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CASE REPORT

Intrapulmonary Biphasic Mesothelioma Misdiagnosed as Adenocarcinoma: Case Report and a Potential Diagnostic Pitfall

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Background: Mesothelioma is an uncommon malignant tumor with variable clinical presentations, radiological features, and morphological patterns. Mesothelioma with predominantly intrapulmonary growth presents with an insidious onset, similar radiological and even morphological features to lung cancer, and poses a diagnostic pitfall.

Case Presentation: Herein, we reported a 53-year-old female with biphasic mesothelioma misdiagnosed as poorly differentiated adenocarcinoma with focal sarcomatoid carcinoma. Computed tomography (CT) scan of the chest at the first visit revealed a solid lobulated nodule in the basal segment of the lower lobe of the right lung, which was suspicious of lung cancer. Microscopically, the tumor was composed of epithelioid and spindle cells, both of which were diffusely and strongly positive for CK7, and negative for TTF-1, Napsin A, P40, Melan A, S-100, SMA, and CD34. It was originally misdiagnosed as poorly differentiated adenocarcinoma with focal sarcomatoid carcinoma at initial presentation. Until her second admission with the discovery of a nodule in the right diaphragmatic angle, the peculiar location and biphasic component reminded us of biphasic mesothelioma. Immunohistochemically, tumor cells in both pulmonary and diaphragmatic nodules were positive for calretinin, D2-40, and WT-1, but negative for BerEP4 and MOC31. The patient was treated with a chemotherapy regimen of pemetrexed and carboplatin. After 11 months of follow-up, the patient recovers well without recurrence or metastasis.

Conclusion: Mesothelioma with predominantly intrapulmonary growth is extremely rare and poses a diagnostic pitfall. For this entity, subtle morphological features, selection of immunohistochemical markers, and electron microscopy are of great significance for definite diagnosis.

Keywords: mesothelioma, localized mesothelioma, predominantly intrapulmonary growth, lung cancer, misdiagnosis

Introduction

Mesothelioma is a rare malignant tumor with variable clinical presentations, radiological features, and morphological patterns, accounting for 0.2% of all new cases of malignant tumors worldwide.[1] Depending on whether the lesion is localized or diffuse, mesothelioma is divided into localized and diffuse mesothelioma, both share an identical but wide range of morphological features and immunohistochemical phenotypes. Diffuse mesothelioma often manifests as unilateral pleural effusion, dyspnea, chest pain, and even progressive pleural thickening leading to the compression of lung parenchyma. Localized mesothelioma is significantly rare, accounting for 0.5% to 1.6% of all mesothelioma.[2] Patients with localized mesothelioma have an insidious onset and are often asymptomatic. In particular, localized mesothelioma is most challenging to diagnose when it presents as intrapulmonary growth in the absence of overt pleural disease and is often misinterpreted as a pulmonary adenocarcinoma.[3,4] The rarity of the disease, insidious onset, predominantly intrapulmonary growth, and diverse histological features result in a low rate of definite diagnosis and a high rate of misdiagnosis of localized mesothelioma. Herein, we report a 53-year-old female patient with biphasic mesothelioma who had an incidental finding of a mass in the right lower lobe of the lung that was misdiagnosed as poorly

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differentiated adenocarcinoma with focal sarcomatoid carcinoma at initial presentation. Furthermore, Mesothelioma with a predominantly intrapulmonary growth does pose a diagnostic challenge. This unique entity is discussed, along with a literature review (Table 1) and potential diagnostic pitfalls.

Case Presentation

A 53-year-old female without any symptoms was admitted to our hospital on 14th February 2022, due to a nodule in the lower lobe of the right lung found fortuitously for more than 7 months. Computed tomography (CT) scan of the chest revealed a solid lobulated nodule measuring 20 × 15 mm in the basal segment of the lower lobe of the right lung (Figure 1A). Radiologists considered it as suspicious of primary lung cancer. The remaining laboratory and imaging examinations are unremarkable. The patient had a history of partial thyroidectomy for unknown reasons, while no history of smoking or asbestos exposure. She underwent a lobectomy on 22nd February 2022, and a pathological biopsy was carried out. Gross examination showed a subpleural lobulated mass with medium texture and well-defined borders, measuring 2.0 × 1.5 × 1.0 cm.

Under low magnification, the lobulated tumor was composed of nests of tumor cells with patchy necrosis and circumscribed margins (Figure 1B and C). Under high magnification, the nests of tumor cells were composed of epithelioid cells with abundant eosinophilic cytoplasm, vacuolated nuclei, and obvious nucleoli. Upon careful observation, spindle cells and infiltrating lymphocytes distributed around the nests of tumor cells can be seen (Figure 1D and E). However, it was difficult to distinguish morphologically whether these spindle cells are reactive fibrous tissue or tumor cells. Based on morphological features, poorly differentiated adenocarcinoma or squamous cell carcinoma, mesenchymal tumors, and malignant melanoma were considered. The immunohistochemical analysis showed that both the epithelioid and spindle cells were diffusely and strongly positive for CK7 (Figure 1F), while negative for TTF-1, Napsin A, P40, Melan A, S-100, SMA, and CD34. EBER in situ hybridization was negative as well. The pathological diagnosis at the initial presentation was poorly differentiated adenocarcinoma with focal sarcomatoid carcinoma.

Subsequently, the patient was treated with albumin-paclitaxel and nedaplatin regularly in outpatient. However, she was readmitted to the hospital 21 months after surgery because of the discovery of a nodule in the right diaphragmatic angle. Chest CT showed a nodule in the right diaphragmatic angle, measuring approximately 23 × 12 mm. Microscopically, the morphological characteristics of the nodule in the right diaphragmatic angle were similar to those of lung lesion. Nests of epithelioid tumor cells intermingled with spindle tumor cells as well as the special location reminded us of biphasic mesothelioma. Both epithelioid and spindle tumor cells were diffusely positive for calretinin and D2-40, focally positive for WT-1, GATA-3, and negative for Cytokeratin 5/6 (CK5/6), BerEP4, MOC31, and BAP-1, supporting the diagnosis of biphasic mesothelioma as well (Figure 2A–D). True for lung lesions is the same (Figure 2E–H). Finally, a diagnosis of biphasic mesothelioma was rendered. The patient received chemotherapy combined with pemetrexed and carboplatin. After 11 months of follow-up, the patient recovers well without recurrence or metastasis.

Discussion

In 1976, Harwood et al reported 6 patients with a unique type of primary lung cancer, which possessed a close resemblance to mesothelioma on radiological examination, clinical presentation, and gross examination, and proposed for the first time the name of "pseudomesotheliomatous carcinoma".[13] In turn, mesothelioma characterized by a broad spectrum of radiologic features, clinical manifestations, and morphological patterns can also mimic lung cancer[3] and, more rarely, resemble interstitial lung disease[14] or epithelioid hemangioendothelioma.[11] Especially when localized mesothelioma mainly involves the lung parenchyma, the results of chest radiography and macroscopic examination are highly suggestive of lung cancer, while histological examination is inconclusive. This is more likely to lead to misdiagnosis. Rossi G et al reported that a patient with a solid subpleural nodule that showed the predominant lepidic growth pattern microscopically was misinterpreted as primary lung cancer during an intraoperative examination.[3] Furthermore, Muramatsu Y et al reported a case of local mesothelioma with predominantly intrapulmonary growth and centrally hyaline stroma similar to epithelioid hemangioendothelioma.[11]

In addition, there is another rare intrapulmonary growth pattern of mesothelioma – diffuse intrapulmonary mesothelioma (DIM), which presents with diffuse lesions with predominantly intrapulmonary growth patterns and no or minimal

Table 1 Literature Review of Mesothelioma with a Predominantly Intrapulmonary Growth

Reference	Cases	Age(y)	Gender	Smoking history	Asbestos exposure	Sites	Pleural involvement	Symptoms	Morphological pattern	Follow-up time	Outcome
Mann S et.al[5]	4	70	Male	No	No	Lingula	Yes	Incidental	Epithelioid	35m	Relapse
		65	Male	No	No	Right upper lobe	Yes	Cough, fever	Epithelioid	39m	DOD
		42	Female	No	No	Right upper lobe	Yes	Incidental	Sarcomatoid	2m	LOF
		78	Female	No	No	Left lower lobe	Yes	Chest discomfort	Epithelioid	84m	Alive
Wang T et.al[6]	1	71	Male	/	No	Right lung	/	Weakness, nausea and poor appetite	Epithelioid	5m	DOD
Laforga J et.al[7]	1	54	Male	Yes	/	Right upper lobe	/	COPD	Biphasic	/	/
Rossi G et.al[3]	1	79	Male	Yes	No	Right upper lobe	/	Cough, dyspnea	Epithelioid	/	/
Guo X et.al[8]	1	80	Male	Yes	Yes	Right interlobar Pleural fissure	Yes	Incidental	Epithelioid	12m	Alive
Andrews W et.al[9]	1	82	Male	Yes	/	Left lower lobe	Yes	Left-sided back pain	Epithelioid	10m	Alive
Ertan G et.al[10]	1	44	Male	Yes	No	Left upper lobe lingular segment	/	Diplopia	/	a few months	DOD
Asioli S et.al[4]	2	69	Male	No	No	Left upper lung	Yes	Severe chest pain	Biphasic	7m	DOD
		62	Male	Yes	No	Left upper lobe	Yes	Incidental	Epithelioid	20m	Alive
Muramatsu Y et.al[11]	1	72	Male	Yes	Yes	Posterior basal segment (S10) of the right lung	Yes	Progressive dyspnea on exertion	Biphasic	/	/
Gotfried M H et.al[12]	1	61	Female	Yes	No	Left lower pulmonary field	Yes	Left pleural effusion	Epithelioid	3m	DOD
Current case	1	53	Female	No	No	Lower lobe of the right lung	Yes	Incidental	Biphasic	11m	Alive

Abbreviations: DOD, died of disease; LOF, lost of follow-up, m, month; y, years old; /, not known, COPD, chronic obstructive pulmonary disease.

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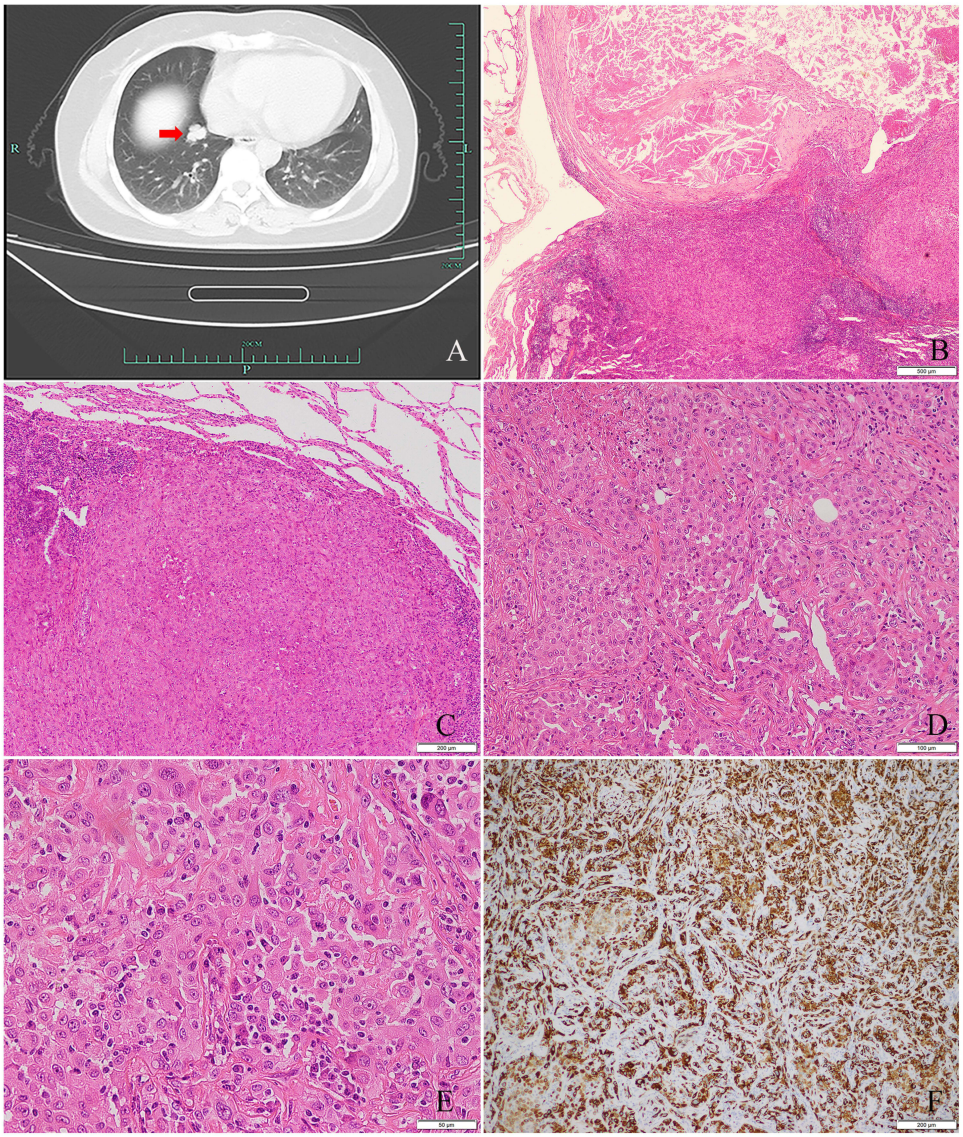

Figure 1 Chest CT image, morphological characteristics, and immunohistochemistry results of lung mass. Chest CT showed a lobulated nodule in the lower lobe of the right lung (red arrow points to the nodule) (**A**); Under low magnification, large areas of necrosis (**B**), well-defined borders, and nests of tumor cells (**C**) can be observed; Under high magnification, nested of epithelioid cells were intermingled with spindle cells and lymphocytes (**D**); epithelioid cells were characterized abundant eosinophilic cytoplasm, vacuolated nuclei, and obvious nucleoli (**E**); Both epithelioid and spindle cells were positive for CK7 (**F**). [figures magnification: B, 40x; C,F, 100x; D,200x; E,400x].

pleural involvement. DIM has a variety of histological growth patterns that are very similar to lung adenocarcinoma, such as lepidic, alveolar, papillary, or micropapillary.[15]

In these cases, imaging studies, gross examination, and clinical symptoms are of little help in distinguishing mesothelioma from lung adenocarcinoma, and similar histologic features can further be confusing. However, some clues to cytologic features, immunohistochemical results, and electron microscopic features can aid in confirming the diagnosis.

The common cytologic features of epithelioid mesothelioma are mildly atypical low columnar to cuboidal cells characterized by abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli. Meanwhile, the tumor cells of lung adenocarcinoma are characterized by a hobnail-like appearance with hyperchromatic nuclei and inconspicuous nucleoli.[16] Just like the case reported by Rossi G et al, even if a lepidic growth, the tumor cells presented with a globous appearance with abundant eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, which is different from the cytological features of lung adenocarcinoma, thus avoid misdiagnosis.[3]

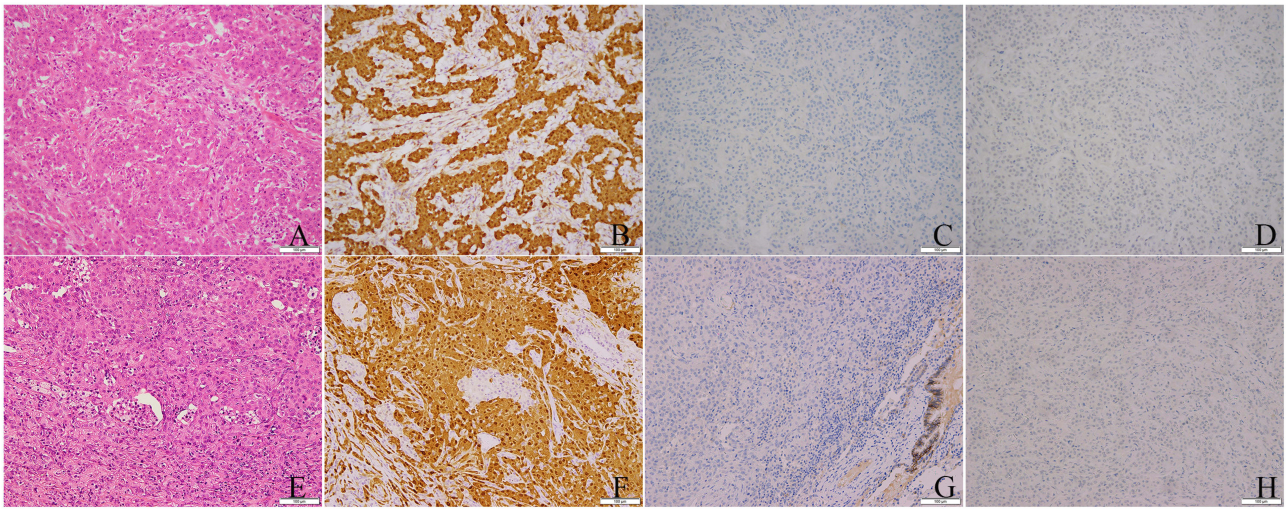

Figure 2 Morphological features and immunohistochemistry results of the right diaphragmatic angle and lung masses. Tumor cells of the right diaphragmatic angle were composed of epithelioid and spindle-shaped cells (**A**), as well as positive for calretinin (**B**), but negative for BerEP4 (**C**) and BAP-1 (**D**). True for lung is the same (**E**,H&E; F, calretinin, G, BerEP4; H, BAP-1). [figures magnification: A-H,200x].

Establishing mesothelial origin is the first and vital step in diagnosing mesothelioma. A panel of immunohistochemical markers of calretinin, CK5/6, WT-1 (nuclear staining only), and D2-40 (Podoplanin) is recommended for mesothelial origin. For epithelioid mesothelioma, the sensitivities of calretinin, CK5/6, WT-1, and D2-40 were 80–100%, 51–100%, 70–100%, and 80–100%, respectively, while for sarcomatoid mesothelioma were 50–60%, 13–29%, 10–45%, and 75–90%, respectively.[17] Furthermore, BAP-1 loss and homozygous *CDKN2A* deletion have a specificity of nearly 100% but low sensitivity in differentiating mesothelioma from benign mesothelial proliferation. BAP-1 loss has been detected in approximately 50–65% of pleural mesothelioma, with epithelial mesothelioma being the most common (61–77%), followed by biphasic mesothelioma (33–49%), and finally sarcomatoid mesothelioma (0–22%).[17] Similarly, the homozygous deletion of *CDKN2A* detected by fluorescence in situ hybridization (FISH) harbors only 50–65% sensitivity for pleural mesothelioma, 80–100% for sarcomatoid mesothelioma.[17] Loss of cytoplasmic MTAP staining could be a substitute for *CDKN2A* homozygous deletion, due to the frequent co-deletion of the *MTAP* and *CDKN2A* gene.[18]

Currently, two epithelial markers and two mesothelial markers are recommended for distinguishing epithelioid mesothelioma from cancer, such as lung adenocarcinoma.[19] Claudin-4 is the best epithelial marker to distinguish non-small cell lung cancer, including poorly differentiated lung adenocarcinoma, from epithelioid mesothelioma, with high specificity and comparable sensitivity, even in effusion cytology specimens.[20–22] Sarcomatoid mesothelioma is poorly sensitive to mesothelial markers and loss of BAP-1 nuclear staining. On the other hand, epithelial markers like claudin 4, BerEP4, and MOC31 are also less sensitive to sarcomatoid areas of sarcomatoid lung carcinoma.[19] These add difficulty in distinguishing sarcomatoid carcinoma and sarcomatoid mesothelioma. Focal positivity of TTF-1, Napsin A, or P40 may provide clues for the diagnosis of sarcomatoid lung carcinoma. Furthermore, diffuse expression of GATA-3 is found in 70% of sarcomatoid mesothelioma but lacks specificity.[19] Therefore, a panel of immunostains including multiple epithelial and mesothelial markers should be performed in rare cases that are difficult to diagnose.

It has been reported that in some diagnostically challenging cases, electron microscopy can provide valuable clues to confirm the mesothelial origin of tumor cells. The main distinctive ultrastructural features of epithelioid mesothelioma are abundant, branched, elongated microvilli, tight junctions, and giant desmosomes.[23] Fortarezza F et al reported a case of epithelioid pleural mesothelioma with a history of breast cancer, whose immunohistochemical results were not decisive for the distinction of mesothelioma or breast cancer metastasis, which was diagnosed by electron microscopy.[23]

Mesothelioma has a poor prognosis and few treatment options. Currently, trimodal treatment consisting of surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy are indicated for resectable mesothelioma, particularly in patients without nodal involvement.[24] According to the 2023 Chinese expert consensus on the treatment of malignant pleural mesothelioma, the first-line chemotherapy regimen for mesothelioma is a combination of pemetrexed and cisplatin or a triple-

drug combination of pemetrexed, cisplatin and bevacizumab.[25] After a complete surgical resection of the lesions, our patient received a chemotherapy regimen of carboplatin combined with pemetrexed and is currently recovering well.

In conclusion, we reported a case with biphasic mesothelioma, predominantly intrapulmonary growth, misdiagnosed as poorly differentiated adenocarcinoma with focal sarcomatoid carcinoma. The rarity of this entity and the similarities to primary lung cancer concerning imaging and even histological features make diagnosis challenging. However, some subtle cytologic features, selection of immunohistochemical markers, and electron microscopy can aid in the definite diagnosis of diagnostically challenging cases.

Abbreviations

CT, computed tomography; DIM, diffuse intrapulmonary mesothelioma; CK5/6, cytokeratin 5/6; FISH, fluorescence in situ hybridization.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Guiqian International Hospital. Our institution approved the publication of the case details. Written informed consent has been obtained from the patient for the release of relevant clinical and imaging data from their cases, including consent for the publication of the case details.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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