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Original Article

Primary pulmonary myxoid sarcoma: report of one case and literature review

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Abstract: Background: Primary pulmonary sarcoma is extremely rare and mostly metastatic, and primary pulmonary myxoid sarcoma PPMS is a rare low-grade malignant sarcoma. The clinical manifestations of PPMS patients are relatively non-specific, sometimes found by physical examination. We report a case designed to explore the clinicopathologic features, diagnosis, and differential diagnosis of primary pulmonary myxoid sarcoma (PPMS). A 44-year-old man was found to have a primary myxoid sarcoma in the upper right lung on physical examination. The patient did not have any symptoms of discomfort. Histologically, the tumors had well-defined borders, and with grayish-white or grayish red cut surfaces. Under the microscope, the tumor cells were composed of oval and spindle cells arranged in a network or strips in a mucus-like stroma. Immunohistochemically, neoplastic cells showed diffuse and strong vimentin expression and focal weak EMA, and Bcl-6 staining. The expression of AE1/AE3, ALK, CD34, CD68, SMA, and CD99 were all negative. The Ki-67 index was low. Conclusion: PPMS is a rare low-grade malignant primary pulmonary sarcoma without characteristic clinical symptoms and difficult to diagnose. It is mainly diagnosed by immunohistochemistry and genetic testing.

Keywords: Primary pulmonary myxoid sarcoma, FISH, EWSR1 gene, immunohistochemistry

Introduction

Primary pulmonary myxoid sarcoma is a relatively rare low-grade sarcoma. In 1999, it was first reported by Nicholson with 2 cases of low-grade mucinous tumor in the bronchus [1]. In 2011, Thway found through further research that the tumor has a characteristic chromosomal translocation of t (2; 22) (q33; q12), which leads to the EWSR1-CREB1 fusion. Thus he reclassified it as the EWSR-CREB1 fusion gene of primary pulmonary myxoid sarcoma [2]. Currently the tumor was first incorporated into the pulmonary mesenchymal tumor in the 2015 edition of the World Health Organization lung tumor tissue classification [3]. Primary myxoid sarcoma of the lung is clinically nonspecific, and sometimes it can be found only by physical examination. To date, there were only 37 cases reported worldwide and most cases occurred in adult patients [1, 2, 4-13]. In this paper, we present a 44-year-old male with PPMS in the right upper lung, and analyze all the clinical and pathological features from the literature. We aim to improve the understanding of PPMS.

Materials and methods

One patient was diagnosed with PPMS at The First Affiliated Hospital of Bengbu Medical College. Their medical and pathologic records were reexamined by 2 experienced pathologists. All medical information was obtained from hospital clinical records, and follow-up investigations were permitted by our patients. Informed consent for the publication of the data was obtained from the patient. PubMed and CNKI (China National Knowledge Internet) were searched for all cases up to May 2020. This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Bengbu Medical College and conducted following the ethical guidelines of the Declaration of Helsinki. (Approval No: 2020KY035).

The excised specimens were fixed in 10% neutral formalin and embedded in paraffin with

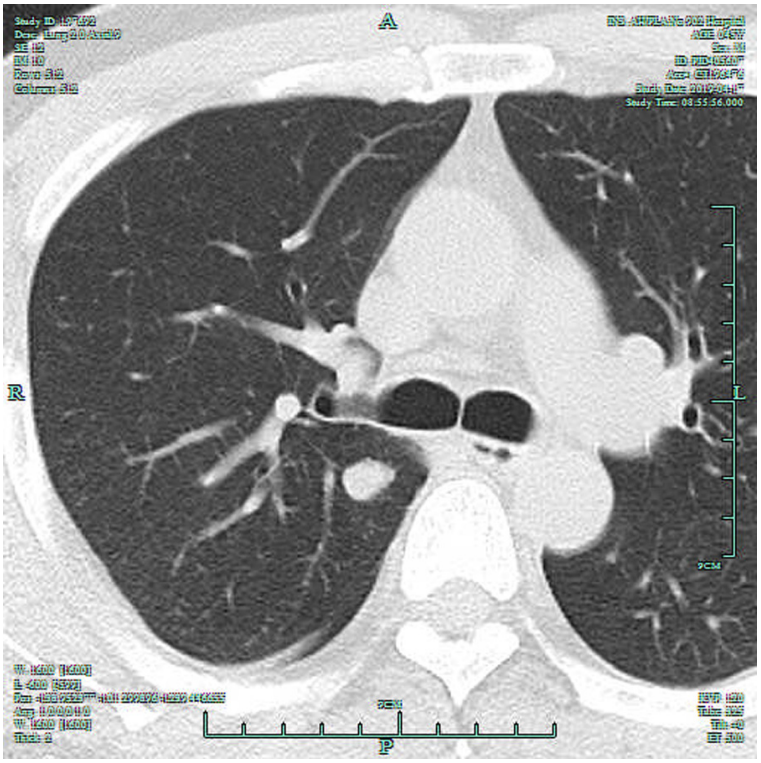

Figure 1. Computed tomography (CT) findings. Computed tomography (CT) examination revealed a 2 cm solid nodule in the right upper lung, near the azygos vein.

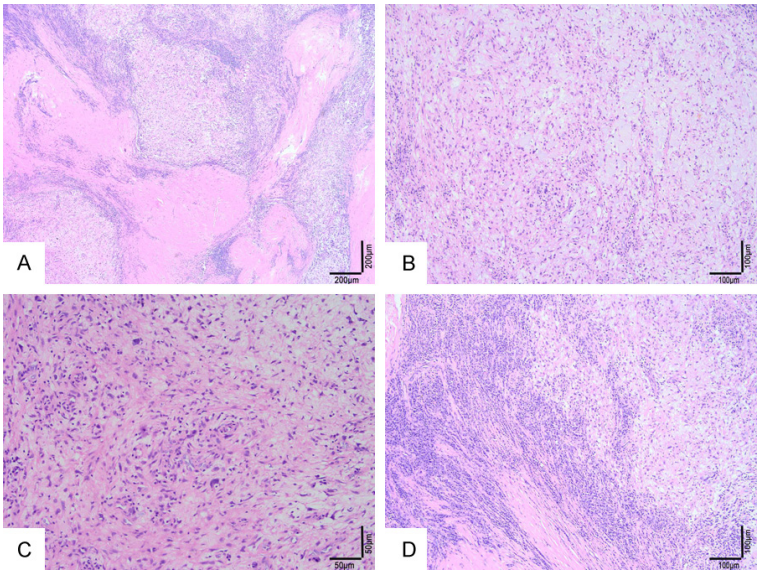

Figure 2. Histologic features of PPMS. (A) The tumor cells are distributed in a nodular manner and the interstitium is significantly collagenized (H&E stain, × 40). (B, C) A large number of round and oval cells are arranged in a reticular or ribbon-like arrangement in the mucinous background (B: H&E stain, × 100; C: H&E stain, × 200). (D) The fibrous septum and surrounding tumor are infiltrated by lymphocytes and plasma cells (H&E stain, × 100).

staining by hematoxylin-eosin (H&E). The immunohistochemistry used Elivision method. Antibodies Vimentin, EMA, Bcl-6, AE1/AE3, ALK-Ventana, CD34, CD68, SMA, CD99 and Ki-67 were all products of Fuzhou Maixin Company, and the procedure was operated strictly in accordance with the instructions. FISH detection was performed in the Department of Pathology, Fudan University Shanghai Cancer Center. SPSS 17.0 was used for statistical analysis.

Results

Clinical information

The patient was a 44-year-old male. Small nodules were found in the upper right lung and bilateral thyroid glands during physical examination, without any physical discomfort. Positron emission tomography (PET) showed multiple cystic nodules of the thyroid with calcification, small lymph nodes in the right lower neck area IV, and nodules in the right upper lobe of the lung. All nodules showed abnormally increased FDG metabolism. A radiologist considered thyroid carcinoma with lymph node and lung metastasis, with suspicion of primary lung cancer in the right lung. Computed tomography (CT) examination revealed a 2 cm solid nodule in the right upper lung, near the azygos vein (**Figure 1**).

Pathological morphology

Microscopically, frozen section showed spindle cell proliferative lesions, with rich mucoid background and accompanied by a large lymphocyte and plasma cell infiltrate. It was difficult to determine whether it was benign or malignant. By H&E staining, the tumor cells were distributed in a nodular manner with significant collagen interstitium (**Figure 2A**). Tumor

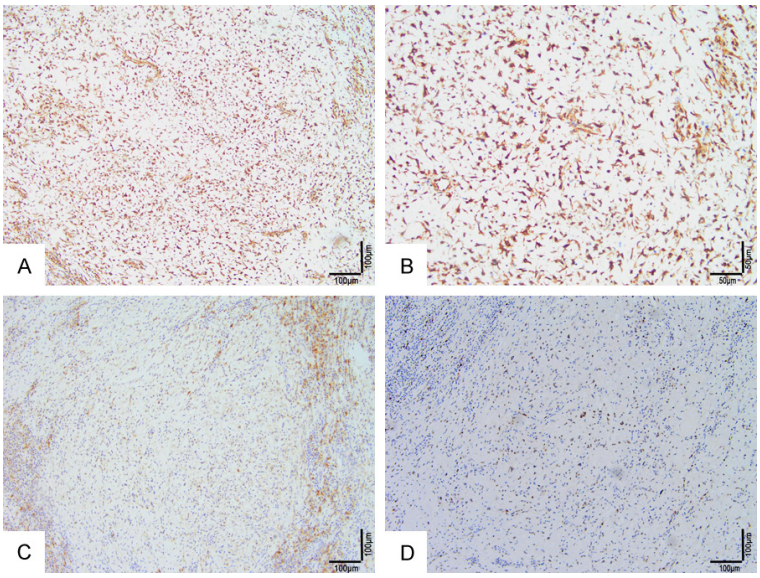

Figure 3. Immunohistochemical markers of PPMS. (A, B) Tumor cells were diffusely positive for vimentin (A: magnification, × 100; B: magnification, × 200). (C) EMA was focally weakly positive (magnification, × 100). (D) The Ki-67 proliferation index was low, approximately 10% (magnification, × 100).

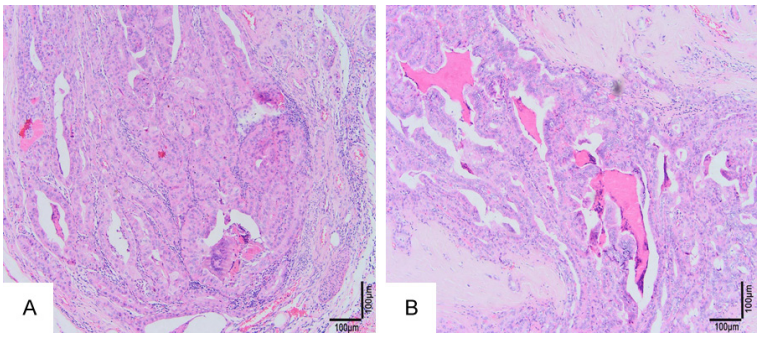

Figure 4. Histologic features of tumors in papillary thyroid carcinoma. A. Trabecula-like arrangement of closely packed papillae (H&E stain, × 100). B. Local bone formation in PTC (H&E staining, × 100).

cells were round and oval and arranged in a reticular or ribbon-like arrangement in a mucoid background (**Figure 2B**, **2C**). Atypia in tumor cells was mild to moderate. The mitotic activity was lower than 2/10 HPF (high-power fields). The tumor was characterized by a mucinous background, many lymphocytes and plasma cells in the infiltrate, and proliferation of many spindle cells (**Figure 2D**).

Immunohistochemistry and molecular genetics

Immunohistochemical results showed the tumor cells were diffusely positive for vimentin. EMA and Bcl-6 were focally weakly positive. The Ki-67 proliferation index was low, approximately 10% (**Figure 3A**, **3B**). It was negative for AE1/AE3, ALK-Ventana, CD34, CD68, SMA, and CD99. The patient then went to the Department of Pathology, Fudan University Shanghai Cancer Center for pathological consultation and FISH detection. The FISH analysis demonstrated EWSR1 rearrangement.

Results of treatment and follow-up

The patient underwent thoracoscopic right upper lobectomy and lymph node dissection. During the operation, a 2.0 cm × 1.0 cm hard mass was found in the right upper lung near the azygos arch. No obvious enlargement of hilar lymph nodes was noted. 3 months later, the patient received total thyroidectomy and cervical lymph node dissection, and the pathologic findings showed papillary thyroid carcinoma (**Figure 4A**, **4B**). After surgical treatment, the patient was followed up for 1 year in good health and no disease.

Discussion

PPMS was first reported by Nicholson et al. in 1999 [1]. In 2011, Thway et al. first named it as PPMS based on the finding through research of the genetic characteristics of EWSR1-CREB1 [2]. In 2015, the WHO included PPMS for the first time as a lung mesenchymal tumor [3]. In this paper, we report one case of PPMS with papillary thyroid carcinoma.

The clinical manifestation of primary mucoid sarcoma of the lung is relatively nonspecific. Sometimes it is found by chance during physical examination when cough is the main symptom. A few cases may have expectoration, blood in sputum, hemoptysis, and weight loss. According to the literature, a total of 37 cases, including our one case, were reported. The data of 19 females and 18 males were collected,

showing slightly higher distribution of females. Patients were aged from 23 to 80 years old, with a median age of 44 years (**Table 1**). PPMS was mostly located in the right lung (62%, 23/37) (**Table 1**). Mostly, PPMS always was closely related to the bronchus, with 85% (29/34) of patients having a location near the bronchus, except for unreported cases. The tumor size ranged from 1.5 cm to 14.0 cm (average 5 cm). There were 5 patients with different sites of metastasis [2, 7, 11]. Only 1 case showed brain metastasis and the patient died soon after [2] (**Table 1**).

Generally, PPMS is nodular with clear boundaries. The cut surface is grayish-white, pale yellow, and mucus-like. It is lobulated under the microscope, with or without fibrous pseudocysts. Microscopically, tumor cells are composed of spindle-shaped, polygonal and stellate cells, arranged in a mesh or strip in a mucoid stroma. Tumor atypia is mild to moderate, and mitotic numbers are often <5/10 HPE. The stroma is often accompanied by heavy infiltrate of lymphocytes and plasma cells. PPMS shows no characteristic immune markers. The immunohistochemical results always showed strongly diffuse vimentin expression, focal weak EMA and CD99 staining, with a complete absence of desmin, SMA, CD31, CD34, TTF-1, synaptophysin, HMB45, S-100 and Melan-A expression. There was only one case with positive vimentin, CD68, CD163 and synaptophysin. Besides, the Ki-67 proliferation index was low. EWSR1-CREB1 fusion gene or EWSR1 gene rearrangement is an important genetic feature in PPMS and the most important basis for diagnosis. FISH genetic testing can also improve confidence in the diagnosis, as 84% (27/32) of PPMS presented with EWSR1 gene rearrangement and about 78% (17/23) of PPMS produced EWSR1-CREB1 fusion genes through RT-PCR and direct sequencing (**Table 1**). Thus, it is essential to take full consideration of the histopathologic characteristics, immunochemical features, and FISH results for diagnosing PPMS.

PPMS is mainly distinguished from the following diseases. (1) Extraskeletal myxoid chondrosarcoma (EMC): the tumor cells are distributed in a single cell, cord-like pattern in a mucin-like matrix with fibrous separation, and the tumor cells are uniform in size. EMC constantly expresses vimentin, and 20%~50% are positive for S-100 protein. The two are morphologically similar, but the two organs are different, and EMC is rare in the lung [14]. EMC has the characteristic NR4A3-EWSR1 fusion gene, NR4A3-TAF15 fusion gene, and rare EWSR1-CREB1 fusion gene. (2) Angiomatoid fibrous histiocytoma (AFH): the tumor cells are round or spindle-shaped, epithelioid cells grow in nodular form, and there is abundant eosinophilic cytoplasm in the mucoid stroma. Angiomatous structures can be seen in most cases. It can be distinguished by the immunophenotype of desmin-positive and EWSR1-ATF1 gene translocation [15]. A case reported in the literature was intra-bronchial AFH with EWSR1-CREB1 positive, which has focal morphologic characteristics of PPMS. These findings provide new evidence that PPMS and AFH may represent a range of diseases with similar histologic, immunohistochemical, and molecular genetic characteristics [16]. (3) Inflammatory myofibroblastic tumor (IMT): is composed of fusiform cells, with distinct blood vessels or clear collagen stroma, and contains a large number of plasma cells and lymphocytes. IMT often expresses SMA, desmin, and ALK, and molecular genetics showed translocation of RANBP2-ALK and RRBP1-ALK genes. (4) Myoepithelial tumor (MT): it is mainly composed of myoepithelial cells and often expresses S-100, desmin and EMA; and molecular genetics shows translocation of EWSR1, ZNF444, PBX1 and POU5F1 genes [17].

Given the rarity and nonspecific clinical features of PPMS, there is no definite factor affecting its prognosis. Generally, surgical excision and close follow up are common treatments performed in all patients, including wedge resection, segment resection, lobectomy and pneumonectomy. In our case, the patient underwent thoracoscopic right upper lobectomy and lymph node dissection under general anesthesia. No postoperative radiotherapy or radiotherapy was performed after the surgical treatment. After 3 months, the patient underwent bilateral total thyroidectomy and neck lymph node dissection. No signs of recurrence or metastasis were found during the follow-up period of 12 months. However, close follow-up is still required even for low-grade or intermediate biologic behavior of the tumor. Most reported patients recovered well after the operation

Table 1. Reported cases of PPMS

Case	Age (years)/Sex	Smoking history	Presentation	Site/Tumor size (cm)	Adjacent to bronchus	FISH Result	RT-PCR Result	Treatment	Follow-up (years)
1 [1]	27/F	Never	NS	RLL/4	+	NR	NR	Surgery	NED/3
2 [1]	43/F	20 years	Bronchitis	L/13	+	NR	NR	Surgery	NED/0.5
3 [4]	60/M	NR	Asthma	R/9	-	NR	NR	Surgery	NED/3.8
4 [2]	27/F	Ex	NS	RLL/4	-	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/15
5 [2]	33/F	Current	Cough	LUL/3.5	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/12
6 [2]	45/F	NR	Cough	RUL/1.5	+	EWSR1 gene rearrangement	Neg	Surgery	NED/1
7 [2]	36/F	NR	Neural symptom	L/NR	NR	Neg	Neg	Surgery	Death followed a few months after the brain metastases
8 [2]	32/F	NR	Weight loss	RUL/NR	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NR
9 [2]	28/M	Never	Cough, fever hemoptysis, Weight loss	LLL/2.8	+	Neg	EWSR1-CREB1 fusion	Surgery	Left renal metastasis, alive/3
10 [2]	67/M	Current	NR	LLL/2.8	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NR
11 [2]	68/F	NR	NR	RUL/2.0	+	Neg	Neg	Surgery	NR
12 [2]	63/F	Ex	hemoptysis	LUL/NR	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/4
13 [2]	51/M	NR	HIV^+	RLL/2.0	NR	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NR
14 [2]	31/M	Never	NS	LLL/2.7	+	NR	EWSR1-CREB1 fusion	Surgery	NED/5.8
15 [6]	66/F	NR	Obstruction of the lung	LUL/4.0	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/1.5
16 [6]	28/M	NR	Cough, hemoptysis	RLL/8.5	NR	EWSR1 gene rearrangement	Neg	Surgery	NED/1.3
17 [6]	28/M	NR	Stethalgia	RUL/6.0	+	Neg	Neg	Surgery	NED/0.3
18 [7]	26/M	NR	Cough, hemoptysis	LLL/9	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/0.7
19 [7]	49/F	Never	NS	RLL/4	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/9.7
20 [7]	54/F	Never	NS	RLL/4.5	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/12.6
21 [7]	65/M	Never	Cough, stethalgia, expectoration	LLL/13	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	Metastases to lung/0.5, alive/6
22 [8]	29/F	NR	NS	L/3	-	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/1.4
23 [9]	32/F	Never	Cough, Weight loss	RUL/3.5	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/8
24 [10]	80/F	NR	tussiculation	LLL/NR	+	EWSR1 gene rearrangement	NR	Surgery	NED/3
25 [11]	48/M	Current	Cough	L/>14	+	Neg	Neg	Surgery	Metastases to Cerebellar/1, alive/1.7
26 [12]	41/F	NR	Stethalgia, dyspnea	R/5.1	+	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/0.9
27 [13]	45/F	Never	NS	RUL/2.1	-	EWSR1 gene rearrangement	EWSR1-CREB1 fusion	Surgery	NED/3.1
28	24/M	Never	NS	RLL/5	-	EWSR1 gene rearrangement	NR	Surgery	NED/0.5
29	64/F	Never	Cough	RUL/5.5	+	EWSR1 gene rearrangement	NR	Surgery	Metastases to pleural/0.8; Metastases to bone/1.1, alive/2
30	27/M	Current	Cough, hemoptysis	RLL/5.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/2.4
31	45/M	Current	Cough	LLL/<3.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/1.9
32	43/M	Current	Cough	RLL/2.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/2.4
33	23/M	Current	Cough, fever	RLL/<3.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/2

34	45/F	Never	Cough	RUL/2.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/0.3
35	49/M	20 years	Cough, blood-stained sputum	R/14	+	NR	EWSR1-CREB1 fusion	Surgery	NED/0.1
36	47/M	NR	NS	RUL/2.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/0.25
37 (Present case)	44/M	Never	NS	LUL/2.0	+	EWSR1 gene rearrangement	NR	Surgery	NED/1

F, female; M, male; NS, No symptom; NR, not reported; NED, no evidence of disease; RUL, Right upper lobe; RLL, Right lower lobe; LLL, Left lower lobe; LUL, Left upper lobe; L, Left lung; R, Right lung; Adjacent to bronchus, endobronchial component involved (+) or not involved (−); Neg indicates negative no EWSR1 gene rearrangement or EWSR1 gene rearrangement.

without recurrence or metastasis, and were disease-free sfor 1 to 180 months after the operation. There were about 5 patients with different sites of metastasis, including 1 case with brain metastasis who died soon after [2], 1 case of kidney metastasis [2], 1 case of metastasis to the contralateral lung [7], 1 case of cerebellar metastasis [11], and 1 case of pleural and bone metastases who survived for 23-72 months (**Table 1**). No malignant histologic findings were found in the patient with brain metastasis, and there was no EWSR1-CREB1 fusion gene or EWSR1 gene rearrangement found by gene detection [2]. Due to the rarity of cases, whether genetic characteristics are related to survival needs further study.

Conclusion

In summary, PPMS is relatively rare, with only a few dozen of cases have been reported, mostly in adults. This report confirms that the clinical features of PPMS are not specific, and lung masses are usually found accidentally. The etiology and prognostic factors of PPMS are still unclear, and ESWSR1-CREB1 genetic rearrangement is necessary to confirm the diagnosis of PPMS. PPMS is a malignant tumor that merit further study. Most patients have a better prognosis after surgical resection. However, the disease has low-grade or intermediate biologic behavior, so close follow-up is required.

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Informed consent for the publication of the data was obtained from the patient. We would like to thank the patient for agreeing to our report and for providing a detailed medical history. This case has been reviewed by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Approval No. (2020KY035).

Disclosure of conflict of interest

None.

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