Primary pulmonary epithelioid angiosarcoma with thyroid tumor history: A case report and literature review

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Abstract. Primary pulmonary epithelioid angiosarcoma is a rare tumor type without any specific clinical and imaging features. Therefore, it is associated with high rates of misdiagnosis. The present study reports the case of a 54-year-old female patient who was admitted after complaining of cough, expectoration and bloody sputum for >5 months in May 2021. The patient reported a previous history of papillary thyroid carcinoma in 2003 and had undergone treatment through surgery, postoperative chemotherapy and iodine^{131} therapy. Chest computed tomography (CT) was performed in May 2021, which indicated that the disease had progressed rapidly since February 2021. CT-guided lung biopsy and immunohistochemical staining of the tumor indicated positivity for CD31, CD34 and E26 transformation-specific-related gene markers. The tumor was negative for thyroid cancer-associated antibodies; thus, a diagnosis of primary pulmonary epithelioid angiosarcoma was made. The patient died 3 months after the diagnosis. Primary pulmonary epithelioid angiosarcoma is a rare tumor type with high recurrence and metastasis rates. This tumor has no specific clinical symptoms and signs and is thus easily misdiagnosed. Biopsy is essential for diagnosis of the disease, particularly if patients have a tumor history.

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Abbreviations: PPA, primary pulmonary angiosarcoma; PEA, primary pulmonary epithelioid angiosarcoma; CT, computed tomography; GGO, ground glass opacity

Key words: angiosarcoma, epithelioid, lung cancer, pulmonary nodule, thyroid carcinoma, ground glass opacity, case report

Introduction

Angiosarcoma is a rare, fatal, malignant vascular tumor type. It may occur in any organ and is characterized by aggressive clinical features, as angiosarcoma mainly originates from endothelial cells. Angiosarcoma accounts for ~2% of all sarcoma cases (1). The most common primary sites of angiosarcoma include the skin and subcutaneous tissues of the head and neck (2). Of note, common metastasis sites of angiosarcoma include the lungs, liver, bones and lymph nodes (3,4). Pulmonary angiosarcoma is usually secondary tumors, whereas primary pulmonary angiosarcoma (PPA) is rare and only ~30 cases have been reported (5). Due to the lack of specific clinical features and CT manifestations of PPA, it is difficult to diagnose, particularly in patients with a history of cancer.

The present study reports on a rare case of pulmonary nodules in a middle-aged female patient with a history of thyroid cancer. The patient presented with symptoms such as persistent cough, expectoration and bloody sputum. Due to the non-specificity of clinical features, according to the thyroid cancer history, the case was initially considered to be pulmonary metastasis of papillary thyroid carcinoma. The diagnosis was confirmed through lung biopsy. Immunohistochemical staining was positive for CD31, CD34, E26 transformation-specific-related gene and vimentin, and no obvious tumor sign was observed in any other sites, indicating that the case was a primary pulmonary epithelioid angiosarcoma (PEA). The clinical features, diagnosis, differential diagnosis and treatment of this disease are outlined below.

Case report

A 54-year-old female patient was admitted to the Department of Pulmonary and Critical Care Medicine of Taihe Hospital (Shiyan, China). The patient presented with cough and expectoration with blood-stained sputum for >5 months and aggravation for one day in May 2021. The patient underwent a series of chest CT scans at our hospital (Fig. 1). A CT scan performed in July 2019 was normal (Fig. 1A and B). The patient had been admitted to the hospital in February 2021 after reporting bloody sputum. The patient underwent symptomatic and supportive treatment, which improved the symptoms, and the patient was discharged. Chest CT performed on

admission in February 2021 revealed a small nodular shadow (Fig. 1C and D). Hemoptysis recurred and the patient was re-admitted to the Department of Pulmonary and Critical Care Medicine in May 2021. The patient reported a medical history of hypertension and coronary heart disease. In addition, the patient had a history of papillary thyroid carcinoma diagnosed in 2003 and had undergone treatment through surgery, post-operative chemotherapy and iodine 131 therapy. Furthermore, the patient had a history of postoperative recurrence, which was treated through residual thyroid lobectomy. Thyroid tissue immunohistochemistry results indicated the presence of cytokeratin 19 (CK19), human bone marrow endothelial cell marker-1 (HBME-1) and galectin. Reexamination of the patient through thyroid ultrasound indicated no significant abnormality in February 2021. The patient was then treated with Euthyrox and had no family history of tumor. The body temperature, heart rate, respiration and blood pressure of the patient were normal at the time of admission in May 2021. The thyroid gland was not enlarged. Serum tumor biomarker analysis indicated that the level of carbohydrate antigen 125 was 70.5 U/ml, whereas other laboratory parameters had no obvious abnormality. The patient had heart palpitations, chest tightness and other types of discomfort after admission. Cardiac color ultrasound indicated large amounts of pericardial effusion. Pericardiocentesis was performed on the day after admission in May 2021. An ultrasound-guided 16G-percutaneous transhepatic cholangiography needle was used to penetrate the pericardial effusion and 350 ml of bloody fluid was withdrawn. Pericardial effusion cytology and microscopic examination indicated a moderate level of mesothelial cells, a small number of lymphocytes and no obvious atypia of cells with no clear malignant cells. Basic pericardial effusion routine analysis indicated a dark red color and the absence of clots, and the Rivalta test was positive. The total blood cell count was $3.317x10^6$/l, the nucleated cell count was $2,000x10^6$/l, the monocyte percentage was 30% and the multinucleated cell percentage was 70%. Biochemical analysis of pericardial effusion indicated that the total protein content was 54.07 g/l, glucose level was 5.72 mmol/l, total cholesterol level was 3.16 mmol/l, the lactate dehydrogenase content was 372.3 U/l, adenosine deaminase levels were 9.3 U/l, the amylase content was 25.3 U/l and the quantitative level of high-sensitivity C-reactive protein was 1.66 mg/l; these results indicate exudate. Reexamination of the patient through chest CT on admission in May 2021 indicated multiple nodular and small patchy high-density shadows of different sizes with clear boundaries. Certain lesions displayed ground glass opacities (GGO) around them. Patchy high-density shadows were observed on the left lower lobe with blurred boundary and low levels of pleural effusion were observed on the left side (Fig. 1E and F). Thoracentesis was performed and 600 ml of blood-stained pleural fluid was drawn. Pleural fluid cytology indicated a small number mesothelial cells and a moderate number of acute and chronic inflammatory cells under the microscope. The cells exhibited no obvious atypia and had no clear signs of malignancy on microscopic examination. CT-guided lung biopsy was performed on the sixth day after admission in May 2021, when the patient's condition was stable. Rapid on-site evaluation of lung tissue revealed granulomatous inflammation and a small number of lymphocytes were observed under the microscope without clear necrosis. Lung puncture tissue pathology revealed a soft-tissue neoplasm with a sheet-like arrangement or storiform pattern of spindle-like and epithelioid cells with prominent nucleoli, with a certain amount of multinucleation. Furthermore, interalveolar spindle cell proliferation was observed with a high Ki67 index, an increased tendency to mesenchymal characteristics of the tumor was present and it was not possible to exclude angiosarcoma (Fig. 2A). Tissue *Mycobacterium tuberculosis* PCR analysis was negative. Special staining was performed and periodic acid Schiff reaction was negative, silver staining was negative and acid-fast staining was negative. Immunohistochemical results indicated the presence of CD31 (Fig. 2B), ERG (Fig. 2C) and Ki67 (+30%) (Fig. 2D), and negative results for CD56, CK19, galectin 3, HBME1, thyroid transcription factor (TTF1), thyroglobulin antibody and napsin A; furthermore, positive staining for vimentin and absence of progesterone receptor, epithelial membrane antigen and CK pan were observed (Fig. 2E). At the Department of Pathology (Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China), lung tissue pathology analysis was performed, indicating vascular tumor, possibly angiosarcoma. Immunohistochemical analysis was positive for ERG, CD34 and friend leukemia virus integration 1 (FLI1), and negative for calretinin, Wilm's tumor 1 and transcription factor E3. According to the histopathology and immunohistochemical results, and the fact that no obvious tumor sign was observed in any other sites, the patient was finally diagnosed with primary pulmonary epithelioid angiosarcoma. Chest CT was conducted in the 10th, 13th and 14th week after admission in May 2021 and the CT scan indicated enlarged lung nodules, pleural nodules and pleural effusion as compared with the previous CT scan, indicating that the patient exhibited rapid progression of the tumor (Fig. 1G-L). The patient died 3 months after the diagnosis.

Discussion

Angiosarcoma is a subtype of soft tissue sarcoma. Angiosarcoma is an aggressive malignant endothelial cell tumor of vascular or lymphatic origin (3). Angiosarcoma most commonly occurs in the skin of the head and neck, particularly on the scalp, in elderly individuals, accounting for approximately half of all of these tumors. Other common sites include the breast, thyroid, heart, liver, kidney, spleen, pulmonary vessels and limbs (6,7). Pulmonary angiosarcomas are invariably (>90%) metastatic tumors from primary malignancies of the skin, bone, liver, breast or heart (8). Primary pulmonary angiosarcoma (PPA) is a rare tumor arising from arterial or venous pulmonary vessels of various sizes (9), and only ~30 cases of PPA have been reported to date (5,7). PPAs are more common in males and the majority of patients are aged 40 years or above (7,10).

The pathogenesis of the PPA has remained to be fully elucidated. Angiosarcoma originates from blood vessels or lymphatic vessels; thus, abnormal activation of vascular endothelial growth factor (VEGF) and its receptor VEGFR may result in angiosarcoma (6). According to previous reports, the risk factors for PPA are radiotherapy, thorium dioxide, poly-vinyl chloride, radon, thorotrast, copper mining dust, mastectomy, chronic empyema and tuberculosis (3,8,10-12).

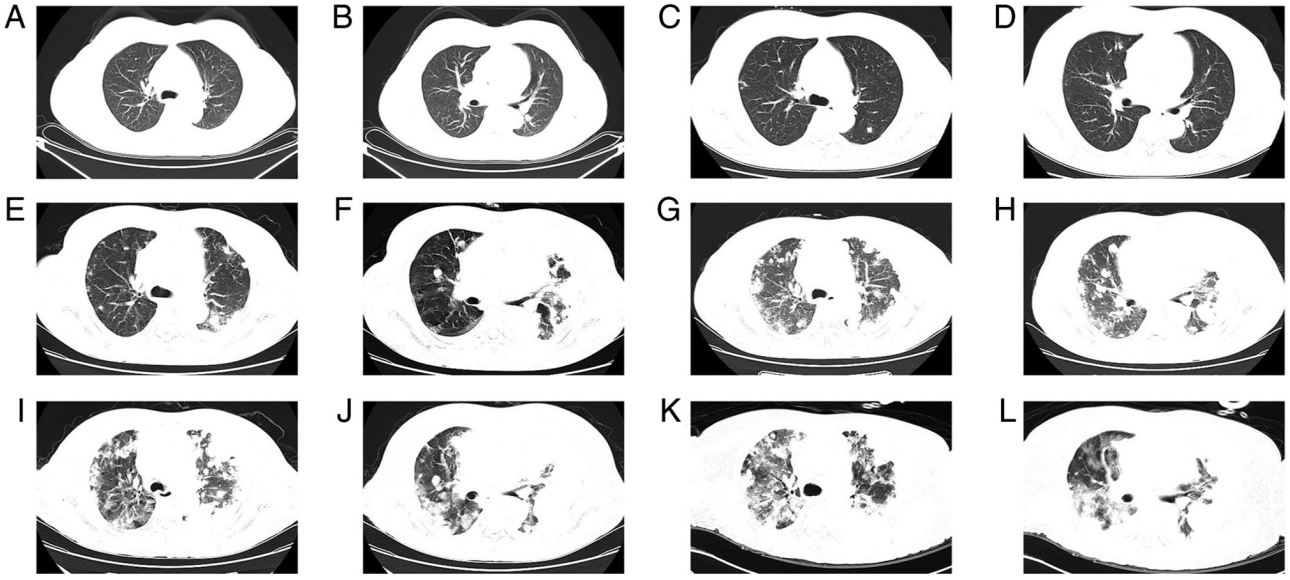

Figure 1. Chest CT scanning slice images of the patient at different time-points. Normal lungs as displayed on CT performed in July 2019, at (A) the carina level and (B) intermediate bronchus level. Several nodules were observed in both lungs as indicated by CT scan performed in February 2021, at (C) the carina level and (D) intermediate bronchus level. Multiple nodules in both lungs as revealed by CT scan in May 2021, at (E) the carina level and (F) intermediate bronchus level. Enlarged nodule with ground glass shadow as displayed by CT scan conducted in July 2021, at (G) the carina level and (H) intermediate bronchus level. Nodules were fused, as indicated by CT scan in August 2021, and significantly larger compared with the previous time-points, at (I) the carina level and (J) intermediate bronchus level. Enlarged lung nodules, pleural nodules and pleural effusion as revealed by CT scan performed in August 2021, 4 days after the previous scan, at (K) the carina level and (L) intermediate bronchus level. CT, computed tomography.

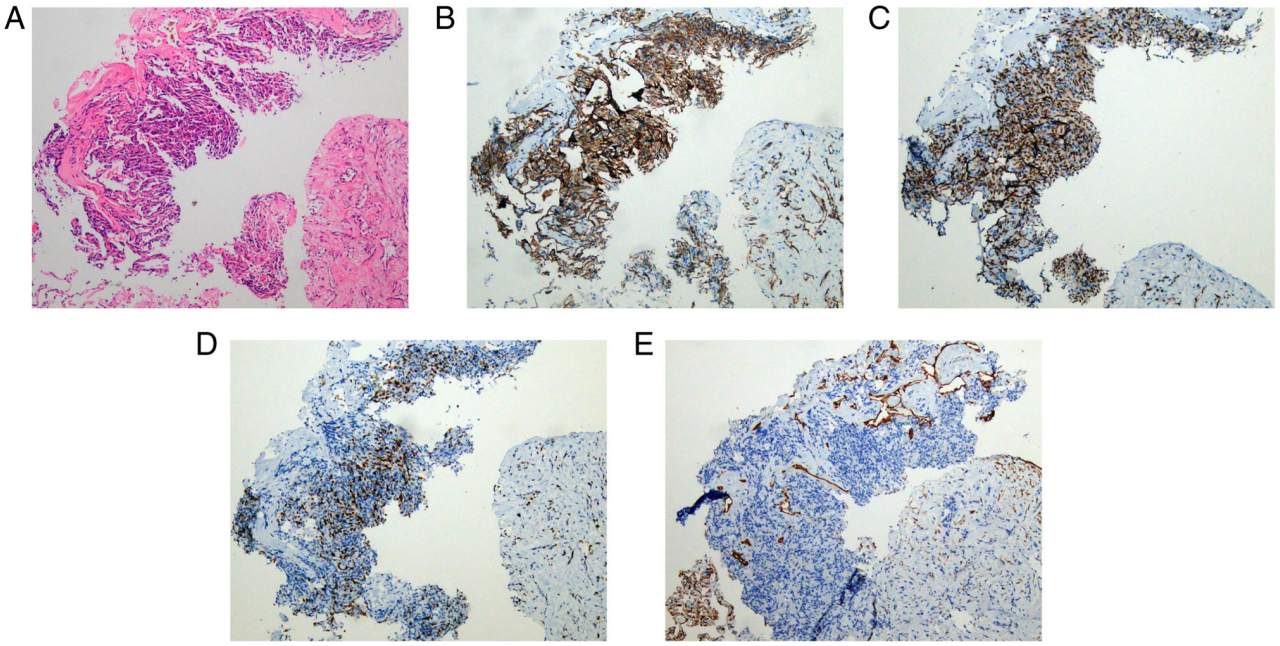

Figure 2. Pathological characteristics of the lung tissue obtained in May 2021. (A) Specimen stained with hematoxylin and eosin exhibited histological features of possible primary pulmonary angiosarcoma; (B) positive immunohistochemical staining for CD31; (C) positive immunohistochemical staining for E26 transformation-specific-related gene; (D) immunohistochemical staining for determining the Ki-67 proliferation index (30%); (E) immunohistochemical staining for cytokeratin pan was negative (magnification, x100 in all images).

The patient of the present study received iodine 131 therapy. The mechanism of immunosuppression in angiosarcoma has not been fully elucidated and immunodeficiency may be correlated with the pathogenesis of angiosarcoma (13). However, epidemiological studies should be performed to confirm this.

PPA is associated with symptoms such as cough, hemoptysis, chest pain, shortness of breath, pneumothorax, spontaneous hemothorax, cyanosis, syncope or rarely massive pulmonary hemorrhage and weight loss (6-8,10,11). In addition, most patients present with cough and hemoptysis as the initial symptoms (6). However, up to 20% of PPA cases are asymptomatic and diagnosis mainly occurs incidentally during autopsy (3,6,11). PPA does not have any specific clinical manifestations and thus, it is easily misdiagnosed as

similar diseases, such as lung cancer, metastatic malignancies, malignant pleural mesothelioma, malignant endobronchial lesions, pulmonary embolism, interstitial pneumonia associated with autoimmunological disease or infectious pneumonia (e.g. invasive pulmonary mycoses, tuberculosis) (6-9). The patient of the current study was admitted to the hospital after presenting with cough and hemoptysis as the initial symptoms.

The main CT features include a solitary or multiple lung nodules, interstitial infiltration, diffuse consolidation, GGO, pulmonary nodules surrounding GGO, diffuse pleural thickening, pleural effusion, chest wall invasion, ipsilateral thorax volume loss, hemothorax, pneumothorax and bilateral cystic lung disease (5,9,14-21). An endobronchial presentation of a PPA is extraordinarily rare (8,17,22). In the present case, the chest CT revealed multiple nodules and small patches of increased density in both lungs. Furthermore, halo-like ground glass shadows were observed around certain lesions. The patient reported a previous history of thyroid cancer and chest CT was performed after admission. Multiple pulmonary nodules accompanied by rapid growth of pericardial effusion occurred in a short period of time, indicating that the potential cause was multiple metastases of thyroid cancer and other tumors. However, the pulmonary nodules were not typical in shape and no significant abnormalities were observed for thyroglobulin and thyroid function. Lung tissue immunohistochemistry results indicated that TTF1, CK19, HBME-1 and galectin were negative, implying that it was not a case of thyroid cancer metastasis. Immunohistochemistry also revealed the presence of vascular endothelium-related markers and thus, the possibility of primary pulmonary angiosarcoma was considered. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT is a valuable auxiliary tool to stage or restage and monitor tumor response and recurrence (7). A previous study suggested that high-grade angiosarcomas had significantly higher maximum standardized uptake value for the primary tumor (pSUVmax) and primary tumor-to-blood ratio (TBR) according to ^{18}F-FDG-PET/CT (23). Furthermore, a higher pSUVmax, metabolic tumor volume, whole-body total lesion glycolysis (TLG), primary TBR and whole-body TLG ratio were significantly associated with unfavorable overall survival in angiosarcomas (23).

Due to the lack of characteristic clinical manifestations of PPA, histopathological and immunohistochemical results are required. More importantly, due to certain patients exhibiting multiple nodules in the lungs, it is similar to metastatic angiosarcoma of the lung; a diagnosis of primary disease requires a complete clinical and radiological examination of the body in order to ensure that there are no primary lesions outside of the chest (20).

The histological features of PPA may range from well-differentiated tumors with variable endothelial atypia to high-grade spindle cell malignancies (12). In well-differentiated areas, abnormal endothelial cells form functioning vascular sinusoidal channels that are continuous with normal vascular channels. In patients with progressively more aggressive disease, the architecture becomes more chaotic, with less clearly defined vascular spaces. In poorly differentiated areas, the malignant endothelial cells form continuous monolayers, usually with an epithelioid morphology that defines the epithelioid angiosarcoma (12,17). PEA is a rare type of angiosarcoma, with a structure characterized by single or multifocal tumors composed of sheets of atypical epithelioid cells. The main pathological manifestations of PEA include diffuse patchy distributions of spindle cells, abundant cytoplasm of cancer cells, prominent capillary-like vasoformative elements, hemorrhage pools, papillary growth, prominent nucleoli, marked atypical nuclei and necrosis (7,24).

Angiosarcoma is characterized by high expression levels of vascular endothelial markers, including factor VIII-related antigens, CD31, CD34, FLI-1 and ERG (6-8,17,24). Factor VIII-related antigen has the highest specificity; however, it has the lowest sensitivity (17). CD31 may be detected in ~90% of angiosarcoma cases, which is relatively specific and highly sensitive, particularly in poorly differentiated cases (6,7,17). Angiosarcoma express cytokeratin in ~30% of all cases (17). As with all types of angiosarcoma, the epithelioid variant is strongly vimentin-positive. Factor VIII-related antigen, CD34 and CD31 are specific markers for tumors derived from the endothelium (12). Among these markers, CD31 and ERG are considered to be the most reliable markers of vascular differentiation (7,25). In the present case, immunohistochemical staining was positive for CD31 and ERG and also positive for CD34, FLI-1 and vimentin (data not shown). Abdominal CT and brain CT did not indicate any obvious tumor signs and echocardiography did not reveal any obvious structural abnormalities (data not shown). The patient was diagnosed with primary epithelioid pulmonary angiosarcoma based on her histopathological and immunohistochemical results.

Angiosarcoma is a rare disease, and thus, there is currently no standard treatment plan, particularly not for PPA. Patients with pulmonary angiosarcoma have been treated with surgical resection (5,11,17,22), adjuvant radiotherapy (8,20,22), chemotherapy (20,26), immunotherapy (27,28) and combined therapy (10,16,20). It has been proposed that surgery was the most effective treatment, which should be considered as early as possible for resectable tumors (5,17). Yang *et al* (7) reported that one patient was still alive 59 months postoperatively, despite the development of postoperative adjacent pleural invasion. The most common chemotherapy regimens may be gemcitabine plus docetaxel (20,26). Wilson *et al* (26) presented a case of PPA with complete radiographic response to gemcitabine and docetaxel, with a sustained complete response for over 12 months and markedly prolonged survival of 39 months. The other effective chemotherapy regimens include doxorubicin/ifosfamide/mesna (10), adriamycin/ifosfamide (29), cyclophosphamide/gemcitabine/docetaxel (30) and docetaxel/cisplatin (16). Previous studies reported that immunotherapy is effective against angiosarcoma (31,32). Radiotherapy and immunotherapy with recombinant interleukin-2 (rIL-2) was also reported to be effective (33). However, the potential efficacy of rIL-2 alone cannot be assessed (34). Immunotherapy [anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1)] has exhibited efficacy against certain sarcoma subtypes, including angiosarcoma (35,36). Xu *et al* (28) reported that a patient with PPA benefited from anti-PD-L1 treatment (pembrolizumab 200 mg) with high PD-L1 expression (70%); 9 days after the first pembrolizumab infusion, a CT scan demonstrated a confirmed size reduction of certain lesions compared with original lesions. A previous study indicated that a case of stage IV PPA had an excellent response

to immunotherapy (pembrolizumab 2 mg/kg every 21 days) after progression on first-line chemotherapy (paclitaxel) and had stable disease after 1 year of immunotherapy treatment, which the patient was able to tolerate well (27). It has been indicated that patients with low expression of aldehyde dehydrogenase (ALDH) in primary pulmonary angiosarcoma have a favorable prognosis, whereas patients with high expression of ALDH have poor prognosis (20). These findings provide a basis for ALDH targeted therapy, which may be an effective treatment strategy for this malignant tumor type. The patient in the present study was in a poor condition and was not able to tolerate surgery, further radiotherapy and chemotherapy. The patient only received symptomatic and supportive treatment. While no treatment has been clinically proven to be effective, anti-PD-1 or anti-PD-L1 in combination with chemotherapy may be a promising strategy for advanced-stage PPA. The prognosis of PEA is particularly poor and the survival time ranged from less than one month to >59 months after clinical presentation (5,7,17,22).

In conclusion, the rate of early diagnosis of PPA is low owing to nonspecific respiratory manifestations and atypical laboratory test results. Diagnosis of PPA mainly relies on pathological analyses. Surgical resection is the first-line treatment strategy for patients in the early stage. However, the disease is frequently diagnosed at a late stage and beyond the indications for surgery. For advanced-stage patients, chemotherapy may be effective with the combined regimen of gemcitabine and docetaxel. Anti-PD-1 or anti-PD-L1 in combination with chemotherapy may be a promising strategy for advanced-stage PPA. As the disease may develop and progress rapidly and aggressively, timely diagnosis and early treatment are important to effectively prolong the survival time of patients.

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Availability of data and materials

All data generated or analyzed in the present study are included in this published article.

Authors' contributions

LY and YS obtained and analyzed the patient's information and wrote the manuscript. MW and XQ obtained and analyzed the patient's information and reviewed the discussion part of the clinical manifestations and imaging features. LY analyzed pathological figures and reviewed the discussion part of the pathological analysis. QW and XQ designed the study and reviewed the manuscript. All authors read and approved the final manuscript. LY and XQ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Taihe Hospital (Shiyan, China).

Patient consent for publication

Written informed consent for publication of the clinical details and clinical images was obtained from the patient's guardian.

Competing interests

The authors declare that they have no competing interests.

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