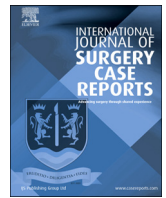




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An extrapulmonary manifestation of lymphangioleiomyomatosis: A rare case report



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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare and fatal disease which occurs almost exclusively in young women. The disease often affects lungs and most of the patients die from respiratory failure. It is often initially misdiagnosed as asthma or chronic obstructive pulmonary disease. The most common presentations of pulmonary LAM (P-LAM) include dyspnea and coughing. Chylothorax and spontaneous pneumothorax may be seen in advanced cases. Although rare, it may present with extrapulmonary LAM (E-LAM). Renal angiomyolipomas and abdominal lymphadenopathies (LAPs) are common in E-LAM cases. Pelvic retroperitoneal masses are very rare and often require exploratory laparotomy. Herein, we report a 36-year-old female case of a rare extrapulmonary manifestation of LAM who was treated with abdominal and thoracic surgery, radiotherapy and finally sirolimus.

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1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare, systemic, progressive disease characterized by proliferation of abnormal, smooth muscle-like LAM cells in lymph vessels, inducing obstruction and cystic formation [1]. It is also regarded as a low-grade, destructive, and rare neoplasm with metastatic potential [2]. In general, LAM occurs sporadically (S-LAM); however, in about 40% of the cases, it affects women with autosomal-dominant inherited tuberous sclerosis syndrome (TSC-LAM) [3]. It mostly affects young women. The thorax is the most commonly affected part of the body and the disease typically presents with pulmonary symptoms (P-LAM). The presentation of abdominal LAM without pulmonary findings is unusual [4], which results in a number of unnecessary interventions due to misdiagnosis or delayed diagnosis.

Although several treatment options have been reported for LAM in the literature, its specific treatment is still unclear. Surgery often yields unsatisfactory results in most of the patients [1] and there is a limited number of data on the efficacy of radiotherapy (RT) [5,6]. In addition, the prognosis is poor and mortality is usually associated with respiratory failure [3].

Herein, we report a 36-year-old female case of a rare extrapulmonary manifestation of LAM who was treated with abdominothoracic surgery, abdominal radiotherapy, and finally

sirolimus, a mammalian target of rapamycin inhibitor. This work has been done in line with the SCARE criteria [7].

2. Clinical case description

A 36-year-old female patient was admitted to an external center due to the intermittent claudication in the left leg and pelvic abdominal pain for the past six months. The patient was previously operated with the preliminary diagnosis of a malignant mass originating from the left ovary. Based on the presence of an unusual cystic mass surrounding the left iliac artery and vein during surgery, the operation was terminated and the patient was referred to our clinic with the diagnosis of a retroperitoneal tumor.

Abdominal computed tomography (CT) showed a homogeneous, well-limited mass (10 × 9 × 7 cm) located next to the left ovary, surrounding the left iliac artery (Figs. 1 and 2). An accompanying conglomerated lymphatic tissue originating from the paraaortic space and extending through the left renal hilus was also detected. Chest X-ray showed normal findings, except for sequelae fibrotic changes. An ultrasound (US)-guided fine-needle aspiration cytology (FNAC) was performed for the cystic mass, which was closely adjacent to the vein, upon aspiration of non-bloody fluid, and CT-guided fine-needle aspiration biopsy (FNAB) was performed for the definite diagnosis. The result of the FNAC was reported as a low-grade mesenchymal neoplasm and the result of the FNAB was reported as an extra-renal angiomyolipoma and possible retroperitoneal leiomyomatosis due to strong positive immunohistochemical reaction for actin, desmin, and HMB-45.

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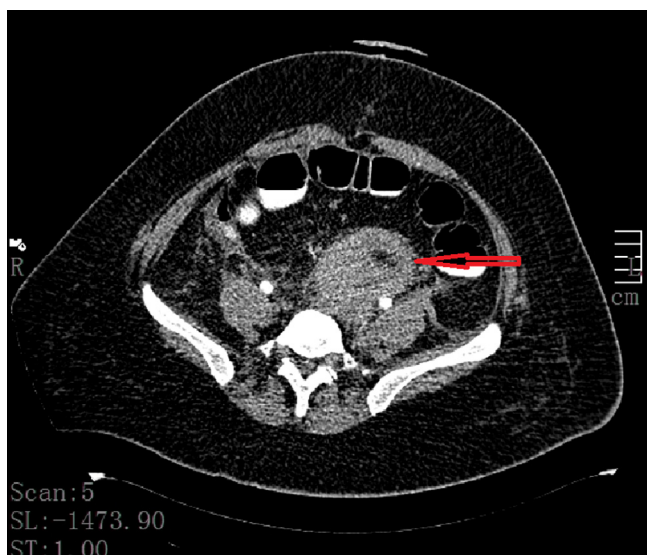


Fig. 1. A 10 × 9 cm cystic mass surrounding left iliac artery appearance on axial computed tomography (red arrow).

A written informed consent was obtained from the patient and she was operated due to a symptomatic mesenchymal tumor, and the cystic mass around the iliac veins was removed. The patient was discharged on the third postoperative day.

The permanent pathological examination revealed a low-grade (Grade I) vascular leiomyosarcoma. Meanwhile, the patient was re-admitted on the ninth postoperative day with dyspnea and chest X-ray showed massive pleural effusion in the right hemithorax.

A tube thoracostomy was performed. Thoracic CT showed small, well-limited air cysts in the parenchyma, suggesting LAM (Fig. 3). There was a complex fluid collection in the abdomen as assessed by US. Since the pleural drainage did not decrease, a ligation of the thoracic duct and a mechanical pleurodesis was performed through thoracic surgery. The patient was referred to another hospital which specializes in thoracic surgery, since the drainage was unable to be controlled with these interventions. She underwent partial diaphragmatic resection and mechanical pleurodesis and was put on a fat-free diet. Five months later, she presented to our department with dyspnea and underwent left total pleurectomy due to left chylothorax. Since pleural drainage did not decrease following surgery, a decision was made to perform abdominal RT based on limited reports [4,5]. A three-dimensional conformal RT was applied in 17 fractions (total 3060 cGy), beginning from the left renal hilus and extending to the left paraaortic lymph nodes with an upper margin crossing the L1 vertebra and a lower margin at the level of the left capitis femoris. Following the first RT session, pleural drainage stopped. After three months of the fat-free diet, she was re-admitted with recurrent pleural effusion and re-underwent pleurodesis. After fat-free diet for three years, she was recommended a normal diet. At 129 months of follow-up, the patient had no chylothorax. However, at 97 months, she suffered from respiratory insufficiency requiring oxygen support. At 104 months, in the light of the recent reports in the literature, we initiated sirolimus treatment at 2 mg/day to maintain the blood concentration at 8–12 ng/mL. Bilateral hand eruption spontaneously disappeared during follow-up. However, statin therapy was initiated due to hypercholesterolemia. At 24 months of treatment, the patient showed a favorable clinical response and is currently functionally better in her daily activities (Table 1). At

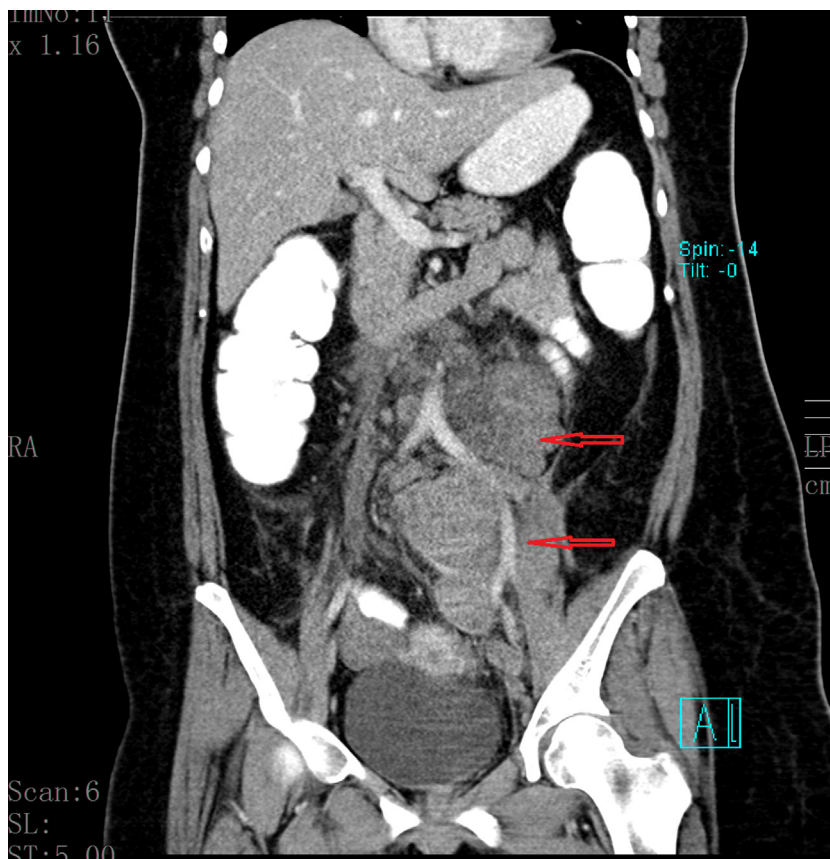


Fig. 2. A 10 × 9 cm cystic mass surrounding left iliac artery appearance on coronal computed tomography (red arrow).

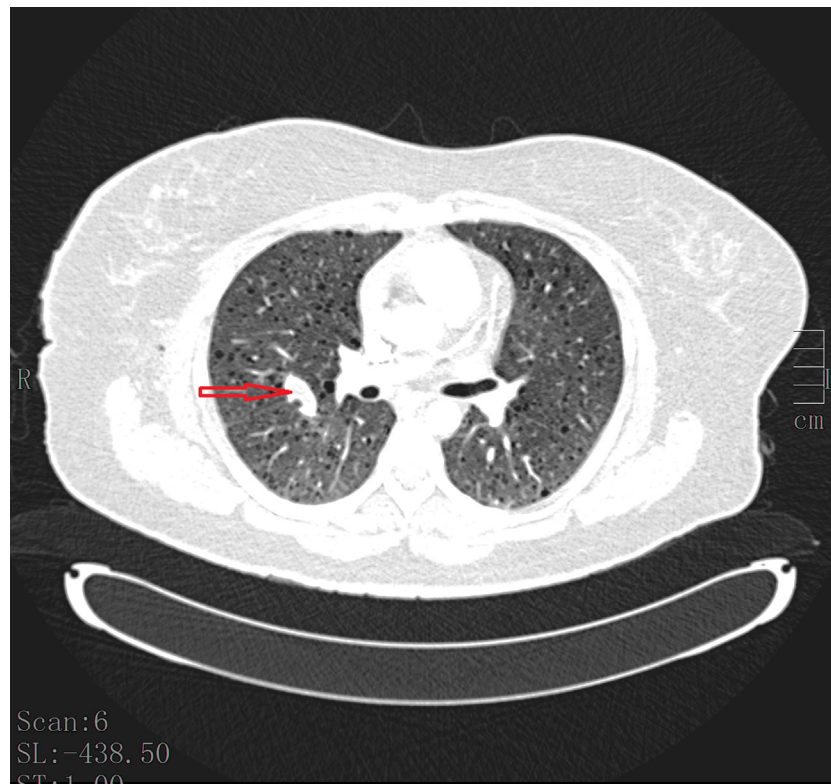


Fig. 3. Thoracic high-resolution computed tomography showing multiple thin-walled cysts throughout lungs. Drainage tube in the right hemithorax (red arrow).

Table 1

Baseline and 24-month values with Sirolimus treatment.

	FEV ₁ (L/sec)	FEV ₁ (%)	FVC (L/sec)	FVC (%)	FEV ₁ /FVC (%)	DLCO _{adj} (%)	DLCO/VA _{adj} (%)
Baseline	0,73	23	2,34	73	31	19	34
Month 24	0,83	35	2,71	97	31	19	28

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; VA, alveolar volume.

129 months of follow-up, she is still alive, although she is a strong candidate for lung transplantation.

3. Discussion

Lymphangiomyomatosis is a rare systemic disorder which almost exclusively affects women of childbearing age [1]. Two forms of LAM have been described as S-LAM and TSC-LAM [3]. The latter is an autosomal dominant syndrome characterized by hamartoma-like tumor growths in various organs, cerebral calcifications, seizures, and mental retardation. There is a limited number of epidemiological data, and the prevalence of sporadic LAM widely varies from 3,3 to 7.4 per million women [1,2,4].

Its origin still remains unknown, although lymphatic system has been accused [3]. The disease is characterized by the destruction and cystic formation of the pulmonary parenchyma. The TSC complex regulates the mammalian target of rapamycin (mTOR) which controls the cell size, proliferation, and survival by integrating signals from the growth factors, energy, and stress. Dysregulation of the mTOR signaling pathway is the leading cause of abnormal LAM cell proliferation [2]. Smooth muscle cell proliferation, which can be detected microscopically, is the main cause of obstruction of bronchioles and blocked air in the alveoli, which leads to spontaneous pneumothorax. In addition, the blockage of lymphatic vessels leads to chylothorax and chylous ascites, while the blockage of veins leads to hemosiderosis and hemoptysis [3]. Extrapulmonary manifestation is rare, and P-LAM is often diagnosed

within two years following E-LAM diagnosis. In patients with E-LAM, mediastinal and upper abdominal retroperitoneal LAPs and renal angiomyolipomas are common, although pelvic involvement is rare [8]. Abdominal masses can be misdiagnosed as ovarian malignancies, sarcomas, or lymphomas [4,8]. Similarly, our case had a rare extrapulmonary manifestation of LAM in whom unnecessary interventions were performed which led to a delayed diagnosis and associated morbidities.

An accurate tissue diagnosis is of utmost importance in the treatment of masses which may suggest an intra-abdominal neoplasm. Definite tissue diagnosis can be achieved by US- or CT-guided percutaneous biopsy. Compared to the US-guided FNAC, US-guided FNAB can be performed with similar complication rates without leading to needle tract spread and with higher accuracy rates [9].

The mean time from the symptom onset to diagnosis is about three to six years [4]. Early diagnosis is often difficult. Chest X-ray usually shows normal findings, or there may be minimal pleural effusion. Thoracic high-resolution CT is valuable in diagnosis. Multiple cysts full of air with variable diameters and a wall thickness of 1 mm are pathognomonic. Definitive diagnosis is confirmed by biopsy [3].

Although the standard approach was previously palliative treatment for pneumothorax, pleural effusion, and drainage of chylous ascites, currently treatment of LAM is primarily medical. Pleurectomy is an option for intractable pleural effusion, while chemical pleurodesis may be partially successful for controlling chylous effusions when thoracic duct ligation does not work [1]. A minimal-fat

diet which contains medium-chain fatty acids also provides partial benefits in chylous effusion [3]. In addition, RT can be helpful in intractable cases [5,6]. However, steroids and chemotherapeutics have shown no effect in symptomatic relief. Recent studies have demonstrated positive effects of doxycycline, statins, and tyrosine kinase inhibitors [1].

In the literature, the efficacy of mTOR inhibitors such as sirolimus has been investigated in LAM and TSC patients with TSC mutation positivity. In a study, Mc Cormack et al. [2], showed that sirolimus stabilized lung function and reduced symptoms with improved quality of life. In our case, we achieved 100 mL increase in the forced expiratory volume in one second (FEV1) and 370 mL increase in the forced vital capacity (FVC) with significantly improved dyspnea and quality of life at the end of 24 months of treatment. However, we were unable to achieve an improvement in the diffusion values, possibly due to permanent structural alterations in the lung.

Respiratory failure is the leading of death in most of the patients. Pulmonary transplantation is the most optimal treatment option for advanced disease [3]. The 10-year survival rate is about 86%, and the estimated median transplant-free survival time for LAM patients in the United States is 29 years from symptom onset and 23 years from diagnosis [4].

In our case, since the data on LAM cases were limited in 2006, we were only able to manage symptoms of the disease through surgical interventions and abdominal RT. The follow-up period of our case was complicated, as no specific center or national institution was available for these patients. Our case was diagnosed with S-LAM due to the lack of TSC findings, and US-guided FNAB raised the suspicion of LAM. However, a thoracic high-resolution CT could have confirmed the diagnosis and prevented unnecessary laparotomy and an exacerbation of LAM. Eventually, structural alterations in the lung could have been delayed with early effective medical treatment and the need for transplantation could have been avoided or alleviated.

4. Conclusion

Genetic and pathophysiology-based effective treatment modalities are currently being utilized instead of historical anecdotal treatment options, based on limited case experiences. Awareness and increased knowledge of physicians, as well as the establishment of local and national organizations playing a role in the follow-up and treatment of these patients, is of vital importance in the early diagnosis of LAM and to achieve prolonged patient survival.

Conflicts of interest

The authors declare no conflict of interest to disclose.

Financial disclosure

The authors declare no competing financial interest.

Ethical approval

Not required.

Informed consent

A written informed consent was obtained from the patient.

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None.

Author contribution

1. L.Volkan Tümay – Study concept, manuscript writing, critical review of literature.
2. Osman S. Güner – Data collection.
3. Abdullah Zorluoğlu – Proof reading, comments.

Guarantor

Professor Dr. Abdullah Zorluoğlu, Acibadem University, Department of Surgery, Istanbul.

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