

A Rare Case of Localized Malignant Pleural Mesothelioma Mimicking an Anterior Mediastinal Mass

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AUTHORS' CONTRIBUTIONS

Hong Wan Yap is the corresponding author and project lead. Salahudeen Mohamed Haja Mohideen is the main supervisor of the project and contributed to the radiological discussion section. Chun Yuen Chow contributed to the pathological discussion section, provided the histology slides and contributed to the histological findings for the case discussed. Boon Hean Ong is the surgeon in charge of the case discussed and contributed to the clinical discussion portion of the manuscript. All authors have reviewed the manuscript drafts including the final manuscript and are agreeable for it to be published.

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No

ABSTRACT

Pleural mesotheliomas commonly present as diffuse nodular involvement of the affected pleural lining, whereas a localized form of pleural mesothelioma is rare. We report a rare and unusual case of localized pleural mesothelioma that initially mimicked an anterior mediastinal mass on radiographs and computed tomography with atypical features such as the lack of asbestos exposure history and pleural effusion, which prompted other differentials of anterior mediastinal masses during tumor board discussions. This case emphasizes the consideration of localized mesothelioma in the differential diagnosis of focal masses involving the mediastinal pleura.

CASE REPORT

BACKGROUND

Pleural mesothelioma commonly presents as a diffuse form whereas localized pleural mesothelioma is a rare presentation. The presented case is significant as the lesion mimicked an anterior mediastinal mass on initial imaging findings, which led to differentials such as thymoma or lymphoma being considered and a diagnostic dilemma given that the patient had no known risk factors. This is an interesting case to highlight for radiologists to consider localized mesothelioma as a differential in anterior mediastinal masses. In addition, based on the criteria from WHO and the proposed guidelines by Marchevsky et al, a localized pleural mesothelioma should present as a single mass, which was not the same for this case as there was an additional pleural based nodule. However, we propose that our case may still represent a localized presentation with two separate foci of

involvement, given the presence of only one additional nodule while fulfilling the rest of the proposed guidelines. The relatively indolent nature of the tumor in our patient who remained disease free at one-year follow up post-surgery, without adjuvant chemotherapy supports the diagnosis of localized presentation of pleural malignant mesothelioma and underscores the potential therapeutic value of surgical resection in such cases that may not necessarily fit into the proposed guidelines.

CASE REPORT

A 69-year-old male patient presented with a 3-week duration of intermittent non-exertional chest discomfort. There was no associated breathlessness, diaphoresis or palpitation. He was a non-smoker with no known history of exposure to asbestos. He worked as a building contractor with significant history of

hypertension, hyperlipidemia and gastritis. He was investigated for a history of chest pain one year ago and a dipyridamole stress perfusion test performed at that time showed no evidence of myocardial ischemia.

On physical examination, the heart sounds were normal, chest auscultation was clear and there was no evidence of cervical lymphadenopathy.

Imaging Findings

Initial chest radiograph showed a mass projected over the left hilum with preserved hilar vascular shadowing (hilar overlay sign). The mass was also inseparable from the left atrial border and the contours of the descending thoracic aorta were preserved, suggestive of an anterior mediastinal mass.

Contrast enhanced Computed Tomography (CT) of the chest confirmed the presence of a lobulated heterogenous enhancing mass measuring 6.3 x 4.4 x 6.7cm inseparable from the mediastinal pleura. No definite invasion into the mediastinal fat or major vascular structures was evident. There was no enlarged mediastinal or hilar node. However, there was a smaller pleural based nodule measuring 1.8 x 0.8 x 1.1cm at the posterior left lung apex. Combination of these findings raised the possibility of an anterior mediastinal mass with left pleural metastasis and the differentials considered at this stage included thymoma and lymphoma. There were no features of macroscopic fat or calcification to suggest a teratoma.

An Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG PET-CT) was subsequently performed showing an intensely FDG avid mass in the region of anterior mediastinum and mild degree of FDG uptake within the left pleural apex nodule. No other sites of disease were detected.

Pathology description

Initial CT guided biopsy of both the dominant mass in the region of anterior mediastinum and left lung apex pleural nodule showed diffuse proliferation of epithelioid cells. On immunohistochemistry, these tumor cells were positive for CK7, variably positive for CK20 and showed strong diffuse positive staining for calretinin, WT1, D2-40, and CK5/6. Both the anterior mediastinal mass and pleural nodule had similar histological features with identical immunoprofile. Findings suggested a pleural epithelioid mesothelioma.

Management and follow up

Given the discordant radiological and pathological findings during a tumor board discussion, decision was made to obtain further tissue sampling via Video-Assisted Thoracic Surgery (VATS) of the dominant mass and excision of the left apex pleural nodule, which again confirmed a pleural epithelioid mesothelioma. One month later, the patient underwent surgical resection of the mass via a left anterior thoracotomy. Intraoperatively, the tumor was confirmed to be attached to the

anteromedial aspect of the left upper lobe near the hilum of the left lung. A left upper lobectomy was performed to remove the entire tumor en bloc with surrounding lung parenchyma. A systematic lymph node dissection and random pleural biopsies were also performed at the time of surgery. The patient made an uneventful recovery post-surgery. Post-operative histopathology demonstrated a high-grade epithelioid mesothelioma invading into the lung parenchyma, with clear resection margins. All 21 excised lymph nodes removed and random pleural biopsies were also negative for malignancy. Recent post operative CTs showed mild residual left sided pleural thickening attributed to post-surgical change and no residual tumor was seen at 1 year follow up.

DISCUSSION

Etiology and demographics

Mesothelioma is an aggressive primary malignancy that can affect the pleura. Other sites of concern include the peritoneum, pericardium and tunica vaginalis [1]. Risk factors include radiation, simian virus 40 and chronic pleural/peritoneal inflammation. They primarily affect older males (Mean age 58.9 ± 13.9 years in a literature review, and 70-75% affecting males), though they can also occur in younger patients, with genetic predisposition such as BAP1 tumor predisposition syndrome or early exposure to other carcinogenic material being potential risk factors. An important risk factor is asbestos exposure, for which there is a long latency period of 40 years from the first asbestos exposure to tumor development [2].

The incidence of mesothelioma is 1.25/100,000 in Great Britain and 1.1/100,000 in Germany [3], and accounts for 0.2% of new cancer cases in 2020 [4]. Mesothelioma can present in both diffuse forms or rarely in a localized form. Localized malignant pleural mesothelioma (LMM) is a rare entity, with a systemic review by Marchevsky et al in 2020 [5] demonstrating 101 cases in the English literature with additional 72 cases contributed by the international mesothelioma panel at the time of the review. The incidence of LMM is estimated to be only 0.5–1.6% of cases diagnosed as malignant mesothelioma in two institutions that contributed to the international mesothelioma panel.

Clinical and Imaging Discussion

Pleural mesothelioma is frequently diagnosed late due to non-specific presentation of cough and chest pain [6], usually secondary to pleural effusion and disease involvement [7]. Paraneoplastic syndromes are a rare presentation [8].

Radiographic findings of diffuse pleural malignant mesothelioma (DMM) can typically present as a unilateral pleural effusion on chest radiograph. A pleural based mass may also be present, along with diffuse pleural thickening and lung encasement. Pleural plaques are the most common finding associated with asbestos exposure occurring up to 20% of patients.

On CT, the typical features of diffuse mesothelioma include unilateral pleural effusion which can occur to up to 80% of patients [7], nodular or lobular pleural thickening as well as interlobar fissure thickening. Rind-like encasement of the lung with ipsilateral volume loss is seen in advanced-stage disease. CT features that can help differentiate malignant from benign causes include circumferential pleural thickening involving the mediastinal pleura [9], thickening of the interlobar fissure and the presence of pleural plaques. A malignant pleural mesothelioma encroaching the mediastinum can mimic a mediastinal mass [10], which has broader differentials including lymphoma, thymoma, and teratoma.

LMM on the other hand, is seen as a localized mass at presentation. Based on the proposed guidelines by Marchevsky et al, a localized malignant mesothelioma should comprise of a well-circumscribed serosal/subserosal mass with absence of additional nodules or serosal spread. Possible additional findings in patients with localized malignant mesothelioma include pleural effusion (14/72) and pleural thickening (8/72) with a positive asbestos exposure present in 55.2% in a series of patients diagnosed by the International Mesothelioma Panel [5].

Pathology Discussion

The diagnosis of mesothelioma usually requires careful histologic examination aided by appropriate immunohistochemistry to establish the mesothelial lineage with markers such as calretinin, WT1, D2-40, and CK5/6. Loss of BAP1 nuclear staining is another common finding in mesothelioma. Mesotheliomas are also assigned a histologic grade that correlates with the disease prognosis. In this case, it was a high-grade mesothelioma due to moderate nuclear atypia, increased mitotic count and the presence of tumor necrosis (nuclear grade 2 with necrosis). However, the histopathological and immunophenotypical features of LMM are identical to DMM [5], making it important to achieve a consensus on a multidisciplinary tumor board.

Treatment and prognosis

Extrapleural pneumonectomy may be considered for a small subset of DMM patients with early stage tumors (stage 1 or 2). For unresectable tumors, systemic chemotherapy, immunotherapy and radiotherapy are options with limited survivability. LMM has grounds for neoadjuvant therapy and aggressive surgical resection to give the patient the best change of treatment. In addition, the median survival rate for patients post-surgical resection was 134 months [5] which was considerably better than patients with DMM (23-40 months among stage 1 DMM patients who underwent resection) [11]. Local recurrence rates were reported to be 14 of the 51 post treatment (27.4%) patients in a survival analysis [5] of LMM patients. Hyperthermic intrathoracic chemotherapy (HITHOC) is a known treatment for DMM patients but not currently performed in our institution. From the seven studies in a systemic review for HITHOC in malignant pleural mesothelioma [12], results were heterogenous

and only one study was related to localized mesothelioma which concluded that HITHOC is a safe treatment that may improve survival [13].

We describe an unusual case of epithelioid malignant mesothelioma with 2 separate localized foci in the mediastinal and costal pleura respectively. Firstly, the location of this tumor, inseparable from the medial left upper lobe and anterior mediastinum with localized mass effect, initially mimicked an anterior mediastinal mass. The radiological findings prompted the initial differential diagnoses of lymphoma and thymoma, which resulted in discordance with the initial CT guided needle biopsy histological findings. There was no pleural effusion or diffuse pleural thickening, aside from the smaller pleural based lesion along the left lung apex, which also lowered the initial suspicion for mesothelioma, particularly given the unclear exposure history to asbestos. Other random sites of pleural biopsy were also negative for malignancy in this patient. Based on the criteria from WHO [14] and the proposed guidelines by Marchevsky et al. [5], only a solitary localized mass without the presence of additional nodules can be considered as LMM. However, we propose that our case may still represent a localized presentation with two separate foci of involvement, given the presence of only one additional nodule while fulfilling the rest of the proposed guidelines. The relatively indolent nature of the tumor in our patient who remained disease free at one-year follow up post-surgery, without adjuvant chemotherapy supports the diagnosis of localized presentation of pleural malignant mesothelioma and underscores the potential therapeutic value of surgical resection in such cases.

Differential Diagnoses (radiology)

Differentials of localized malignant mesothelioma depends on site of origin and includes solitary fibrous tumor (SFT), thymomas or lymphomas. They often demonstrate similar features, such as a homogeneously enhancing lobulated lesion and thus difficult to accurately differentiate LMM from SFT or even thymomas just based on imaging findings. Other pleural based masses like synovial sarcomas or teratomas can be easier to differentiate from LMM if they display typical characteristics such as heterogenous enhancement or fat-fluid levels on CT respectively.

TEACHING POINT

LMM should be considered in the differential diagnosis of localized masses involving the mediastinal pleura, particularly when the imaging mimics a mediastinal mass. Recognition of LMM within a multidisciplinary tumor board setting is crucial, as its management greatly differs from that of DMM and patients with LMM may benefit from surgical resection.

QUESTIONS

Question 1: The following are imaging characteristics of diffuse pleural mesothelioma except?

1. Unilateral pleural effusion
2. Pleural plaques

3. Macroscopic intralesional fat (applies)
4. Interlobular fissure thickening
5. Mediastinal pleural thickening

Explanation: [Typical features of diffuse mesothelioma include unilateral pleural effusion which can occur to up to 80% of patients, nodular or lobular pleural thickening as well as interlobar fissure thickening. Rind-like encasement of the lung with ipsilateral volume loss is seen in advanced-stage disease. CT features that can help differentiate malignant from benign causes include circumferential pleural thickening involving the mediastinal pleura, thickening of the interlobar fissure and the presence of pleural plaques]. Macroscopic intralesional fat is not a known imaging characteristic of mesothelioma.

Question 2: The differential diagnoses for localized pleural mesothelioma on CT include:

1. Solitary fibrous tumor (applies)
2. Synovial sarcoma
3. Thymoma (applies)
4. Lymphoma (applies)
5. Teratoma

Explanation: Typically, synovial sarcoma and teratomas appear as heterogeneously enhancing masses. Teratomas can also present with fat-fluid levels which differentiate it from the rest of the mediastinal masses. Solitary fibrous tumors, thymoma and lymphomas can present as homogeneously enhancing lobulated masses which are difficult to differentiate from localized pleural mesothelioma. The features are described in [Differential table].

Question 3: Which of the characteristics suggest a diagnosis of localized mesothelioma rather than diffuse mesothelioma based on proposed guidelines?

1. Single mass (applies)
2. Lack of pleural effusion
3. Involvement of lymph nodes
4. Invasion into surrounding structures
5. Histopathology is identical to that of diffuse mesothelioma (applies)

Explanation: [Based on the proposed guidelines by Marchevsky et al, a localized malignant mesothelioma should comprise of a well-circumscribed serosal/subserosal mass with absence of additional nodules or serosal spread]. The [histopathological and immunophenotypical features of LMM are identical to DMM]. Localized mesothelioma can present with pleural effusion, and dependent on the aggressiveness, it can spread to lymph nodes and invade locally.

Question 4: Which of the following immunohistochemical markers support the diagnosis of mesothelioma?

1. Retained BAP-1 nuclear staining
2. Calretinin (applies)
3. WT1 (applies)
4. D2-40 (applies)
5. CK5/6 (applies)

Explanation: [The diagnosis of mesothelioma usually requires careful histologic examination aided by appropriate

immunohistochemistry to establish the mesothelial lineage with markers such as calretinin, WT1, D2-40, and CK5/6. Loss of BAP1 nuclear staining is another common finding in mesothelioma].

Question 5: The following are recognized risk factors for mesothelioma except?

- a) Germline BAP 1 mutation
- b) Alcohol (applies)
- c) Simian virus 40
- d) Asbestos exposure
- e) Radiation

Explanation: Risk factors include radiation, simian virus 40 and chronic pleural/peritoneal inflammation. They primarily affect older males (Mean age 58.9 ± 13.9 years in a literature review, and 70-75% affecting males), though they can also occur in younger patients, with genetic predisposition such as BAP1 tumor predisposition syndrome or early exposure to other carcinogenic material being potential risk factors. An important risk factor is asbestos exposure, for which there is a long latency period of 40 years from the first asbestos exposure to tumor development.

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FIGURES

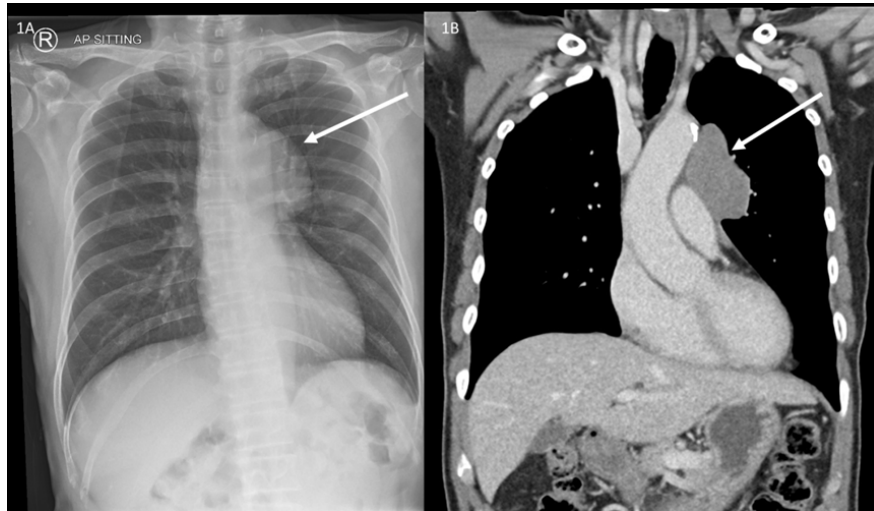


Figure 1A: AP Chest radiograph demonstrating a mass overlapping the left hilum suggestive of an anterior mediastinal mass (white arrow).
Figure 1B: Contrast enhanced coronal CT confirming a soft tissue mass overlapping the hilar structures. *TECHNIQUE:* CT – 90.0 KV; Slice thickness – 3mm; Late arterial phase.

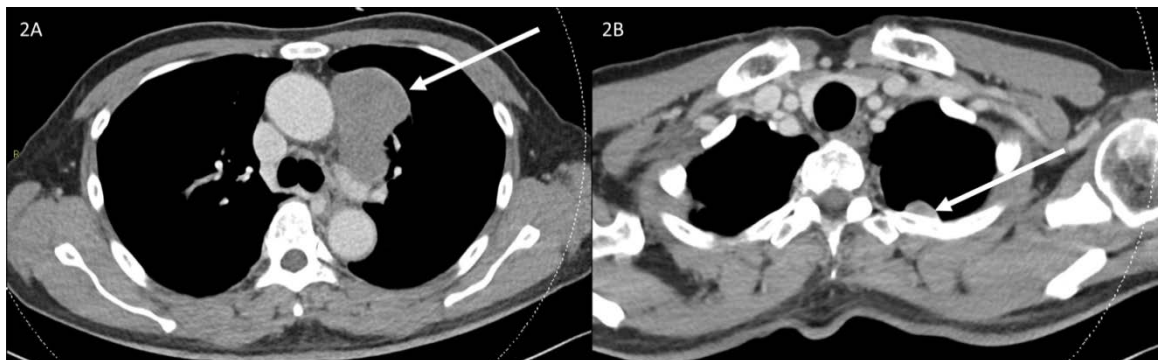


Figure 2A and B: Axial contrast enhanced CT demonstrating (white arrows) a lobulated soft tissue mass inseparable from the left mediastinal pleura anteriorly mimicking an anterior mediastinal mass (2A) and a left lung apex pleural based nodule (2B). *TECHNIQUE:* CT – 90.0 KV; Slice thickness – 3mm; Late arterial phase.

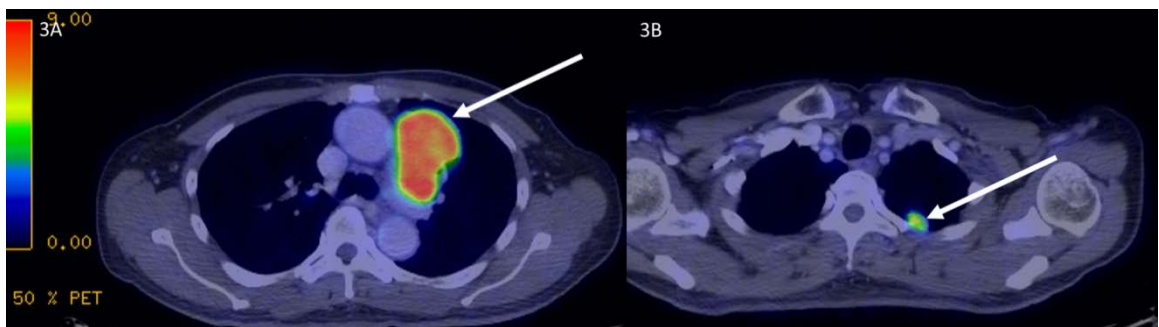


Figure 3A and B: FDG PET-CT axial sequences demonstrating (white arrows) the intensely FDG avid mass in the region of anterior mediastinum (3A) and mildly FDG avid left pleural nodule (3B). *TECHNIQUE:* 7.5 mCi of F-18 Fluorodeoxyglucose; CT – 100.0 kV; Slice thickness – 3.75 mm.

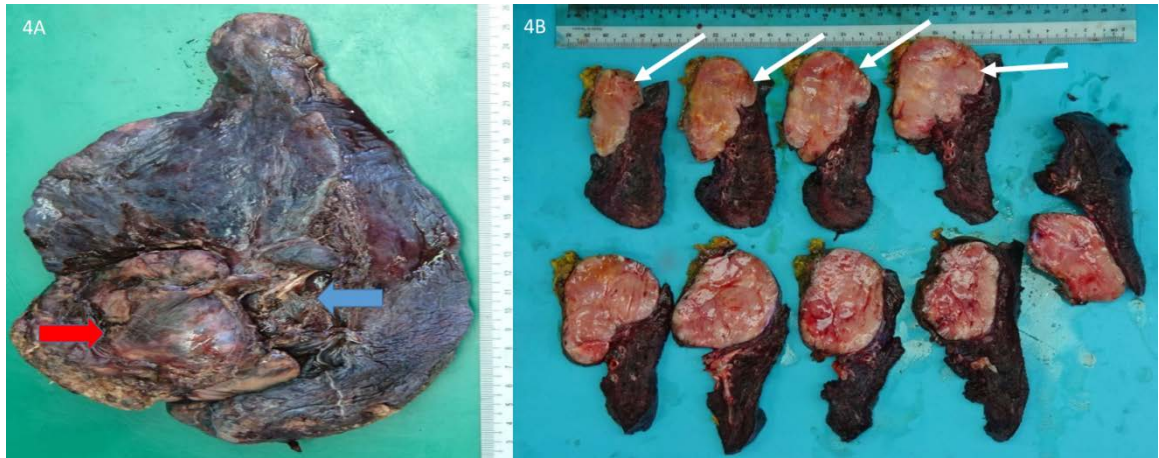


Figure 4A: Gross specimen images of the lobectomy specimen showed the tumor (red arrow) arising from the anteromedial aspect of the left upper lobe near the hilum (blue arrow).

Figure 4B: shows serial sections of the exophytic tumor with solid and fleshy cut surface (white arrows).

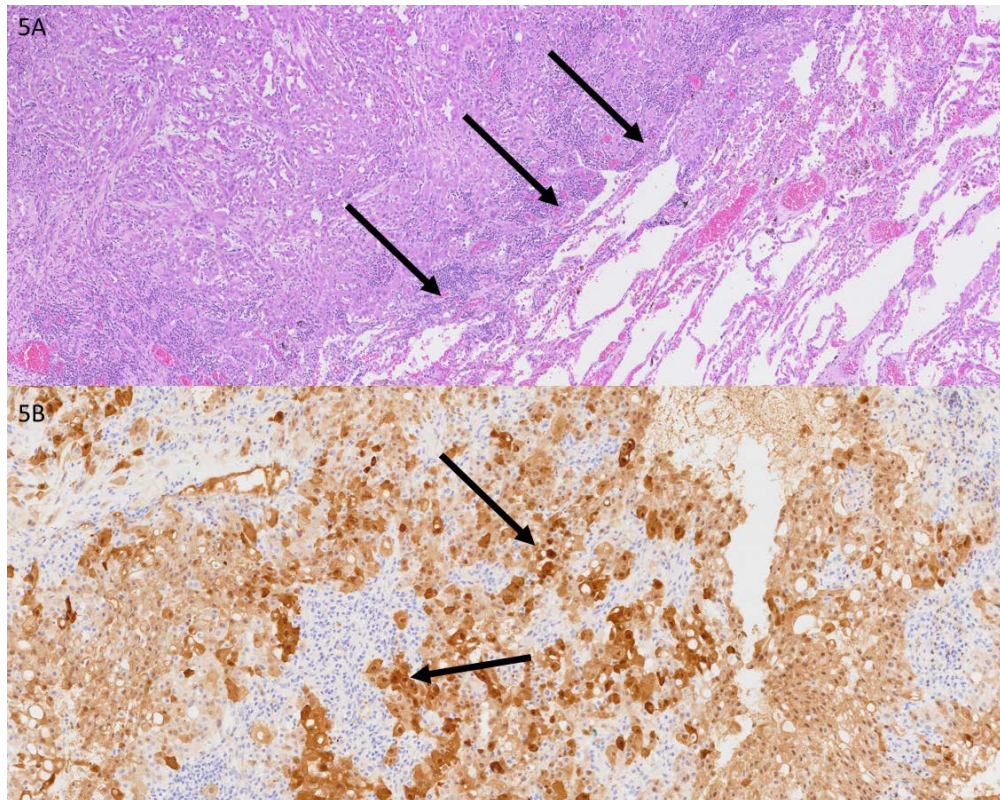


Figure 5A: Hematoxylin and eosin (H&E) x50 magnification of the resected specimen showing tumor invasion into underlying lung parenchyma.

Figure 5B: Calretinin immunohistochemical stain: Tumor cells showed positive nuclear and cytoplasmic staining.

Summary table: Localized pleural mesothelioma

Etiology	Malignant neoplasms arising from the serosal membranes
Incidence	0.5–1.6% of cases diagnosed as malignant mesothelioma
Gender ratio	70-75% in Males
Age predilection	Older patients, Mean age 58.9 +/-13.9 years in a literature review
Risk factors	Radiation, simian virus 40 and chronic pleural/peritoneal inflammation, BAP1 tumor predisposition syndrome, asbestos exposure
Treatment	Neoadjuvant therapy and surgical resection
Prognosis	Better prognosis (134 months post treatment)
Findings on imaging	Well circumscribed mass, with no additional nodules or pleural thickening

DIFFERENTIAL TABLE

Differential diagnosis of mediastinal masses	CT
LMM	Well-circumscribed serosal or subserosal mass with absence of additional nodules or serosal spread. Possible additional imaging findings include pleural effusion and pleural thickening although pleural thickening raises question about the diagnosis.
DMM	Unilateral pleural effusion, pleural based mass and diffuse nodular costal or mediastinal pleural thickening and lung encasement, with ipsilateral volume loss in advanced cases. Pleural plaques are the most common finding associated with asbestos exposure.
Solitary fibrous tumor	Homogenous, well defined lobulated soft tissue mass. It can arise from the pleura or within the interlobar fissure. Larger lesions may demonstrate necrosis and intralesional calcifications. Involvement of the mediastinum is rare but possible. The malignant form can demonstrate invasion into surrounding structures.
Synovial Sarcoma	Heterogeneously enhancing mass with well-defined margins, with or without calcifications. It can also present with tumor infiltration of the chest wall musculature and also destruction of adjacent bone cortex.
Teratoma	Heterogenous mass in the anterior mediastinum demonstrating a combination of fat, fluid, calcification and soft tissue densities. Fat-fluid level is highly specific but uncommon.
Thymoma	Smooth lobular homogeneously enhancing mass. One third of patients may demonstrate heterogenous enhancement due to areas of necrosis, cystic changes or coarse intralesional calcifications. Higher grade lesions can demonstrate vascular invasion, pericardial and pleural involvement.
Lymphoma	Predominantly a lobulated anterior mediastinal mass, with homogenous soft tissue attenuation. Within the lesion, there are possible areas of haemorrhage, necrosis or cystic degeneration. Larger masses can cause compression of mediastinal vasculature. Enlarged lymph nodes may be present.

KEYWORDS

Localized pleural malignant mesothelioma; Pleura tumor; Mediastinal tumor; thorax; lymphoma

ABBREVIATIONS

LMM = LOCALIZED PLEURAL MALIGNANT MESOTHELIOMA
DMM = DIFFUSE PLEURAL MALIGNANT MESOTHELIOMA
CT = COMPUTED TOMOGRAPHY
FDG PET-CT = FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY
SFT = SOLITARY FIBROUS TUMOR
VATS = VIDEO-ASSISTED THORACIC SURGERY

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