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Contents

Thrice Monthly Volume 9 Number 24 August 26, 2021

OPINION REVIEW

- 6964 Reconsideration of recurrence and metastasis in colorectal cancer
Wang R, Su Q, Yan ZP

MINIREVIEWS

- 6969 Multiple immune function impairments in diabetic patients and their effects on COVID-19
Lu ZH, Yu WL, Sun Y
- 6979 Discontinuation of antiviral therapy in chronic hepatitis B patients
Medas R, Liberal R, Macedo G

ORIGINAL ARTICLE

Case Control Study

- 6987 Textural differences based on apparent diffusion coefficient maps for discriminating pT3 subclasses of rectal adenocarcinoma
Lu ZH, Xia KJ, Jiang H, Jiang JL, Wu M

Retrospective Cohort Study

- 6999 Cost-effective screening using a two-antibody panel for detecting mismatch repair deficiency in sporadic colorectal cancer
Kim JB, Kim YI, Yoon YS, Kim J, Park SY, Lee JL, Kim CW, Park IJ, Lim SB, Yu CS, Kim JC

Retrospective Study

- 7009 Novel model combining contrast-enhanced ultrasound with serology predicts hepatocellular carcinoma recurrence after hepatectomy
Tu HB, Chen LH, Huang YJ, Feng SY, Lin JL, Zeng YY
- 7022 Influence of volar margin of the lunate fossa fragment fixation on distal radius fracture outcomes: A retrospective series
Meng H, Yan JZ, Wang B, Ma ZB, Kang WB, Liu BG
- 7032 Case series of COVID-19 patients from the Qinghai-Tibetan Plateau Area in China
Li JJ, Zhang HQ, Li PJ, Xin ZL, Xi AQ, Zhuo-Ma, Ding YH, Yang ZP, Ma SQ
- 7043 Patients' awareness about their own breast cancer characteristics
Geng C, Lu GJ, Zhu J, Li YY
- 7053 Fracture risk assessment in children with benign bone lesions of long bones
Li HB, Ye WS, Shu Q

SYSTEMATIC REVIEWS

- 7062** Mothers' experiences of neonatal intensive care: A systematic review and implications for clinical practice
Wang LL, Ma JJ, Meng HH, Zhou J

META-ANALYSIS

- 7073** *Helicobacter pylori* infection and peptic ulcer disease in cirrhotic patients: An updated meta-analysis
Wei L, Ding HG

CASE REPORT

- 7085** Tuberous sclerosis complex-lymphangiomyomatosis involving several visceral organs: A case report
Chen HB, Xu XH, Yu CG, Wan MT, Feng CL, Zhao ZY, Mei DE, Chen JL
- 7092** Long-term survivor of metastatic squamous-cell head and neck carcinoma with occult primary after cetuximab-based chemotherapy: A case report
Große-Thie C, Maletzki C, Junghanss C, Schmidt K
- 7099** Genetic mutations associated with sensitivity to neoadjuvant chemotherapy in metastatic colon cancer: A case report and review of literature
Zhao L, Wang Q, Zhao SD, Zhou J, Jiang KW, Ye YJ, Wang S, Shen ZL
- 7110** Coexistence of cervical extramedullary plasmacytoma and squamous cell carcinoma: A case report
Zhang QY, Li TC, Lin J, He LL, Liu XY
- 7117** Reconstruction of the chest wall after resection of malignant peripheral nerve sheath tumor: A case report
Guo X, Wu WM, Wang L, Yang Y
- 7123** A rare occurrence of a hereditary Birt-Hogg-Dubé syndrome: A case report
Lu YR, Yuan Q, Liu J, Han X, Liu M, Liu QQ, Wang YG
- 7133** Late-onset Leigh syndrome without delayed development in China: A case report
Liang JM, Xin CJ, Wang GL, Wu XM
- 7139** New mechanism of partial duplication and deletion of chromosome 8: A case report
Jiang Y, Tang S, He F, Yuan JX, Zhang Z
- 7146** S-1 plus temozolomide as second-line treatment for neuroendocrine carcinoma of the breast: A case report
Wang X, Shi YF, Duan JH, Wang C, Tan HY
- 7154** Minimally invasive treatment of hepatic hemangioma by transcatheter arterial embolization combined with microwave ablation: A case report
Wang LZ, Wang KP, Mo JG, Wang GY, Jin C, Jiang H, Feng YF
- 7163** Progressive disfiguring facial masses with pupillary axis obstruction from Morbihan syndrome: A case report
Zhang L, Yan S, Pan L, Wu SF

- 7169** Idiopathic basal ganglia calcification associated with new *MYORG* mutation site: A case report
Fei BN, Su HZ, Yao XP, Ding J, Wang X
- 7175** Geleophysic dysplasia caused by a mutation in *FBN1*: A case report
Tao Y, Wei Q, Chen X, Nong GM
- 7181** Combined laparoscopic-endoscopic approach for gastric glomus tumor: A case report
Wang WH, Shen TT, Gao ZX, Zhang X, Zhai ZH, Li YL
- 7189** Aspirin-induced long-term tumor remission in hepatocellular carcinoma with adenomatous polyposis coli stop-gain mutation: A case report
Lin Q, Bai MJ, Wang HF, Wu XY, Huang MS, Li X
- 7196** Prenatal diagnosis of isolated lateral facial cleft by ultrasonography and three-dimensional printing: A case report
Song WL, Ma HO, Nan Y, Li YJ, Qi N, Zhang LY, Xu X, Wang YY
- 7205** Therapy-related myeloid leukemia during erlotinib treatment in a non-small cell lung cancer patient: A case report
Koo SM, Kim KU, Kim YK, Uh ST
- 7212** Pediatric schwannoma of the tongue: A case report and review of literature
Yun CB, Kim YM, Choi JS, Kim JW
- 7218** Status epilepticus as a complication after COVID-19 mRNA-1273 vaccine: A case report
Šin R, Štruncová D
- 7224** Successful outcome of retrograde pancreatojejunostomy for chronic pancreatitis and infected pancreatic cysts: A case report
Kimura K, Adachi E, Toyohara A, Omori S, Ezaki K, Ihara R, Higashi T, Ohgaki K, Ito S, Maehara SI, Nakamura T, Maehara Y
- 7231** Incidentally discovered asymptomatic splenic hamartoma misdiagnosed as an aneurysm: A case report
Cao XF, Yang LP, Fan SS, Wei Q, Lin XT, Zhang XY, Kong LQ
- 7237** Secondary peripheral T-cell lymphoma and acute myeloid leukemia after Burkitt lymphoma treatment: A case report
Huang L, Meng C, Liu D, Fu XJ
- 7245** Retroperitoneal bronchogenic cyst in suprarenal region treated by laparoscopic resection: A case report
Wu LD, Wen K, Cheng ZR, Alwalid O, Han P
- 7251** Coexistent vestibular schwannoma and meningioma in a patient without neurofibromatosis: A case report and review of literature
Zhao LY, Jiang YN, Wang YB, Bai Y, Sun Y, Li YQ
- 7261** Thoracoabdominal duplication with hematochezia as an onset symptom in a baby: A case report
Yang SB, Yang H, Zheng S, Chen G

- 7269** Dental management of a patient with Moebius syndrome: A case report
Chen B, Li LX, Zhou LL
- 7279** Epidural gas-containing pseudocyst leading to lumbar radiculopathy: A case report
Chen Y, Yu SD, Lu WZ, Ran JW, Yu KX
- 7285** Regression of intervertebral disc calcification combined with ossification of the posterior longitudinal ligament: A case report
Wang XD, Su XJ, Chen YK, Wang WG

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Tuberous sclerosis complex-lymphangiomyomatosis involving several visceral organs: A case report

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Abstract

BACKGROUND

Lymphangiomyomatosis (LAM) is a rare cystic lung disease characterized by the proliferation, metastasis, and infiltration of smooth muscle cells in the lung and other tissues, which can be associated with tuberous sclerosis complex (TSC). The disorder of TSC has a variable expression, and there is great phenotypic variability.

CASE SUMMARY

A 32-year-old Chinese woman with a history of multiple renal angiomyolipoma presented with a productive cough persisting for over 2 wk. High-resolution chest computed tomography revealed interstitial changes, multiple pulmonary bullae, bilateral pulmonary nodules, and multiple fat density areas of the inferior mediastinum. Conventional and contrast ultrasonography revealed multiple high echogenic masses of the liver, kidneys, retroperitoneum, and inferior mediastinum. These masses were diagnosed as angiomyolipomas. Pathology through thoracoscopic lung biopsy confirmed LAM. Furthermore, high-throughput genome sequencing of peripheral blood DNA confirmed the presence of a heterozygous mutation, c.1831C>T (p.Arg611Trp), of the *TSC2* gene. The patient was diagnosed with TSC-LAM.

CONCLUSION

We highlight a rare case of TSC-LAM and the first report of a mediastinum lymphangiomyoma associated with TSC-LAM.

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Core Tip: Lymphangiomyomatosis is a rare cystic lung disease that can be associated with tuberous sclerosis complex (TSC). The disorder of TSC has a variable expression and there is great phenotypic variability. A 32-year-old Chinese woman with a history of multiple renal angioleiomyolipoma since the age of 14 was diagnosed with TSC-lymphangiomyomatosis by high-resolution computed tomography, conventional and contrast ultrasonography, pathology through thoracoscopic lung biopsy, and high-throughput genome sequencing of peripheral blood DNA.

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INTRODUCTION

Lymphangiomyomatosis (LAM) is a rare, cystic lung disease. It belongs to a family of neoplasms with perivascular epithelioid differentiation that causes a multisystemic disorder characterized by the proliferation, metastasis, and infiltration of smooth muscle cells in the lungs and other tissues. The disorder is thought to be caused by the loss of the tuberous sclerosis complex-2 (*TSC2*) gene heterozygosity in the 16p13 chromosome[1]. LAM can occur either sporadically or in association with TSC disease (TSC-LAM) (13%-40% of cases)[1,2]. TSC-LAM is characterized by the presence of pulmonary cysts and other lesion sites, including the brain, heart, kidneys, and skin[1,3]. Symptoms and severity of TSC differ widely between individuals and there is great phenotypic variability because, despite the nearly complete penetrance, this disorder has a variable expression[3]. We hereby present a rare case of TSC-LAM with skin, kidney, liver, retroperitoneum, inferior mediastinum, and lung involvement.

CASE PRESENTATION

Chief complaints

A 32-year-old woman was admitted to hospital with a 2 wk history of a productive cough.

History of present illness

The patient produced white foamy sputum that began 2 wk ago.

History of past illness

The patient was diagnosed with multiple renal angioleiomyolipomas in 2002 when she was 14 years old. In 2002 and 2008, she had multiple renal angioleiomyolipomas excised (Figure 1). After she was pregnant and had a cesarean section in 2013, cutaneous facial angiofibroma developed (Figure 2). In 2016, she was hospitalized for chylothorax. Bilateral pulmonary nodules were found, and thoracic surgery was performed (Table 1).

Personal and family history

The patient had no family history of similar illnesses.

Table 1 Timeline of the case

Year	Summary from initial and follow-up visits	Diagnostic testing	Intervention
2002	Multiple renal angioleiomyolipomas	Ultrasonography	Angioleiomyolipoma resection
2008	Multiple renal angioleiomyolipoma	Ultrasonography	Angioleiomyolipoma resection
2013	Facial angiofibroma after pregnancy and cesarean section	None	None
2016	Chylothorax	HRCT: Bilateral pulmonary nodules	Thoracic operation
2019	TSC-LAM and pulmonary infection	HRCT; Thoracoscopic lung biopsy; High-throughput genome sequencing of peripheral blood DNA; Conventional and contrast-enhanced ultrasonography	Anti-infective symptomatic supportive treatment

HRCT: High-resolution computed tomography; LAM: Lymphangioleiomyomatosis; TSC: Tuberous sclerosis complex.

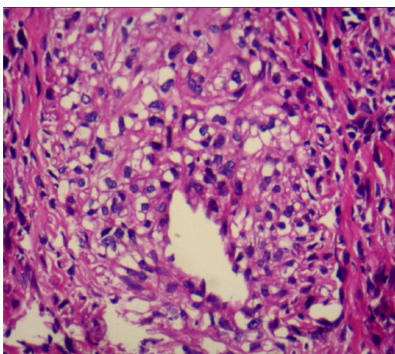


Figure 1 Pathology of the renal angioleiomyolipoma (hematoxylin-eosin staining). The patient had multiple renal angioleiomyolipomas excised in 2002 and 2008. Magnification: × 800.

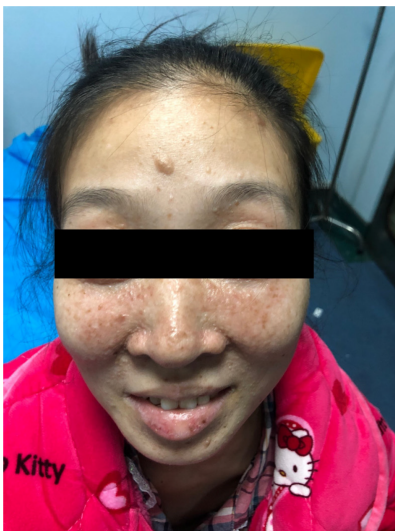


Figure 2 Facial angiofibroma developed after the patient was pregnant in 2013.

Physical examination

Tachycardia, hypertension, and low breath sounds throughout the bilateral chest field were observed. There were no other significant findings.

Laboratory examinations

Thoracoscopic lung biopsy was performed. Pathology confirmed LAM, and immuno-

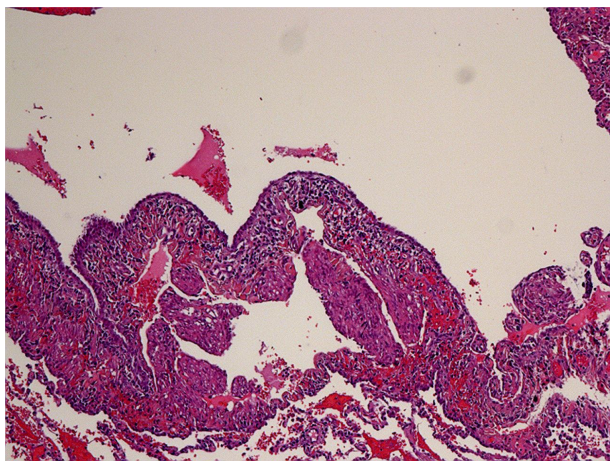


Figure 3 Pathology of lung lymphangioleiomyomatosis (hematoxylin-eosin staining). Magnification: × 200.

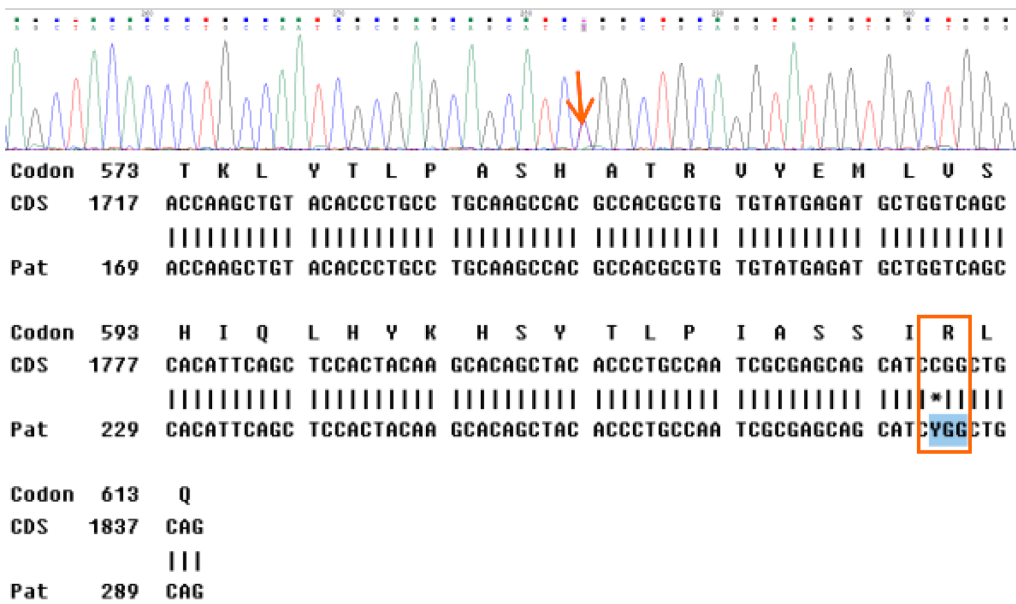


Figure 4 High-throughput sequencing of peripheral blood DNA. The heterozygous mutation c.1831C>T (p.Arg611Trp) in the *TSC2* gene was confirmed.

histochemistry showed human melanoma black-45 (+, sporadic), smooth muscle actin (+), Ki67 (+, 3%), and melan-A (+) (Figure 3). Furthermore, high-throughput genome sequencing of peripheral blood DNA confirmed the presence of the c.1831C>T (p.Arg611Trp) heterozygous mutation in the *TSC2* gene (Figure 4).

Imaging examinations

High-resolution chest computed tomography revealed interstitial changes, multiple pulmonary bullae, bilateral pulmonary nodules, and multiple fat density areas in the inferior mediastinum (Figure 5). Pulmonary function tests showed that the diffusing capacity of the lung for carbon monoxide decreased mildly (67%), forced expiratory volume in 1 s was reduced, and ratio of forced expiratory volume to forced vital capacity decreased, which contributed to severe obstructive ventilatory syndrome.

Conventional (Figure 6) and contrast ultrasonography (Figure 7) revealed multiple high echogenic masses in the liver, kidney (bilateral), retroperitoneum, and right thorax (inferior mediastinum). The masses were diagnosed as angiomyolipomas.

FINAL DIAGNOSIS

TSC-LAM.

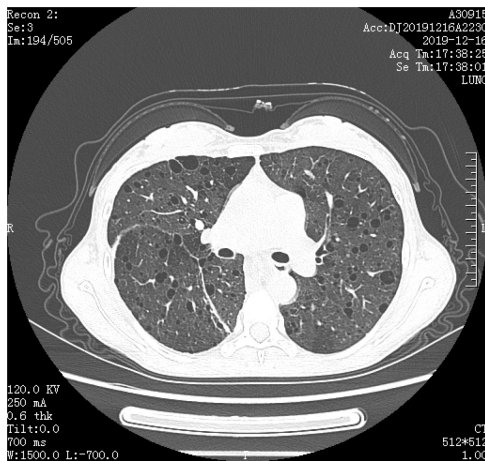


Figure 5 High-resolution chest computed tomography. Computed tomography revealed interstitial changes, multiple lytic and lucent lesions of varying sizes, bilateral pulmonary nodules, and multiple fat density areas in the inferior mediastinum.

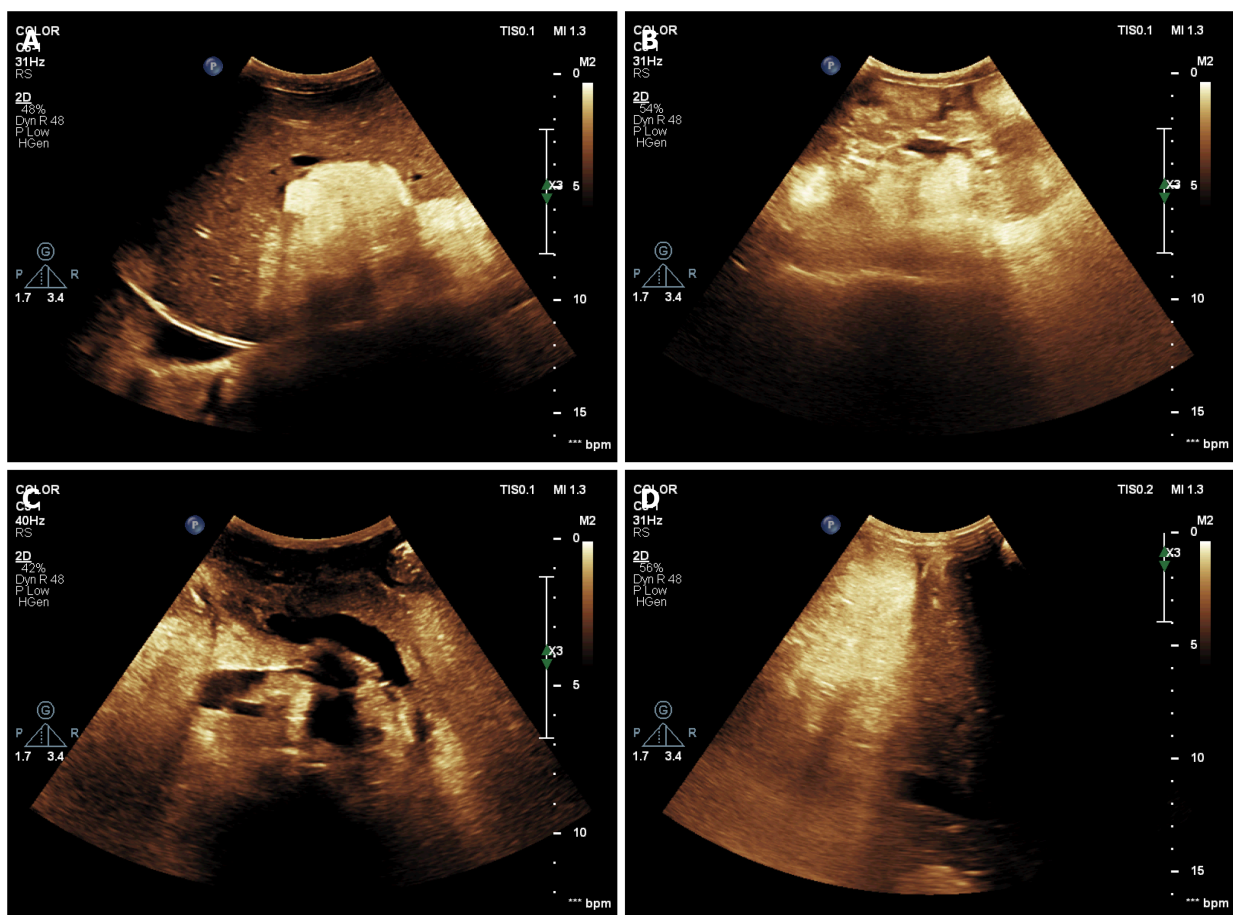


Figure 6 Ultrasonography revealed multiple high echogenic masses. A: Liver; B: Right kidney; C: Retroperitoneum; D: Inferior mediastinum.

TREATMENT

The patient was referred for specific consultation and treatment with sirolimus after recovery of the pulmonary infection.

OUTCOME AND FOLLOW-UP

The patient's symptoms decreased after drug treatment but did not resolve

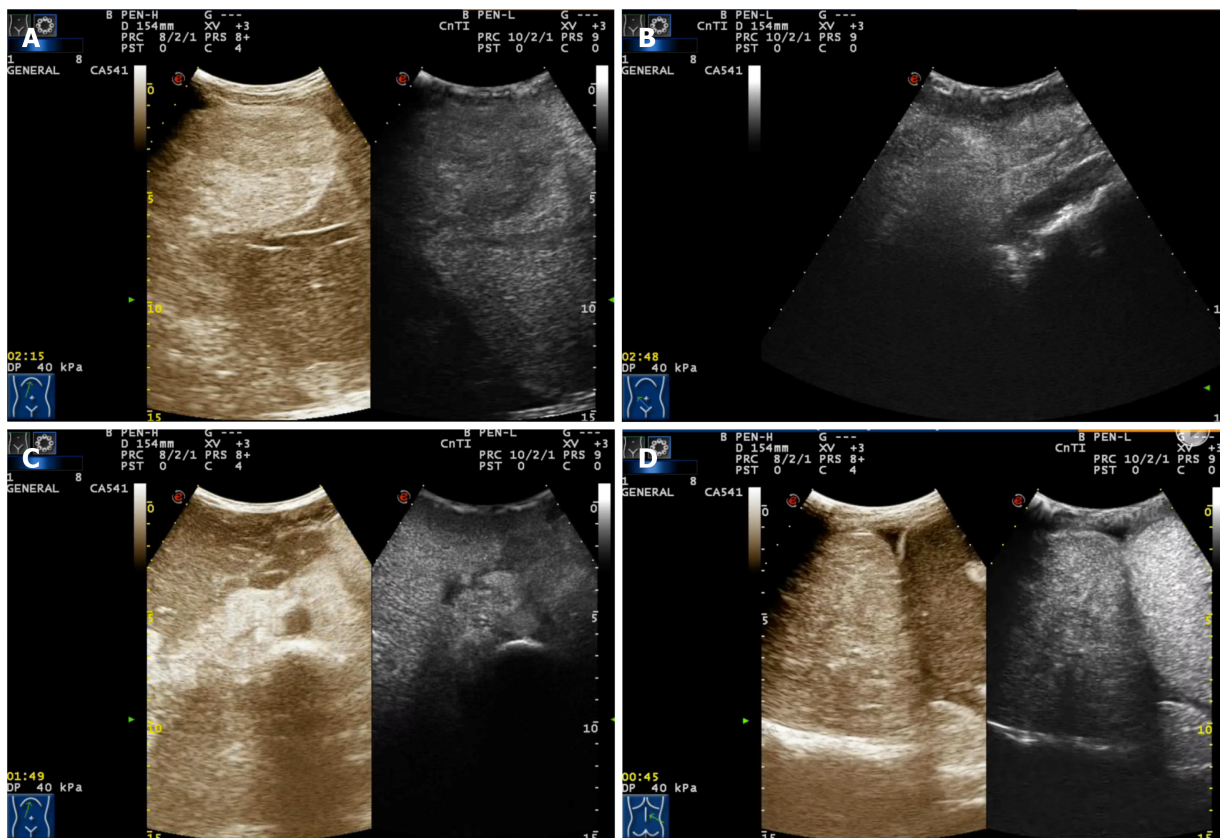


Figure 7 Contrast-enhanced ultrasonography revealed high enhancement of the masses. A: Liver; B: Right kidney; C: Retroperitoneum; D: Inferior mediastinum.

completely. We followed the patient regularly during sirolimus treatment, including ultrasound and lung function evaluation every 3 mo and computed tomography every 6 mo. At the 1-year follow-up, the effects of TSC-LAM on the skin, kidneys, liver, retroperitoneum, inferior mediastinum, and lungs were still observable by imaging analyses, and nothing had changed.

DISCUSSION

LAM is a rare interstitial lung disease[4]. It has an unknown etiology and is characterized by cystic destruction of the lung caused by infiltration of smooth muscle cells. It predominantly affects women in their reproductive years. The average age at diagnosis is 41 years old[2]. The patient in this case was 32 years old, which is much younger than the average age. Although LAM is predominantly a lung disorder, extrapulmonary involvement, such as renal angiomyolipomas and retroperitoneal masses, can occur in up to 75% of cases. A rare finding of abdominal aneurysm was reported before[5].

This patient was previously diagnosed with renal angiomyolipomas but no pulmonary involvement was documented until 2016. Angiomyolipomas or lymphangioleiomyomas of the inferior mediastinum, liver, and retroperitoneum were observed during the patient's most recent hospitalization. To our knowledge, this is the first report of a patient with mediastinum lymphangioleiomyomas associated with TSC-LAM or sporadic LAM. The conventional and contrast ultrasonography imaging of the inferior mediastinum masses were similar to the renal angiomyolipoma imaging. The pathogenesis of mediastinum lymphangioleiomyomas in LAM may be similar to the mechanism of retroperitoneal lymphangioleiomyoma pathogenesis, but further research is needed to confirm this hypothesis.

The prognosis of patients with TSC-LAM is poor. Respiratory insufficiency and death often occurs within 5 years from onset of symptoms, while positive management of the disease and its complications would improve the long-term survival of these patients. The patient in this case accepted a complete evaluation first, and then received a specific consultation and treatment with sirolimus after recovery of her

pulmonary infection.

CONCLUSION

The diagnosis of TSC-LAM in this patient was multisystemic. Affected organs included the skin, kidneys, liver, retroperitoneum, mediastinum, and lungs. This is the first reported case of a patient with a mediastinum lymphangioleiomyoma associated with TSC-LAM. High-resolution chest computed tomography and ultrasonography are critical to detect abnormalities, which may require specific treatment to prevent disease progression and poor outcomes.

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