disease, surgery appears to be curative; however, recurrence and even metastasis is known to occur [1,15]. As the clinical behavior of this lesion is still not completely understood, surgery is usually supplemented with adjuvant therapy [1,6,15]. Two of our patients also received adjuvant chemotherapy. Like any malignant tumor, the localized malignant mesothelioma can recur and metastasize. Metastasis has been reported in kidneys, stomach, small intestine, abdominal and mediastinal lymph nodes, brain, axial skelton and skin [1,15,17,18]. With respect to clinical course and prognosis of localized malignant pleural mesothelioma there is contradictory evidence in literature. Some reports have suggested an aggressive clinical course with poor outcome similar to the diffuse mesothelioma, while other studies suggest a better outcome [1,16]. Gelvez-Zapata et al. [16] analyzed 48 cases reported in the literature and found that median overall survival in these cases was 36 months (range 0 to 132 months) while the median survival calculated by Kaplan–Meier analysis was 29 months. The overall disease free survival in their study was 24 months. Allen et al. [1] found that 10 of their patients with follow-up data available were alive without evidence of disease from 18 months to 11 years after diagnosis. Follow up data on our patients showed disease relapse after 21 and 35 months in two cases, and no evidence of recurrent disease after 84 months in one case, the fourth case lost follow just after 2 months.

4. Conclusion

Localized pleural malignant mesothelioma is a distinct clincopathologic entity. Overall the literature suggests a longer overall survival as compared to the diffuse type; however, the disease progression is difficult to predict. Awareness of this entity and its place in the differential diagnosis of solitary lung lesions is essential to avoid errors in diagnosis, especially in the interpretation of small biopsy specimens.

Conflict of interest

All authors declare no conflict of interest.

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