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A Case of Lung Cancer Associated with Minute Pulmonary Meningothelial-like Nodules: Risk for Misstaging Intraoperatively

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Minute pulmonary meningothelial-like nodules (MPMNs) are rare lesions of the pulmonary interstitium. They comprise small nests of monomorphic round to spindle cells, likely reactive in nature. Although multiple lesions with unilateral involvement of one or even all lobes of the same lung have been described, they are most often single and their average size is 1-3 mm in diameter. Computed tomography (CT) scan did not contribute to the detection of these small pulmonary lesions. These nodules are generally asymptomatic and are usually found incidentally at autopsy or in surgical specimens resected for unrelated causes. Here, we report a patient with solitary pulmonary nodule receiving lobectomy. Intraoperatively, the surgeon found a grey white firm tumor about 1.6×1.2×1 cm in size and four tiny firm satellite nodules in the same lobe. Because of different AJCC pathological stage, it is necessary to examine whether the tumor nodules in the same lobe are separate or not. The intraoperative frozen sections reported adenocarcinoma for the largest one and benign for the other four smaller nodules. The final diagnosis is moderately differentiated adenocarcinoma of lung with pulmonary meningothelial-like nodules. The AJCC pathological staging is pT1aN0M0, stage IA, and mis-staging as stage IIB has been avoided.

Key words: minute pulmonary meningothelial-like nodules, Lung, Progestrone receptors, Immunohistochemistry

INTRODUCTION

Minute pulmonary meningothelial-like nodules (MPMNs) of the lung, previously known as multiple minute chemodectomas (chemodectomatosis), are tiny perivenular, interstitial nodules composed of small, oval to spindle cells arranged in nests not in contact with the air spaces.[1,2] MPMNs are seen in patients 12 to 91 years of age, mostly in the seventh decade.[3] The majority of the cases are seen in women (84%),[3] and in some studies they are seen three times more often in the right lung than left.[4] These lesions have been considered to be miniature carotid body tumors, due to their close association with pulmonary veins.[5,6] However, electron microscopy has failed to reveal the characteristic dense-core granules of chemoreceptor cells instead of cytoplasmic tangles of fibrils and complex interdigitating cell processes connected by desmosomes.[1] These nodules lack neuroendocrine features, differ from mesothelium, and resemble closely meningothelial cells.[7] Previous studies demonstrated an origin from smooth muscle cells or myofibroblasts[8,9] and an origin from arachnoid-like cells of the lung has also been suggested.[4,7] MPMNs have recently been reported to be immunoreactive for progesterone receptors, suggesting their close resemblance to arachnoid cells and a role for sex-steroid hormones in their development.[10,11] During a lung cancer surgery, if these tiny nodules are found in the same lobe, in a different ipsilateral lobe, or in a contralateral lobe, a correct pathological frozen section diagnosis is necessary to confirm the stage. Here, we reported a case of adenocarcinoma of lung-associated MPMNs in the same lobe, AJCC pathological staging pT1aN0M0, stage IA. If the MPMNs were recognized as metastases during surgery, the patient's stage could be misclassified as T3. In addition, if MPMNs were found in a different ipsilateral lobe or in a contralateral lobe, attention should be paid to avoid misstaging as T4 or M1, respectively.

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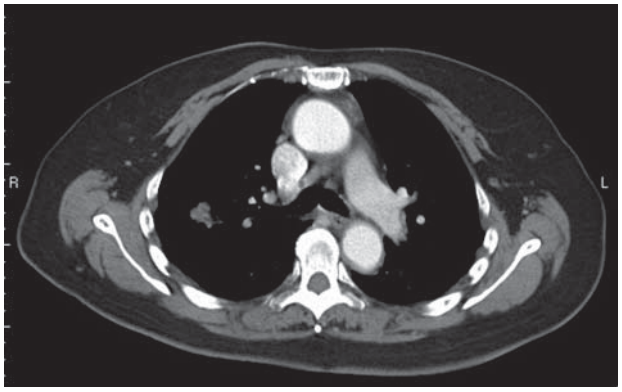

Fig. 1 Computed tomography (CT) of the chest showed a lobulated soft tissue nodule about 1.6 cm in size at right upper lobe (RUL) which was highly suspicious of bronchogenic cancer and several soft tissue nodules in the lower mediastinum, PTRC space, and prevascular region (maximal short axis: about 1-cm) which were considered as malignant lymphadenopathy. No other small pulmonary lesion could be detected.

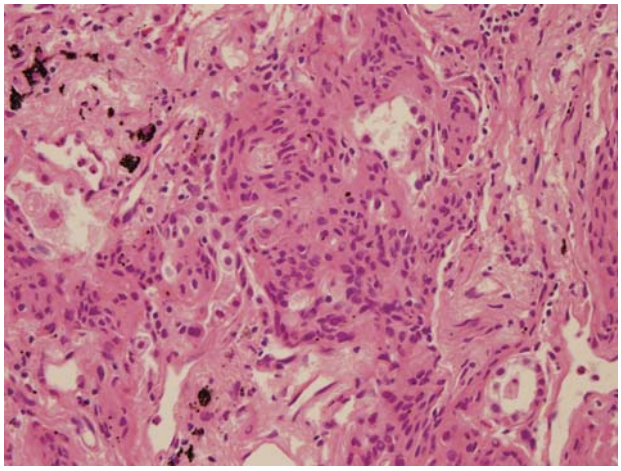

Fig. 2 The tiny nodules showed interstitial round to spindle cells distributed in a perivascular network, with finely granular chromatin (hematoxylin and eosin; original magnification, ×400)

CASE REPORT

A previously healthy 69-year-old woman with traumatic compression fracture of T12 received vertebroplasty with bone cement. Before her current presentation, the patient was independent and mobile, able to perform most of her daily life activities unaided. She is a nonsmoker and with no history of previous pulmonary infectious disease. There was no history of recent weight loss.

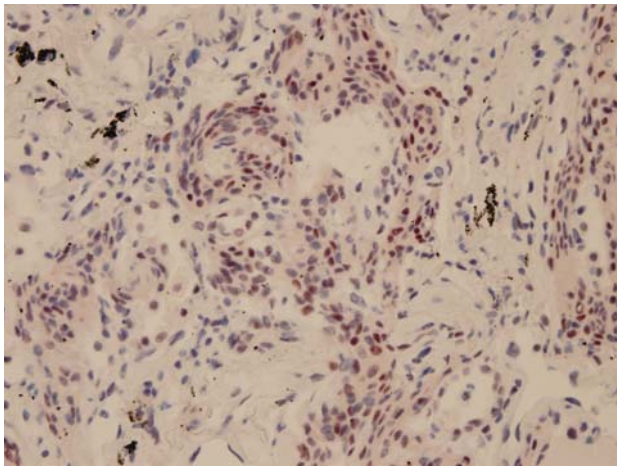

Fig. 3 The tiny nodules showed positive nuclear immunoreacting by anti-progesterone receptor antibody. (×400)

Laboratory findings were unremarkable. Incidentally, a solitary pulmonary nodule was found in chest X-ray. Furthermore, computed tomography (CT) of the chest showed a lobulated soft tissue nodule about 1.6 cm in size at the right upper lobe (RUL), which was highly suspicious of bronchogenic cancer, and several soft tissue nodules about 1 cm in diameter in the lower mediastinum, PTRC space, and prevascular region, which were considered as malignant lymphadenopathy. No other small pulmonary lesions could be detected (Fig. 1). Then she received right limited thoracotomy through the 5th intercostal space with lobectomy of RUL and dissection of mediastinal lymph nodes.

Intraoperatively, a grey white firm tumor about 1.6 ×1.2×1 cm in size and four tiny, tan to yellow, firm satellite nodules were found. The specimen from lobectomy was sent for frozen section to examine whether the tumor nodules in the same lobe were separate or not. Microscopically, the large tumor showed moderately differentiated adenocarcinoma with bronchioalveolar pattern. However, the four tiny nodules revealed interstitial infiltration of round to spindle cells distributed in a perivascular network, with finely granular chromatin (Fig. 2). Dissected lymph nodes showed no tumor metastasis. Immunohistochemical studies revealed that the glandular tumor cells were positive for thyroid transcription factor-1 (TTF-1) and cytokeratin 7. The interstitial round-to-spindle cells were positive for progesterone receptor (Fig. 3), vimentin, epithelial membrane antigen (EMA), and CD56 but negative for estrogen receptor, thyroid transcription factor-1, HMB-45, cytokeratin 7,

CD10, smooth muscle actin, and CD68. In addition, the magnetic resonance image (MRI) of the brain revealed no evidence of meningioma or metastatic lesion. According to the histological and immunohistological findings, the final diagnosis was moderately differentiated adenocarcinoma of lung with pulmonary meningothelial-like nodules, AJCC pathological staging pT1aN0M0, stage IA.

DISCUSSION

MPMNs were first described by Korn et al. in 1960.[6] According to their morphologic features and close relationship with blood vessels, they were initially classified as chemoreceptors and designated as "minute pulmonary tumors resembling chemodectomas". Subsequently, ultrastructural and immunohistochemical studies revealed that they have similar features with meningothelial cells and the term "minute pulmonary meningothelial-like nodules" was recommended by Gaffey et al. in 1988.[7] Characteristics of these tumors include interstitial location, round-to-spindle tumor cells arranged in a nesting pattern, lateral capillary displacement secondary to expansive growth within the alveolar septa, and close association with pulmonary venules.[7]

The exact origin and pathogenesis of MPMNs is still unknown. Patients with these lesions are associated with pulmonary thromboemboli, thus suggesting that they were related to ischemia secondary to vascular occlusion.[5,12] Niho et al. concluded that since not all lesions showed clonal expansion, they most likely represented a reactive proliferation rather than a clonal neoplastic process.[10] In 2004, Ionescu et al. compared minute pulmonary meningothelial nodules with intracranial meningiomas by mutational analysis and found loss of heterozygozity alterations at different chromosomal loci between the two conditions. Therefore, they suggested that the two processes were unrelated and that the former represents a reactive condition.[13]

Approximately two-third of the cases reported have been identified at autopsy and one-third, from surgical specimens. The incidence of these nodules has been reported to range from one case in 300[6] to one in 25.[12] These lesions are most common in the sixth decade of life and reveal female predominance.[7] The percentage of lung cancer associated with MPMN is 1.1%.[11] MPMNs were found more often in patients with malignant pulmonary tumors than in those with benign disease.[14] In particular, MPMNs were found more often in patients with lung adenocarcinoma than with other primary pulmonary malignant tumors.[14] The clinical conditions that are frequently associated with meningothelial nodules include malignancy, pulmonary thromboemboli, and chronic ischemic heart disease.[15]

Pulmonary meningothelial-like nodules have to be histologically distinguished from pulmonary tumorlets.[16] Pulmonary "tumorlets" show aggregation of neurosecretory cells around terminal bronchioles, which can be confused with meningothelial nodules on scanning magnification. Cytologically, the cells of tumorlets represent higher nuclear-cytoplasmic ratios with more stippled chromatin pattern, and are more elongated, instead of having an epithelioid appearance. Immunohistochemically, tumorlets reveal weak cytoplasmic reactivity for cytokeratin and are also immunoreactive with neuroendocrine markers such as chromogranin A, synaptophysin, and neuron-specific enolase, allowing for correct discrimination from MPMNs.[16]

The expression of progesterone receptor in MPMNs emphasizes their close resemblance to meningioma cells, which also reveal the abundant expression of progesterone receptors[17,18], and tumor cells immunoreactive for progesterone receptors have also been found in pulmonary meningiomas.[19] The similar expression of progesterone receptors also indicates a sex-steroid hormone-mediated control of the growth of MPMNs from arachnoid cells of the pulmonary interstitium. Primary meningiomas of the lung and MPMNs also have similar characteristics, showing consistent immunoreactivity for vimentin and epithelial membrane antigen, suggesting that these small lesions may be the predecessor of pulmonary meningiomas.[20] In addition, recent research revealed that positive staining for CD56 in MPMNs lends further support to meningothelial differentiation.[14] Despite these observations, the occurrence of meningothelium in the lung and the relationship between MPMNs and underlying lung disease are still unknown.

CONCLUSION

Minute pulmonary meningothelial-like nodules are often associated with clinical conditions, including malignancy, pulmonary thromboemboli, and chronic ischemic heart disease, and may be the forerunner of pulmonary meningiomas. If the patient's lung biopsy shows these lesions, further examination to rule out the association with other diseases should be performed. In addition, it is necessary to differentiate the separate tumor nodules to obtain correct staging.

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