CLINICAL VIGNETTE

Hemorrhagic Renal Angiomyolipoma as Initial Presentation of Lymphangioleiomyomatosis

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Lymphangioleiomyomatosis (LAM) is a rare, slowly progressive multi-organ disease. It has a high association with tuberous sclerosis complex (TSC) and renal angiomyolipomas (AML). LAM should be considered in patients who present with renal AML, especially women of childbearing age. TSC should be ruled out in patients with bilateral renal AMLs. We describe a patient who presented with flank pain found to have a hemorrhagic renal AML and subsequently diagnosed with sporadic LAM (S-LAM).

Case Report

A 34-year-old female without significant past medical history presented with the sudden onset of right flank and lower abdominal pain. Her symptoms started the day of presentation. The patient noted associated nausea without vomiting. She denied any dysuria, hematuria, fevers, or chills.

Initial blood pressure was 95/59. Her physical examination was remarkable for right costovertebral angle tenderness and right lower quadrant abdominal pain. Laboratory data revealed a hemoglobin of 10.4 and hematocrit of 33. Her white blood cell count was 14.3 with a left shift. Urinalysis was abnormal and concerning for a urinary tract infection (UTI). Abdominal ultrasound revealed a nonspecific large heterogenous soft tissue collection in the right renal fossa and mild to moderate left hydronephrosis. A CT scan of the abdomen and pelvis with intravenous (IV) contrast showed a large 7.5 x 8.3 cm homogenous, partially fat-density mass in the right kidney with moderate perinephric hemorrhage consistent with a ruptured right renal AML. Multiple additional lesions were seen in the right kidney and one lesion in the left kidney, as well as cystic changes within the lower lobes probably representing LAM.

The patient was given IV fluids with prompt improvement in blood pressure. Interventional radiology (IR) urgently embolized the large right renal AML with emboshperes. After the procedure, she was closely monitored in the intensive care unit and started on an antibiotic for the UTI. Her hemoglobin dropped to 7.2, and she received 2 units of packed red blood cells. CT and MRI scans of the brain were negative, and she did not have any physical examination stigmata of TSC. CT scan of the chest showed multiple small air cysts consistent with LAM. She was discharged home with outpatient pulmonary follow-up.

Three months later, the patient presented with right flank pain and upper quadrant pain of 2 days duration. CT scan revealed a large right perinephric hematoma with active extravastion and a 10 mm pseudoaneurysm adjacent to the hematoma. The patient underwent embolization of these areas and was advised to return within 6 months for elective embolization of the 2.3 cm AML in the mid-left kidney. She is currently awaiting referral to a tertiary center for further LAM management.

Discussion

Renal AML is relatively common, affecting approximately 0.1-0.3% of the general population. However, LAM is a rare, slowly progressive systemic disease. Renal AML and LAM have a common progenitor cell, the LAM cell.[1] LAM cells are a proliferation of abnormal smooth muscle cells, which react with a monoclonal antibody, HMB-45.[2,3] LAM is postulated to represent low grade metastasis of LAM cells from a renal AML or another extrapulmonary source.[1] Renal AML is the most frequent extrapulmonary manifestation of LAM, composed of LAM cells, blood vessels, and adipose tissue.[2,4,5] LAM cells infiltrate the smooth muscle resulting in diffuse cystic remodeling of the lungs.[4] Air trapping, bullous formation, and pneumothorax can result from obstruction of the bronchioles by LAM cells. Additionally, lymphatic obstruction and infiltration in the chest and abdomen may cause chlyous fluid collections and fluid-filled lymphangiomyomas.[4,5]

Considerable overlap exists between renal AML, pulmonary LAM, and TSC.[2] LAM cells involve mutations in either TSC1 or TSC2 genes.[1] The activation of the mammalian target of rapamycin (mTOR) from a TSC somatic gene mutation up-regulates uncontrolled growth in the LAM cells.[6] For S-LAM, there is a predominance of TSC2 somatic mutations.[5] LAM occurs in 30% of patients with TSC. In TSC-LAM, about 93% have renal AML, whereas only 30-50% of patients with S-LAM have renal AML. In S-LAM, renal AML tend to be unilateral, small, and singular.[7] However, renal AML occurs in 60-80% of patients with TSC-LAM and tend to be multiple, larger, and with multi-organ involvement of the spleen or liver.[1,2] Due to their larger size, these renal AMLs are prone to hemorrhage.[3]

There is a gender predisposition for renal AML and LAM with greater than 80% of patients being women.[1] The average age at diagnosis is 35 years, affecting women during their

reproductive years.[3,4] This lends credence to theories of hormonal involvement in this disease.[2]

Renal AML can present with flank pain, retroperitoneal bleed, hematuria, or pyelonephritis.[2] However, the majority of patients with renal AML are asymptomatic and found incidentally during abdominal imaging studies.[3] On ultrasound, they appear echogenic with shadowing. Renal AMLs are well-defined soft tissue masses with areas of fat on CT scan. The lesions range in size from a few millimeters to greater than 10cm.[2]

Patients with LAM present with progressive dyspnea on exertion, cough, spontaneous and/or recurrent pneumothorax, chylothorax, or as an incidental finding on CT scan of the chest and/or abdomen.[2-4] CXR is unlikely to show pulmonary cysts associated with LAM. However on high resolution CT (HRCT) scan, the cysts are equally distributed in both lungs. Additionally, retrocrural lymphadenopathy, thoracic duct dilatation, pleural effusion, pneumothorax, and/or pericardial effusion may be seen on CT scan.[8]

Pulmonary function tests in LAM are usually abnormal with decreased diffusing capacity for carbon monoxide (DL_{CO}) and decreased lung volumes.[8] The forced expiratory volume in 1 second (FEV1) declines with the progression of LAM.[6] A mixed pattern with restriction may be seen. Airflow obstruction on spirometry is the most frequent abnormality.[2]

The diagnosis of LAM can be made either clinically, serologically, or pathologically once cystic changes are seen on HRCT. If the patient has evidence of TSC, AML, chylothorax, or lymphatic involvement, then the diagnosis is made clinically. If none of these are present, then serum levels of vascular endothelial growth factor-D (VEGF-D) are drawn.[4] Levels have been shown to correlate with disease severity. If VEGF-D is greater than 800 pg/ml, then lone LAM is diagnosed.[9] If the serum testing is equivocal or negative, then cytology, transbronchial biopsy, or surgical lung biopsy are needed to confirm LAM.[4]

Treatment of renal AML depends on whether the patient is symptomatic and size of the lesion. For asymptomatic cases and a lesion < 4 cm, yearly imaging is recommended. If the lesion is > 4 cm, semi-annual imaging is advised. For symptomatic renal AML and lesion size < 4 cm, monitoring symptoms is warranted. If symptoms persist, then selective arterial embolization or conservative surgery is done. If the symptoms resolve, semi-annual imaging is followed and for symptomatic renal AML > 4 cm, selective arterial embolization or conservative surgery is advised.[2,7]

Early detection of LAM in renal AML patients is important due to severe complications and morbidity associated with the disease. Patients need to be educated about the symptoms and risk of spontaneous pneumothorax.[3] After the first pneumothorax, either chemical or mechanical pleurodesis is recommended since there is a high risk of recurrence.[4] Management of airway disease and hypoxemia can be done with bronchodilators, supplemental oxygen, and pulmonary rehabilitation.[2]

Given theories of hormone influence on LAM, there have been several options for the suppression of estrogen. These have included oopherectomy, progesterone, and anti-estrogen therapy. However, there are very little published data supporting these treatment options.[2,3]

Sirolimus suppresses mTOR signaling in cells with defective TSC genes, improving lung function measured by FEV1 and forced vital capacity (FVC) in some LAM patients. Levels of VEGF-D decreased in response to sirolimus.[6] However, the beneficial effects on lung function only lasted during the treatment period. The decline in lung function continued once discontinued. Sirolimus may be indicated in moderately severe LAM.[4,6] Lung transplantation is reserved for end stage lung disease.

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