



A pulmonary lymphangiomyomatosis with multi-site angiomyolipoma: a case report

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Background: Lymphangiomyomatosis (LAM) is a rare low-grade malignant tumor featured with diffuse cystic changes due to the destructive proliferation of LAM cells, closely related to angiomyolipoma (AML). Here, we reported a rare case of pulmonary LAM coexisting with AMLs in multiple sites of the lung, liver, kidney, and retroperitoneum. We aimed to contribute to the body of knowledge regarding the diagnosis, identification and treatment of such cases.

Case Description: A 48-year-old female with no symptoms underwent a chest computed tomography (CT) scan that showed diffuse thin-walled cysts and multiple solid nodules in the lungs. She received a right nephrectomy due to right kidney AML 30 years previously. The pathological manifestations of the right lower lung mass removed by thoracoscopic surgery was a multifocal AML with mutations in the tuberous sclerosis complex gene. Abdominal magnetic resonance imaging (MRI) reveals a vast area of fat signal shadow behind the peritoneum and multiple scattered fatty signal nodules in the liver parenchyma. No other treatment was given due to personal factors of the patient, and there was no significant change at the 1-year follow-up.

Conclusions: LAM and AML are two different but substantively related rare neoplastic diseases. When typical LAM imaging features are found on chest CT or in pathological specimens collected from patients diagnosed with AML, multisystem screening should be performed for the early detection and diagnosis of LAM.

Keywords: Lymphangiomyomatosis (LAM); angiomyolipoma (AML); rare disease; case report

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Introduction

Lymphangiomyomatosis (LAM) is a rare, low-grade malignant but progressive tumor predominantly occurring in women of childbearing age (1,2). In addition to the characteristic diffuse cystic lung changes, many organs such as the kidneys, liver, lymphatic vessels, and lymph nodes can also be involved. It is a slow onset disease, with the most common first symptoms of LAM are dyspnea, spontaneous

pneumothorax, pleural effusion, and kidney tumors (3). Its pathogenesis has not been fully elucidated, and there is currently no cure for LAM. In 2018, the expert consensus on treating LAM with sirolimus was that sirolimus plays a certain role in maintaining lung function, improving patient quality of life, and reducing chylothorax in patients with LAM, but could not kill LAM cells (4). European scholars reported that patients with LAM have an 91% 10-year survival rate from the first symptom onset (5).

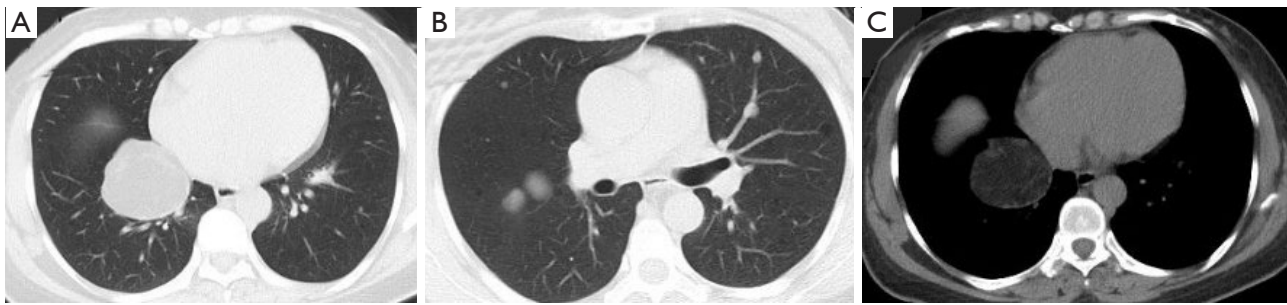


Figure 1 Chest CT on May 25, 2020. (A,B) Chest CT showed diffuse thin-walled cysts and multiple solid nodules in both lungs, the largest nodule located in the right lower lung. (C) The pulmonary nodule appears heterogeneous with fatty components on the mediastinal window. CT, computed tomography.

Angiomyolipoma (AML) is a rare, benign mesenchymal tumor commonly found in the kidney. Most patients with AML have no obvious symptoms, and those with larger volume tumors can be treated with surgery (6). It usually has a good prognosis, although it can occasionally spread to distant places (7).

The prevalence of LAM, which has no characteristic clinical manifestations and involves multiple systems, is extremely low. Clinically, due to an insufficient understanding of the condition, LAM is often misdiagnosed. In this article, the case of a patient with pulmonary LAM concurrent with AML in multiple parts of the lung, liver, kidney, and retroperitoneum is reported, and clinical features, diagnosis, and treatment of this rare tumor are discussed to help clinicians better recognize and manage such cases. We present the following case in accordance with the CARE reporting checklist (available at <https://tc.amegroups.com/article/view/10.21037/tcr-21-2539/rc>).

Case presentation

During a routine health examination, a 48-year-old female with no specific chief complaint underwent a chest computed tomography (CT) scan exhibited diffuse thin-walled cysts and multiple solid nodules in her lungs. The largest nodule was in her right lower lung (*Figure 1*). She had undergone a right nephrectomy due to renal AML 30 years prior.

There were no specific abnormalities upon physical examination. The patient had a temperature of 36 °C, respiratory rate of 18 breaths/minute, a pulse of 84 beats/minute, blood pressure of 110/70 mmHg, and clear cognition. Further physical examination revealed no obvious positive signs except for weakened respiratory

sounds in the right lower lung and an old surgical scar on the right waist. Her complete blood count, urinalysis, and hepatic and renal functions were within normal ranges. However, due to the patient's financial constraints, positron emission tomography (PET)-CT, bronchoscopy, and other examinations were not performed.

With the patient's consent, A right lower lobectomy was performed via video-assisted thoracoscopic surgery on 12 June, 2020. The tumor and the surrounding lung tissue were demarcated. Pathological sections of the right lower lung nodule indicated that the tumor was composed of mature adipose tissue, scattered blood vessels, and focally distributed smooth muscle tissue with an uneven thickness of blood vessels, varying sizes of the lumen, and fusiform, irregularly shaped smooth muscle cells (*Figure 2*). Immunohistochemistry (IHC) revealed positive results of smooth muscle actin (SMA), CD34 (blood vessel), Ki67 (30%), a small amount of Melan-A (Mel-A), melanoma marker (HMB45, MART-1), and negative results for desmin (Des), estrogen receptor (ER), cytokeratin (CAM 5.2), progesterone receptor (PR), cytokeratin 7 (CK7), CD117, S-100 (*Figure 3*). The mass was diagnosed as a multifocal AML (lipoma-like type). However, the first receiving surgeon did not pay sufficient attention to the chest CT and pathology results and neglected to perform further evaluation and differential diagnosis. The patient was discharged after surgical recovery.

In January 2021, the patient returned to the outpatient clinic of the thoracic surgery department for follow-up. Reexamination by chest CT scan revealed the postoperative state of the right lung and diffuse thin-walled cysts and multiple solid nodules in both lungs (*Figure 4*). The outpatient surgeon could not make

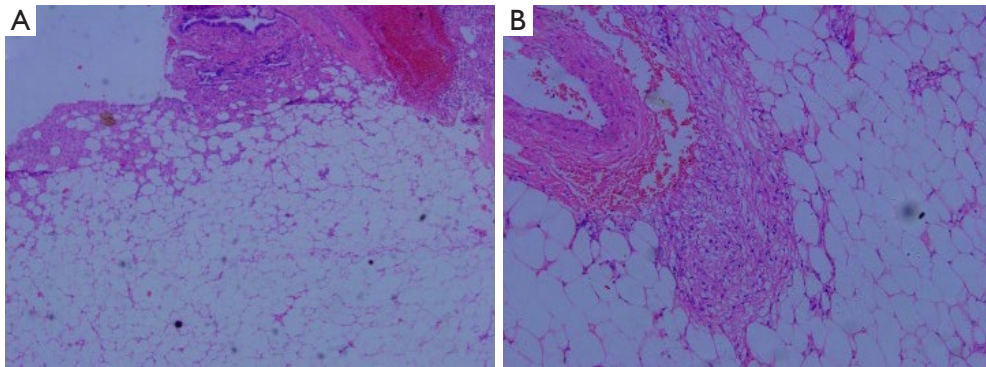


Figure 2 Biopsy specimen of the lung. Low power view of the lung shows the tumor is filled with a lot of mature adipose tissue (hematoxylin-eosin, original magnification $\times 40$) (A). Further magnification of the section shows that the tumor is composed of scattered blood vessels, locally distributed smooth muscle tissue, and mature adipose tissue (hematoxylin-eosin, original magnification $\times 100$) (B).

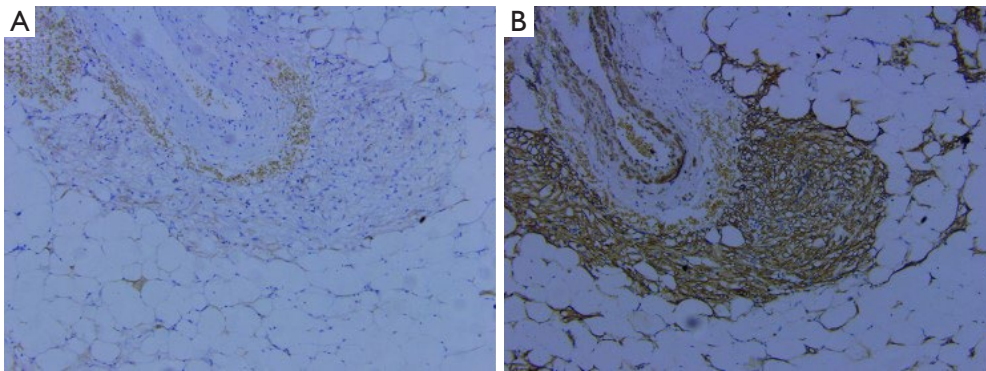


Figure 3 Biopsy specimen of the lung. Immunohistochemical studies reveal the neoplastic cells are positive for MART-1 (A) and SMA (B) (IHC, $\times 100$). SMA, smooth muscle actin; IHC, immunohistochemistry.

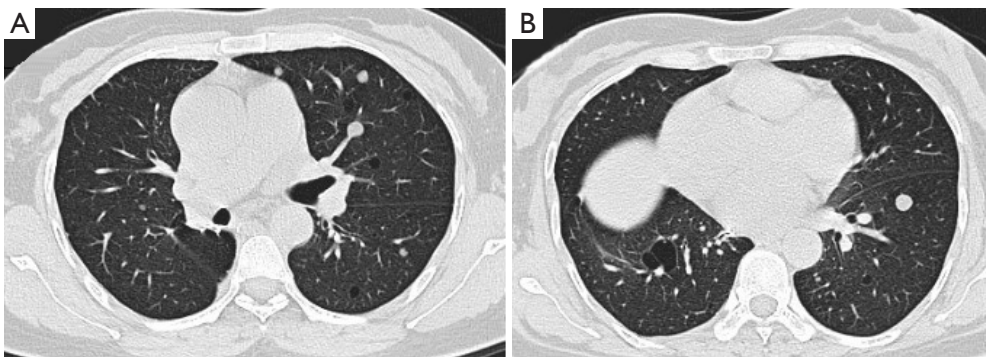


Figure 4 Reexamination of chest CT after surgery on January 19, 2021. A repeat CT after surgery shows the postoperative state of the right lung, diffuse thin-walled round air sacs, and multiple solid nodules in both lungs. CT, computed tomography.

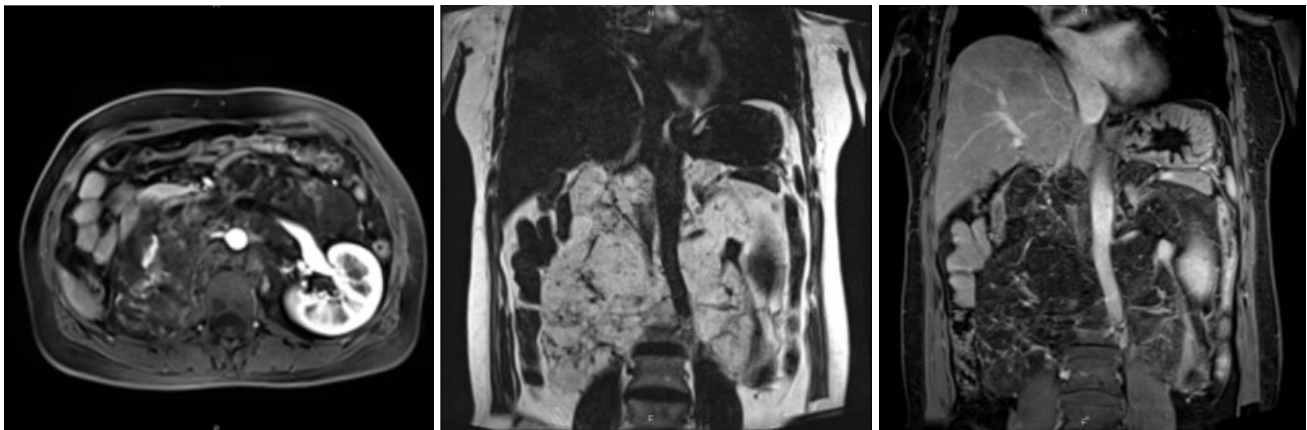


Figure 5 Pelvic MRI scan + enhanced on March 3, 2021. Abdominal MRI shows a huge mass of fat signal shadow behind the peritoneum, passed through by blood vessels after enhancement. MRI, magnetic resonance imaging.

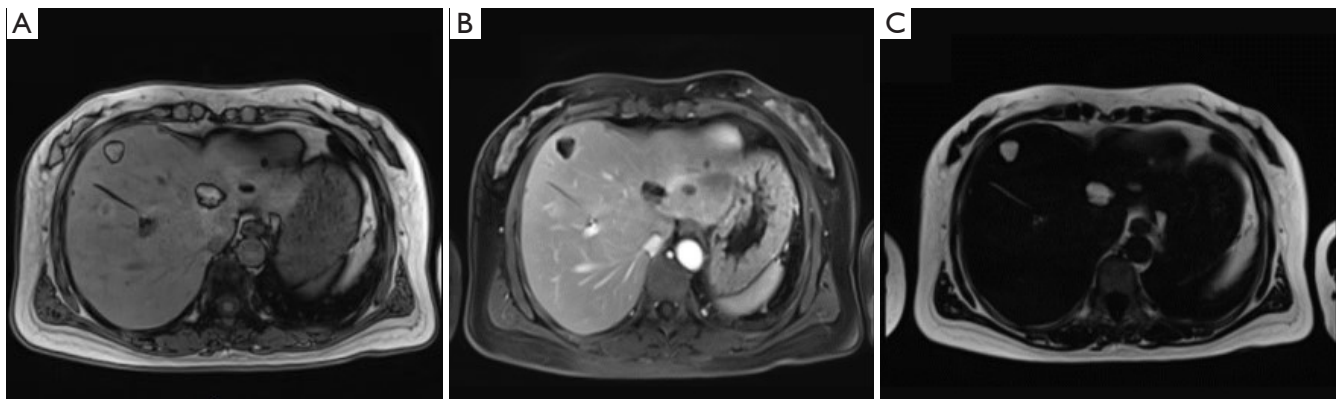


Figure 6 Liver MRI scan + enhanced on March 2, 2021. MRI-T1 shows an abnormal signal shadow in the liver (A), no noticeable enhancement after enhancement (B), a high signal in the fat image (C). MRI, magnetic resonance imaging.

a definite diagnosis and referred her to the Multi-disciplinary team (MDT) for pulmonary tumors. After discussion, experts in the group considered it was LAM, and further examinations were completed. A pulmonary function test showed normal ventilation and diffusion function [forced expiratory volume 1 (FEV1) 103%, FEV1/forced vital capacity (FVC) 84%, and diffusing capacity of the lungs for carbon monoxide (DLCO) 83%]. An enhanced abdominal magnetic resonance imaging (MRI) scan revealed a vast area of fat signal shadow behind the peritoneum, with blood vessels passing through it (*Figure 5*) and scattered multiple fatty signal nodules in liver parenchyma (*Figure 6*). Genetic testing of the pulmonary AML tissue displayed variations in the tuberous sclerosis complex gene *TSC2*, but germinal *TSC* gene variations

were not detected in the blood. The experts explained in detail to the patient the characteristics of the disease and recommended a general surgery consultation for surgical treatment. Generally, if there is a significant decline in lung function, drug treatment such as mammalian target of rapamycin (mTOR) inhibitors can be considered. Considering her lack of symptoms, the high risk associated with surgery, and her financial and personal situation, the patient chose to follow up regularly for observation. In October 2021, an abdominal B-ultrasound accompanying physical examination showed multiple solid masses in the liver and a very large solid mass in the abdominal cavity. Her chest CT scan results were similar to those in January 2021. All procedures performed in this study were in accordance with the ethical standards of the institutional

Table 1 Diagnostic criteria for LAM

Type of diagnosis	Diagnostic criteria
Confirmed LAM	Lung imaging and clinical symptoms are consistent with characteristic LAM manifestations (≥ 10 air-bearing thin-walled cysts, with clear boundaries between the cysts, and increased or unchanged lung volume, which other lung diseases cannot explain) and any of the following: <ul style="list-style-type: none"> • Lung tissue pathology accords with LAM diagnosis • Renal AML or lymphangioma present on imaging or pathologically confirmed • Chylous effusion in the thoracic or abdominal cavity • Extrapulmonary pathological results such as lymph nodes, or abdominal and pelvic tumors aligning with the LAM diagnosis • Known or proposed tuberous sclerosis • Serum vascular endothelial growth factor-D ≥ 800 pg/mL
Proposed LAM	Lung imaging and clinical symptoms consistent with characteristic LAM manifestations or lung imaging in line with LAM (2–10 thin-walled cysts above) and any one of the following: <ul style="list-style-type: none"> • Renal AML • Chylous effusion in the thoracic or abdominal cavity

LAM, lymphangioleiomyomatosis; AML, angiomyolipoma.

and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

LAM is a rare multi-system tumorous disease caused by variations of the tuberous sclerosis complex genes TSC1 or 2, which lead to the activation of mTOR and the abnormal proliferation of LAM cells (2,8). It is classified into 2 main types: tuberous sclerosis complex-related LAM (TSC-LAM) and sporadic LAM (S-LAM) (9). Approximately 85% of patients with LAM have the sporadic type, which occurs predominantly in female patients (10). According to a previous report, about 26–49% of female patients with TSC have TSC-LAM, while only a few male patients with TSC develop the condition (11).

The onset of LAM is slow, and typical early symptoms are dyspnea, spontaneous pneumothorax, pleural effusion, or kidney tumors. Of these, dyspnea is the most common, and early-stage LAM often manifests as shortness of breath after activity. With the disease exacerbation, progressive dyspnea, even respiratory failure would gradually appear (3). The typical high-resolution CT (HRCT) features of

pulmonary LAM include diffuse thin-walled cysts of varying sizes in both lungs, separated from the surrounding lung tissue. As the disease progresses, part of the cysts can fuse into bullae (12). A typical pathology image shows abnormally proliferating LAM cells of 2 types: the first are immature spindle cells and smooth muscle cells expressing specific proteins (such as smooth muscle α -actin, Des, vimentin), and the second are epithelioid cells distributed along blood vessels, lymphatic vessels, and their surroundings expressing HMB-45 (a monoclonal antibody that acts on the GP-100 glycoprotein of melanocytes). Both types can express estrogen and progesterone receptors (13).

As LAM is relatively rare, it is often misdiagnosed clinically due to a lack of knowledge. *Table 1* details the diagnostic criteria for LAM, following the LAM diagnosis and treatment guidelines issued by the American Thoracic Society/Japan Respiratory Society in 2017 and the LAM diagnosis and treatment guidelines issued in China in 2019 (4,14).

In our case study, chest CT images showed diffuse thin-walled cysts and multiple solid nodules in both lungs, consistent with the typical features of pulmonary LAM HRCT. Abdominal contrast-enhanced MRI showed a large area of fat signal shadow in the peritoneum with blood vessels and numerous fatty nodules scattered throughout the liver parenchyma. After the evaluation by the imaging professor and consideration of her medical history, the

patient was diagnosed with hepatic and retroperitoneal AML. The patient presented typical LAM HRCT signs complicated with kidney, lung, liver and retroperitoneal AML, which met the diagnostic criteria for LAM. Examination by a dermatologist and stomatologist showed no evidence of TSC. Although the tumor tissue of this patient has a *TSC2* gene variation, germinal *TSC* gene variation were not detected in the blood and there were no other related manifestations of TSC. The patient did not meet the diagnostic criteria for TSC. According to previous articles, almost 100% of patients with TSC-LAM and 50% of patients with S-LAM have renal AML (15). However, to our knowledge, there has never been a report of a case of pulmonary LAM with multiple AMLs in the kidney, lung, liver, and retroperitoneum.

AML is a mesenchymal tumor composed of adipose tissue, smooth muscle cells, and thick-walled blood vessels and is primarily located in kidneys (16). Most patients with AML have no apparent symptoms, though a small number of them may have abdominal pain and hematuria. In severe cases, they may present with hydronephrosis, renal damage, or hemorrhage (17). Although usually benign, AML can occasionally spread to distant places (7). In this case, lung, liver, and retroperitoneal AML co-occurred after a nephrectomy for renal AML 30 years earlier. At the same time, the histopathology of lung and renal AML was consistent, which could probably be interpreted as distal metastasis.

Both LAM and AML belong to the tumor family of perivascular epithelioid cell tumors composed of HMB45 positive and clear hematoxylin and eosin (H&E) staining or eosinophilic granular cytoplasm epithelioid cells. The family includes AML, LAM, and clear cell “sugar” tumor (10). However, the source of LAM cells has not yet been determined. There are two reasonable hypotheses: one proposes that LAM cells are derived from airways or blood vessels, but LAM cells exist in all lung tissues rather than being concentrated in the trachea and blood vessels; the other proposes that LAM cells originating from AML in the kidney are monoclonal and have metastatic potential to be transported to the lungs (17-19).

In the present case, there were two possible explanations for the coexistence of pulmonary LAM with multiple AML in the kidney, lung, liver, and retroperitoneum. One was that renal AML released tumor cells around the body through the bloodstream during the previous operation, forming metastatic AML in lung, liver, and retroperitoneum and leading to pulmonary LAM over a long period.

Another reason is that 30 years previously, LAM was little understood, so the patient did not undergo CT, MRI, and other examinations to assess the condition of her lungs, liver, and retroperitoneum before nephrectomy. At that time, she might have had already pulmonary LAM and AML in the lungs, liver, and retroperitoneum, metastasized from the kidney.

The prevalence of LAM among women is about 5 per 100 million (20). Due to inadequate knowledge of LAM, the average time from first symptoms to a definitive diagnosis is about 3–6 years (21). In presenting this case, we summarized our experience to help with the early diagnosis of LAM. On the one hand, when thin-walled cysts scattered in the lung fields are found on chest HRCT, the diagnosis of LAM should be highly suspected, and the kidney, liver, abdomen and pelvis should be screened for early detection of AML; On the other hand, for patients with AML found in surgical specimens, chest CT examination should be performed promptly to determine whether the typical imaging features of LAM exist. In addition, for rare or complex cases, multidisciplinary communication and cooperation should be strengthened, especially between clinical and auxiliary departments, who should exchange opinions facilitate accurate diagnose.

LAM is a multi-system disease that seriously threatens women of reproductive age. Its pathogenesis has not been fully elucidated, and there is currently no cure. Study shows that LAM is caused by variation and inactivation of the *TSC1/2* gene and the loss of inhibitory effects, resulting in abnormal activation of downstream mTOR pathway, and stimulating the abnormal growth, proliferation, and migration of LAM cells, thus causing structural destruction and dysfunction of the internal and extrapulmonary systems (8). Therefore, inhibiting the mTOR pathway has become a way of treating LAM. Studies have shown that mTOR inhibitor sirolimus can improve lung function, oxygen levels, and a patient's quality of life, reducing tumor volume and significantly affecting kidney AML in patients with LAM (22,23). However, it is worth noting that sirolimus can reduce the size of LAM cells and inhibit their proliferation, but cannot kill LAM cells. Other treatments for LAM include statins, autophagy inhibitors, such as chloroquine hydroxychloroquine, cyclooxygenase inhibitors, and anti-VEGF small-molecule tyrosinase inhibitors, which are currently under clinical research. Lung transplantation is the last treatment option to improve quality of life for patients with advanced LAM (24). It is a slowly progressive disease, and the median survival time for patients with LAM is

estimated to be greater than 20 years after diagnosis, with a 5-year transplant-free survival probability of 94% and a 20-year survival rate of 64% (25).

Conclusions

This was a rare case which could have easily been misdiagnosed or missed clinically. The detailed report of this case might provide new ideas for future clinical diagnosis, identification, and treatment. However, there were limitations in this study, such as the patient's low enthusiasm for treatment and limited follow-up time.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2539/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2539/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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