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CASE REPORT

Pathological diagnosis and immunohistochemical analysis of minute pulmonary meningothelial-like nodules: A case report

Xin Ruan, Liu-Sheng Wu, Zheng-Yang Fan, Qi Liu, Jun Yan, Xiao-Qiang Li

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Abstract

BACKGROUND

Minute Pulmonary Meningothelial-like Nodules (MPMNs) are rare benign pulmonary nodules, which are more common in elderly women and have a higher detection rate in lung tissues of patients with lung malignant diseases. Its origin is not yet clear. At present, there are few reports on the diagnostic methods such as imaging and pathological manifestations of MPMNs. This article reports a 70-year-old female patient with pulmonary adenocarcinoma combined with MPMNs and reviews of the relevant literature.

CASE SUMMARY

A 70-year-old women was admitted to our institution with feeling sour in her back and occasional cough for more than 2 mo. Computerized electronic scanning scan and 3D reconstruction images in our institution showed there were multiple ground-glass nodules in both of her two lungs. The biggest one was in the apicoposterior segment of left upper lobe, about 2.5 mm × 9 mm in size. We performed thoracoscopic resection of the left upper lung apicoposterior segment of the patient, and the final pathological report was minimally invasive adenocarcinoma. Re-examination of high resolution computed tomography 21 mo after surgery showed multiple ground-glass nodules in both lungs, and a new ground-glass nodule was found in the superior segment of the right lower lobe. We took pathological biopsy of the right upper lung and right lower lung nodules for the patient under thoracoscopy. The histomorphology of the right lower lobe nodule showed multiple lesions in the lung tissue, and the small foci in the alveolar

septum were distributed in mild form of the aggregation of short spindle cells. The immunohistochemistry showed that the lesion was epithelial membrane antigen (EMA) (+), somatostatin receptor 2a (SSTR2a) (+), S-100 (-), chromogranin A (-), Syn (-), cytokeratin (-) and HMB-45 (-). The final diagnosis was minimally invasive adenocarcinoma, accompanied by MPMNs. We recommend that patients continue to receive treatment after surgery and to do regular follow-up observations.

CONCLUSION
The imaging manifestations of MPMNs are atypical, histomorphology and immunohistochemistry can assist in its diagnosis. This article reviews the relevant literature of MPMNs immunohistochemistry and shows that MPMNs are positive for EMA, SSTR2a, and progesterone receptor.

Key Words: Lung; Pathology; Immunohistochemistry; Multiple pulmonary nodules; Minute pulmonary meningothelial-like nodules; Case report

Core Tip: Minute Pulmonary Meningothelial-like Nodules (MPMNs) are rare benign pulmonary nodules, which have a higher detection rate in lung tissues of patients with lung malignant diseases. The diagnosis of MPMN is difficult and often results in unnecessary or inappropriate treatment. Therefore, it is particularly important to correctly identify and diagnose the disease. This article reports a 70-year-old female patient with pulmonary adenocarcinoma combined with MPMNs and reviews of the relevant literature in order to better identify and diagnose MPMN.

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INTRODUCTION

Minute pulmonary meningothelial-like nodules (MPMNs) are rare benign pulmonary nodule, which is often found accidentally in pathological specimens after surgical resection or autopsy due to other lung diseases[1,2]. Studies have shown that MPMNs are common in women, especially elderly women[3]. MPMNs are often manifested as single or multiple small lung lesions, which can be distributed anywhere in the lungs, and are often found in combination with other lung diseases[4,5]. Unlike benign lung diseases, MPMNs are more likely to be detected in lung malignant tumors, and the detection rate in pulmonary adenocarcinoma is higher than other lung diseases[6]. Because the lesions of MPMNs are very small and have no characteristic imaging features, it is difficult to diagnose, or because the imaging appearance is very similar to the misdiagnosis of malignant nodules, unnecessary or inappropriate treatment may be caused[7,8]. Therefore, it is particularly important to correctly identify and diagnose this disease. In this article, we reported a case of lung microinvasive adenocarcinoma with MPMNs, and reviewed the clinical manifestations, imaging features, pathological diagnosis and immunohistochemistry of MPMNs to help better identify and diagnose MPMNs.

CASE PRESENTATION

Chief complaints
Experiencing consistent back pain and an intermittent cough for over two months.

History of present illness
A 70-year-old female patient was admitted to our institution with feeling sour in her back and occasional cough for more than 2 mo. No other special clinical symptoms and signs were complained. Before admission, a computed tomography (CT) scan of her chest revealed multiple pulmonary nodules in both left and right upper lungs. No special treatment was given.

History of past illness
A history of hypertension, regular oral antihypertensive medication treatment, and well-controlled blood pressure.

Personal and family history
Nothing special.

Physical examination

Nothing special.

Imaging examinations

CT scanning scan and 3D reconstruction images showed that there were a ground-glass nodule with rough edges (about 2.5 mm × 9 mm in size) in the apicoposterior segment of left upper lobe, a ground-glass nodule with clear edges (about 6 mm × 4 mm in size) in the lateral basal segment of left lower lobe and ground-glass density shadows were seen in the apex of right lungs, with blurred edges, and the range was approximately 9 mm × 6 mm (Figure 1).

We performed thoracoscopic resection of the left upper lung apicoposterior segment of the patient. During the operation, the rapid freezing pathology suggested that the carcinoma in situ was accompanied by multifocal microinfiltration. Thus, we performed preventive dissection of the mediastinum and hilar lymph nodes for pathological examination. Postoperative pathological report was Minimally Invasive Adenocarcinoma, no metastatic in each group of lymph nodes.

Re-examination of chest CT scan and high resolution computed tomography (HRCT) 21 mo after surgery showed: postoperative changes in the left upper lung, a pure ground-glass nodule in the apical segment of the right upper lobe (about 13.2 mm × 5.6 mm in size), a mixed ground glass in the superior segment of the right lower lobe Nodules (about 4.3 mm × 2.9 mm in size), a pure ground-glass nodule in the lateral basal segment of the left lower lobe (about 7.2 mm × 5.3 mm in size) (Figure 2), and there are other ground-glass nodules about 2-4 mm in diameter in the lower lobe of both lungs. We took pathological biopsy of the right upper lung and right lower lung lesions for the patient under thoracoscopy.

Laboratory examinations

The histological findings of the right upper lobe nodule showed that cancer cells grew in a monolayer, with large nuclei, rich cytoplasm, mitotic figures were not easy to see, focal septal widening, interstitial fiber and fibroblast proliferation, dense proliferation or clustered proliferation of tumor cells, nucleoli was visible.

The immunohistochemistry experimental protocol for this project comprises the following key steps: Sample fixation, dehydration, paraffin embedding, sectioning, antibody staining, and result analysis. Firstly, tissue samples are subjected to fixation, followed by dehydration and paraffin embedding to prepare paraffin sections. Subsequently, specific antibodies such as CK7, thyroid transcription factor-1 (TTF-1), and EMA are used for staining, followed by microscopic observation and image recording. Finally, result analysis and pathological diagnosis are conducted based on the staining outcomes. Immunohistochemistry experiments are a crucial step in the study, utilized to identify immune markers, thereby supporting accurate disease diagnosis and classification.

The pathological manifestation of the right lower lobe nodule was no obvious nodule was visible to the naked eye. Histomorphology showed multiple lesions in the lung tissue, with diameter of 0.5-1.8 mm, and the small foci in the alveolar septum were distributed in mild form of the aggregation of short spindle cells (Figure 3). And the Immunohistochemistry showed that the lesion was positive for Epithelial membrane antigen (EMA) and somatostatin receptor 2a (Figure 4), and negative for S-100, Chromogranin A (CgA), Synaptophysin (Syn), Cytokeratin (CK) and HMB-45.

FINAL DIAGNOSIS

The pathological diagnosis was Micro-invasive Adenocarcinoma with Minute Pulmonary Meningothelial-like Nodules.

TREATMENT

We recommend that patients continue to receive treatment after surgery and to do regular follow-up observations.

OUTCOME AND FOLLOW-UP

The patient recovered after operation, and no recurrence was found after 3 mo.

DISCUSSION

MPMNs, fist describe by Korn *et al*[9] in 1960, who considered they might be kinds of endocrine tumor called *Minute Pulmonary Chemodectoma* based on its cytologic characteristics, arrangement of cells and special relationship to vessels, have been considered to be benign lung lesions. Therefore, Gaffey *et al*[10] renamed it as "Minute Pulmonary Meningothelial-like Nodules". Many subsequent studies have shown that it lacked the immunohistochemical and ultrastructural characteristics of endocrine cells, and did not contain endocrine particles[11,12]. MPMNs patients often have no special symptoms or mild symptoms, or show corresponding clinical symptoms due to other lung diseases[13]. If MPMNs are diffuse in the patient's lungs and involve a large amount of lung tissue, it is called *Diffuse Pulmonary Meningotheliomatosis*,

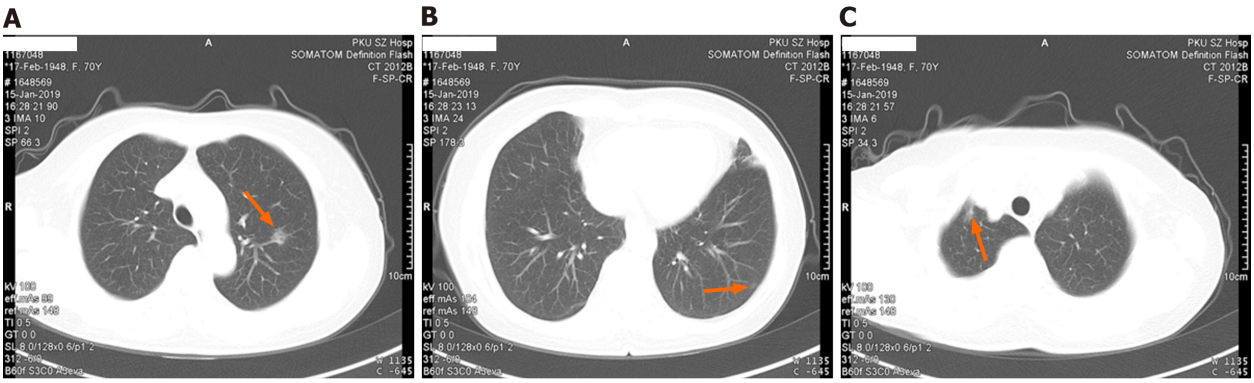

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Figure 1 Computed tomography examination before surgery. A: A ground-glass nodule with rough edges (about 2.5 mm × 9 mm in size) in the apicoposterior segment of left upper lobe; B: A ground-glass nodule with clear edges (about 6 mm × 4 mm in size) in the lateral basal segment of left lower lobe; C: Ground-glass density shadows were seen in the apex of right lungs, with blurred edges, and the range was approximately 9 mm × 6 mm.

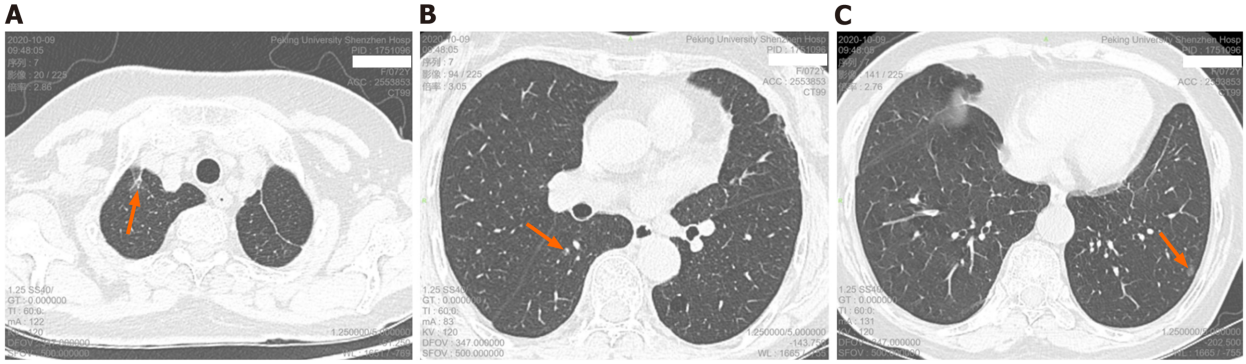

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Figure 2 High-resolution computed tomography 21 mo after surgery. A: A pure ground-glass nodule in the apical segment of the right upper lobe (about 13.2 mm × 5.6 mm in size); B: A mixed ground glass in the superior segment of the right lower lobe Nodules (about 4.3 mm × 2.9 mm in size); C: A pure ground-glass nodule in the lateral basal segment of the left lower lobe (about 7.2 mm × 5.3 mm in size).

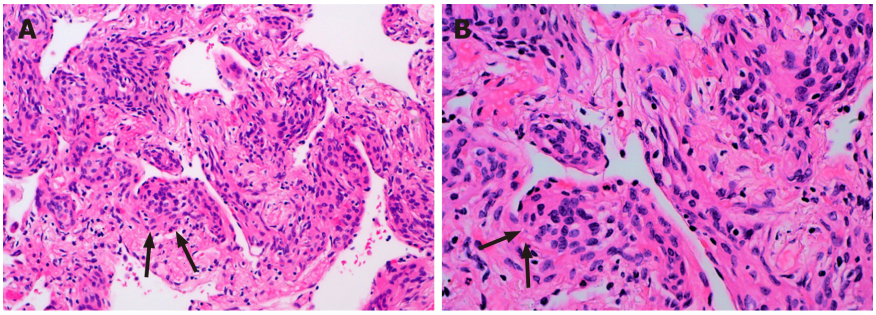

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Figure 3 Histomorphological manifestation of right lower lobe nodule was the small foci in the alveolar septum were distributed in mild form of the aggregation of short spindle cells. A: Original magnification 200×; B: Original magnification 400×.

patients will have more serious respiratory symptoms, such as cough, chest tightness, dyspnea or restrictive lung disease [14]. The CT characteristics of MPMNs are very similar to lung malignant lesions. In most cases, they appear as single or multiple small nodules in the lung, usually less than 10mm in diameter. Kuroki *et al*[15] compared the microscopic examination of MPMNs and believed that HRCT The observed ground glass attenuation may be related to the expansion of the alveolar wall caused by the spread of the lesion along the alveolar wall. The imaging features are ground glass or solid nodules, some lesions may be cystic or hollow, but usually not accompanied by calcification or necrosis[16-18]. HRCT is also used for lung imaging because it can describe the small areas of ground glass attenuation. MPMNs often show ground glass attenuation on HRCT. Due to its lack of characteristic imaging findings, clinical diagnosis is difficult and may lead to inappropriate treatment cause by misdiagnosis. Therefore, fine-needle aspiration or bronchoscopy or

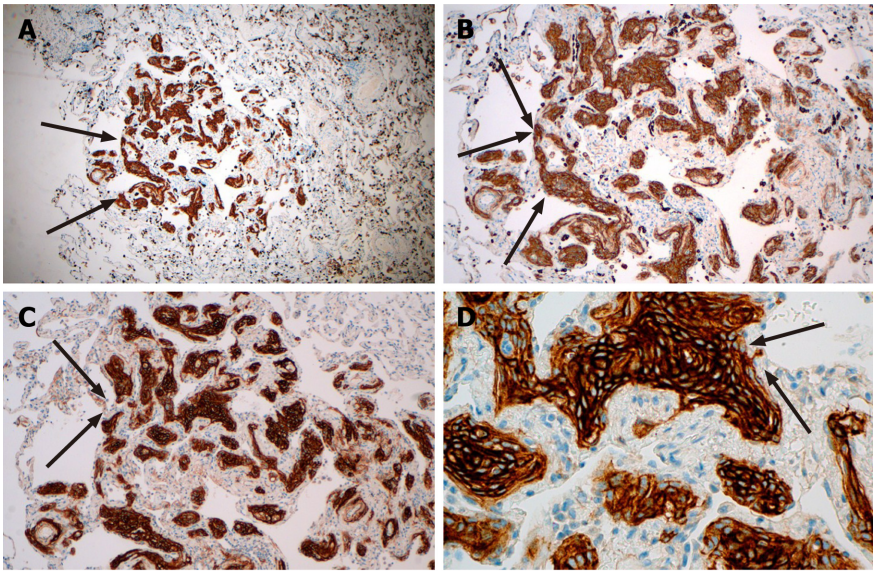

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Figure 4 The Immunohistochemistry showed that the lesion was positive for epithelial membrane antigen and somatostatin receptor 2a. A: The lesion was positive for epithelial membrane antigen, original magnification 200×; B: The lesion was positive for epithelial membrane antigen, original magnification 400×; C: The lesion was positive for somatostatin receptor 2a, original magnification 200×; D: The lesion was positive for somatostatin receptor 2a, original magnification 400×.

thoracoscopic biopsy under appropriate conditions can detect and identify the disease early, help identify malignant pulmonary nodules, and avoid unnecessary treatments. However, because the nodules are generally small, it is difficult to perform a needle biopsy in terms of operation and technology. Pathological biopsy is the gold standard for diagnosis. On gross specimens, MPMNs are often too small to be observed with the naked eye, or the lesions appear as yellow or gray-white solid masses with interstitial nodular hyperplasia[19]. It can be seen under the microscope that MPMNs lesions are mostly located in the alveolar septum, which is composed of oval or fusiform epithelioid cell nests gathered into small foci and arranged in a whirlpool around the central venule. The alveolar septum is often widened due to the presence of the lesion, and there are certain degree of fibrosis.

The immunohistochemistry markers selected for this project include CK7, TTF-1, and EMA, which play crucial roles in pathological diagnosis. CK7 is a cytokeratin commonly expressed in epithelial cells, particularly in tissues like the lung, stomach, and biliary tract, making it highly useful for determining the epithelial origin of tumor cells. TTF-1 is a nuclear transcription factor, highly expressed in normal lung tissue, and frequently found in lung adenocarcinomas, aiding in distinguishing lung cancer from other malignancies. EMA is a membrane-bound antigen specific to epithelial cells, providing valuable assistance in confirming epithelial lesions. The selection of these immunohistochemistry markers is based on their specific expression in lung and epithelial cells, aiding in the identification and classification of MPMNs. Immunohistochemistry experiments rely on the specificity of these markers, assisting in determining pathological types, guiding treatment strategy selection, and providing critical insights into disease progression and prognosis. Therefore, immunohistochemistry plays an indispensable role in MPMN pathological diagnosis, enhancing diagnostic accuracy and precision in clinical management.

The diagnosis of MPMNs needs to be confirmed by immunohistochemistry. Table 1 shows the literature review of MPMNs immunohistochemistry[20]. We can see that almost all MPMNs immunohistochemically showed positive responses to Vimentin, EMA, SSTR-2a, and CD56, and more than half of MPMNs were positive to PR; while negative for S-100, CK, Actin, HMB- 45. Syn and Cga. For NSE, the study[21] found that almost all MPMNs were weakly positive for NSE, but they believed that this behavior was non-specific because normal alveolar epithelium was also weakly positive for the antigen. The source of MPMNs is still unclear. They may come from reactive rather than neoplastic origin. At present, most studies believe that there are similarities between pulmonary meningeal epithelioid nodules and meningiomas in their histological, ultrastructural and immunohistochemical characteristics[22]. According to the research of Higuchi *et al*[23], both MPMNs and meningioma of the central nervous system may be related to the ectopic or deletion of neurofibromatosis type-2 gene, indicating that they may have a common genetic changes. However, a genotypic comparison between MPMNs and meningiomas showed that MPMNs lacked the molecular changes associated with loss of heterozygosity on chromosome 22 in meningioma cells. Imaging examination of the heads of most patients with MPMNs did not find signs of meningioma in some studies, indicating that it is not a metastasis of meningioma. At present, most studies believe that it is very similar to meningeal epithelial cells or meningioma cells. Multiple studies have shown that almost all MPMNs are positive for Vimentin and EMA phenotypes, which are very similar to meningeal epithelial cells or meningioma cells. Almost all MPMNs were positive for progesterone receptors and they believed that this once again proved the similarity between MPMNs and meningeal epithelial cells or meningioma cells, because progesterone receptors are in normal meningeal epithelial cells and the expression in meningiomas has been well confirmed, and it is believed that there might be lung meningeal epithelioid cells in normal lung tissues, while proges-

Table 1 Literature review of the immunohistochemistry of minute pulmonary meningothelial-like nodules

Ref.	Number of nodules/lesions evaluated	Immunophenotype											
		EMA	VIM	PR	CD56	SSTR2a	CK	Syn	Actin	S100	HMB-45	NSE	CgA
Bernabeu *et al*[13], 2013	1	1/0[a]	1/0	1/0	1/0	–	0/1	0/1	0/1	–	0/1	–	0/1
Lee *et al*[18], 2013	1	1/0	1/0	1/0	1/0	–	0/1	–	–	–	–	–	–
Tao *et al*[4], 2019	39	29/10	–	11/28	–	39/0	0/39	0/39	–	0/39	–	–	0/39
Niho *et al*[6], 1999	29	22/0[b]	29/0	9/9	–	–	0/29	2/27	–	10/11	0/28	25/4	1/28
Pelosi *et al*[21], 2002	9	9/0	9/0	9/0	–	–	0/6	0/6	0/6	0/6	0/6	–	–
Peng *et al*[8], 2019	8	7/0	8/0	6/0	–	–	0/2	–	–	–	–	–	–
Agozzino *et al*[19], 2006	1	1/0	1/0	0/1	–	–	0/1	0/1	0/1	0/1	–	0/1	0/1
Kfour *et al*[20], 2012	2	2/0	2/0	2/0	–	–	–	–	–	–	–	–	–
Torikata *et al*[5], 1990	24	0/18	24/0	–	–	–	0/17	–	0/21	0/16	–	0/17	–
Gaffey *et al*[10], 1988	14	12/2	10/2	–	–	–	0/14	–	0/7	0/14	–	0/14	–
Harada *et al*[7], 2019	1	1/0	1/0	1/0	1/0	NR	NR	NR	NR	NR	NR	NR	NR
Total	129	85/30	86/2	40/38	3/0	39/0	0/110	2/74	0/36	10/87	0/35	25/36	1/68

[a]Number of lesions with positive immunocytochemical staining/negative immunocytochemical staining.

[b]Not all nodules/lesions are evaluated for specific immunophenotypes.

EMA: Epithelial membrane antigen; VIM: Vimentin; PR: Progesterone receptor; SSTR2a: Somatostatin receptor 2a; CK: Cytokeratin; Syn: Synaptophysin; NSE: Neuron-specific enolase; CgA: Chromogranin A; NR: Not reported; –: Not evaluated.

terone probably played an important role in controlling their growth. In addition, the retrospective analysis of the immunophenotypes of MPMNs including SSTR-2a, and found that all MPMNs lesions expressed constant expression of SSTR-2a, which once again proved MPMNs immunohistochemical characteristics similar to meningeal epithelial cells.

In terms of treatment, MPMNs are benign lesions and can be treated conservatively, with long-term follow-up without further intervention. The study of Lin *et al*[24] found that patients with MPMNs surgically removed can get a good prognosis, but they believe that compared with the trauma of surgery, long-term follow-up observation may benefit more. However, MPMNs often appear along with other lung diseases. Therefore, it is particularly important to detect and identify their accompanying diseases in time and carry out corresponding clinical interventions. In general, the clinical manifestations of MPMNs are not typical. Image characteristics show single or multiple ground-glass nodules in the lungs with a diameter of no more than 10mm. Pathological biopsy is the gold standard for diagnosis. Immunohistochemically shows positive for Vimentin, EMA, SSTR-2a, CD56, PR, but negative for S-100, CK, Actin, HMB-45, Syn, and Cga. Its source is currently unclear, but most studies currently believe that it is similar to meningeal epithelial cells or meningioma cells. MPMNs are benign lesions and can be treated conservatively, but they often appear along with other lung diseases. Therefore, timely detection and identification of MPMNs and their accompanying diseases, and corres-

ponding clinical interventions are also particularly important.

CONCLUSION

Through a comprehensive pathological diagnosis and immunohistochemical analysis of one case of MPMNs, we delved into the characteristics of this rare condition. The results demonstrated a certain diversity in immunohistochemical markers for MPMNs, with CK7, TTF-1, and EMA playing crucial roles in pathological diagnosis. Literature review further supported our findings. In conclusion, the diagnosis and differential diagnosis of MPMNs remain challenging and require the integration of various clinical and immunohistochemical information to ensure accurate diagnosis and selection of treatment strategies. This study provides valuable insights and references for the clinical management of MPMNs.

FOOTNOTES

Co-first authors: Liu-Sheng Wu, Zheng-Yang Fan, and Qi Liu.

Co-corresponding authors: Jun Yan and Xiao-Qiang Li.

Author contributions: Ruan X and Wu LS analyzed the data and wrote the paper; Li XQ designed the research; Yan J guided the research; Liu Q and Fan ZY collected and downloaded the data of our research; All the authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work; At the beginning, the paper was designed and written by Ruan X and Wu LS as co-first authors; Later, in the first revision, Fan ZY provided the imaging image support and analysis, and Liu Q provided the experimental analysis of HE staining and immunohistochemistry in pathology; Therefore, they all have equally important contributions.

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