CASE REPORT

Lymphangioleiomyomatosis: an explosive presentation of a rare disease

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Abstract

Lymphangioleiomyomatosis (LAM) is a rare cystic lung disease, commonly affecting women in the reproductive age group. Exacerbation of pre-existing disease is common during pregnancy likely due to the up-regulation of estrogen and progesterone receptors present within the proliferating smooth muscle cells. This case highlights a dramatic presentation of LAM for the first time in pregnancy, its rapid progression during gestation, and a partial resolution with delivery. The unusual radiographic imaging in this patient, lacked the characteristic cystic lesions commonly associated with LAM, but instead demonstrated a dense interstitial pattern with micronodular expansion of the interlobular septa suggesting severe lymphatic obstruction.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a slowly progressive cystic lung disease that predominantly affects young females. Histologically, LAM is characterized by dysregulated proliferation of immature smooth muscle cells, commonly referred to as ‘LAM cells’. This unchecked neoplastic process leads to airway and lymphatic obstruction, cyst formation and progressive parenchymal destruction [1]. Multisystem involvement includes the occurrence of angiomyolipomas (AMLs) in the liver, kidney, spleen and uterus. Proliferation of LAM cells is linked to the inappropriate activation of the intracellular mammalian target of rapamycin (mTOR) signaling pathway, responsible for cell cycle regulation. Sirolimus (rapamycin), an inhibitor of mTOR, has been approved for the treatment of LAM [2]. This case describes the initial explosive presentation of LAM during pregnancy, its partial remission following delivery and subsequent stabilization of lung function with Sirolimus.

CASE REPORT

A 26-year-old pregnant female with a history of well-controlled asthma was admitted with worsening cough and hemoptysis for 6 months. She had no improvement in symptoms with antibiotic therapy and had been subsequently started on anti-tuberculosis therapy. On admission, autoimmune and infectious work-up including a transbronchial lavage and biopsy was unrevealing. Tuberculosis quantiferon and sputum for acid-fast bacilli were negative and anti-tuberculosis therapy was stopped after 1 week. Computed tomography (CT) scan at admission (Fig. 1A) demonstrated a diffuse nodular interstitial pattern with thin-walled cysts highly suspicious for LAM. Abdominal imaging revealed a small left renal and extra-renal AML. Tissue obtained from a transbronchial biopsy stained positive for smooth muscle actin, however, only two of five samples were weakly positive for human melanin black-45 antibody (HMB-45). Given the risk of obstetric complications associated with LAM, a decision was
made to deliver the baby at 30 weeks gestation by Cesarean section under epidural anesthesia. Throughout this time the patient remained hospitalized, and frequently experienced episodes of hypoxia requiring high flow oxygen. However, close continuous fetal monitoring confirmed that the fetus remained unaffected. As planned, the Cesarean section was performed at 30 weeks, delivering a healthy infant. On day 41, she was discharged home with supplemental home oxygen for resting hypoxia. One month after delivery, a high resolution CT (HRCT) scan (Fig. 1B) revealed increasing number of small cysts, in addition to the pre-existing nodularity. Spirometry was restrictive with FVC of 2.05L (60% predicted), FEV1 of 1.61L (55% predicted), FEV1/FVC ratio of 78% and diffusion lung capacity (DLCO) of 25% predicted. However, the patient felt symptomatically better not requiring oxygen, which prompted her to refuse medical therapy. Eight months after the initial presentation, she was hospitalized with severe dyspnea. HRCT (Fig. 1C) revealed progression of numerous thin-walled cysts throughout the lung parenchyma. At this time, the patient agreed to initiate therapy with Sirolimus. After 15 months on Sirolimus (Fig. 1D), her spirometry improved remarkably with FVC of 2.70L (87% predicted), FEV1 of 1.99L (75% predicted), FEV1/FVC of 74, no desaturation on 6-minute walk test. However, the DLCO remained impaired at 39% predicted.

**DISCUSSION**

Pregnancy can exacerbate pre-existing LAM [3], however, our patient first developed symptoms during pregnancy that progressed dramatically until delivery. While rare even in its classic presentation, the rapid development of this highly interstitial pattern early on in pregnancy, the absence of significant cystic disease and an equally rapid regression after delivery makes this case noteworthy. The nodular interstitial appearance on HRCT is unique, when compared to the more commonly seen thin-walled cysts.

Histologically, cysts accompany LAM foci, which are islands of proliferating smooth muscle cells [1, 4]. Cells vary in morphology, appearing round, epithelioid or spindle shaped. The epithelioid cells characteristically stain positive for HMB-45, a property associated with LAM. However, proliferating-cell nuclear antigen (PCNA), a marker of cellular proliferation, is often also positive in these patients. Although LAM cells infrequently stain positive for both, cells staining predominantly for HMB-45 are associated with a less proliferative phenotype than those positive for PCNA alone [4]. Although we did not stain for PCNA, we speculate that weak HMB-45 positivity in our case could inversely signify a more proliferative phenotype. This is consistent with the dramatic clinical presentation and rapid evolution of interstitial nodularity. Cysts arising from slow, chronic parenchymal destruction were conspicuously absent when she first presented.

Epithelioid cells within the lung nodules and AML’s exhibit estrogen and progesterone receptors, with an increased ratio of progesterone to estrogen [5]. Intense hormonal stimulation during pregnancy can result in exacerbation of pre-existing LAM [6] or prompt the first clinical presentation [3, 6]. Patients diagnosed during pregnancy have higher rates of pneumothorax [6–8] and obstetric complications like preterm delivery and miscarriage [6]. Elective instrumental delivery is suggested to avoid increasing intrathoracic pressure during normal labor. Epidural anesthesia can also reduce hyperventilation and decrease the chance of pneumothorax [8]. Our patient did not have a pneumothorax or require mechanical ventilation, but the high risk for adverse maternal and fetal outcomes coupled with the steady respiratory decline, resulted in a decision to electively proceed with a cesarean section under epidural anesthesia at 30 weeks.

Interestingly, serial imaging after delivery, but prior to treatment, demonstrated a gradual radiological transition from severe interstitial nodularity to a more diffuse cystic pattern. This change is likely due to the withdrawal of hormonal stimulation after delivery, which was also reflected by the early transient symptomatic improvement. Prior reports describe the use of hormonal treatment and oophorectomy to down regulate estrogen and progesterone receptors [9, 10] further supporting this hypothesis.

Loss of heterozygosity of the tuberous sclerosis 1 and 2 genes results in the dysregulation of the mTOR signaling pathway, which underlies the pathogenesis of LAM. LAM cells invade organ systems like liver, pancreas, kidney and uterus [1] demonstrating cancer cell-like properties. Our patient had a renal AML. Sirolimus (rapamycin), an inhibitor of the mTOR pathway can stabilize lung function, decrease AML volume, reduce symptoms and improve quality of life [2]. Both a restrictive and obstructive pattern can be seen in patients with LAM. The initial severe restriction seen in our patient normalized after treatment with Sirolimus.

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**CONFLICT OF INTEREST STATEMENT**

None declared.

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**ETHICAL APPROVAL**

Not applicable.

**CONSENT**

The patient has been consented, please see attached for the signed consent form.

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