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CASE REPORT OPEN ACCESS

Lymphangioleiomyomatosis in a 43-year-old female Nigerian: Diagnosis and Management

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Abstract
Background: Lymphangioleiomyomatosis (LAM) is a rare disorder that presents in women of childbearing age. The affected patients present with spontaneous pneumothorax, chylothorax, hemoptysis, and slowly progressive dyspnea. There are poor awareness, knowledge, and records about this disease in Nigeria.
Case presentation: We report a case of pulmonary LAM in a 43-year-old woman who presented with progressive shortness of breath with recurrent hemoptysis and pneumothorax. Her imaging and Vascular endothelial growth factor level were in keeping with LAM. The typical features in the current case include the patient's age, gender, radiologic features, and VEGF- D value.
Conclusion: There is a need for a high index of suspicion for LAM in women of child-bearing age with cystic lung diseases. There is also a need for registries for rare lung diseases in Africa.

Keywords: Lymphangioleiomyomatosis, cystic lung disease, rare lung disease, leiomyoma, sirolimus.

Background

Lymphangioleiomyomatosis (LAM) is a rare disease of unknown origin that usually leads to progressive deterioration of lung function and eventual death from respiratory failure. The prevalence of diagnosed LAM is 4.9 cases per million females(range 3.35-7.76) in Europe and North America, and this varies between regions (1). There is poor epidemiological data about the prevalence in Africa. LAM affects mostly women of childbearing age presenting with spontaneous pneumothorax, chylothorax, hemoptysis, and slowly progressive dyspnea (2). The pulmonary complications are due to a hamartomatous proliferation of smooth-muscle cells, preferentially along the Broncho-vascular structures, which compressed the airway leading to obstruction of airflow (3, 4). The obstruction of pulmonary vessels causes venular congestion and disruption, leading to hemoptysis and hemosiderosis.

The diagnosis is made by a combination of clinical features and computed tomography scanning or, in cases of doubt, lung biopsy (5). Treatments including glucocorticoids, cytotoxic drugs, radiation therapy, and hormonal therapies have all been tried with no significant benefit (5, 6). Lung transplantation is considered to be a valuable therapy for patients with end-stage lymphangioleiomyomatosis.

We report a case of pulmonary LAM in a 43-year-old Nigerian woman.

Case presentation

A 43-year-old single lady was referred to the respiratory clinic from the medical outpatient

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clinic on account of recurrent shortness of breath on exertion of about seven years' duration with associated intermittent productive cough and hemoptysis. There was no associated fever, night sweat, or weight loss. She had no history of smoking. She gave a history of a regular menstrual cycle. She had a history of thoracostomy for recurrent pneumothorax. Her previous screening for TB and aspergillosis were negative. Her previous chest x-ray shows widespread bilateral reticular opacities and cystic changes in both lung fields (Fig 1).

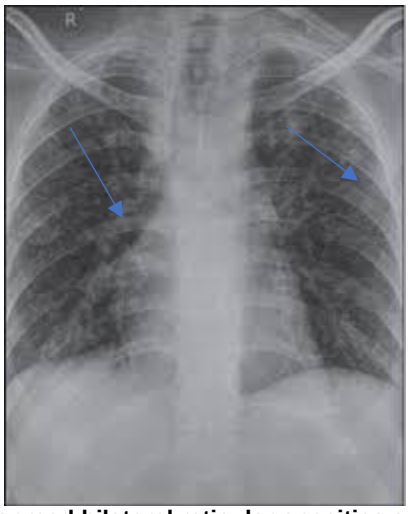

Figure 1: Chest x-ray: showing widespread bilateral reticular opacities and cystic changes in both lung fields

On general examination, she was mildly dyspneic with the use of accessory muscles of respiration and flaring of alar nasi, acyanosed, anicteric, afebrile, and had no pedal edema. On respiratory examination, her respiratory rate was 22 cycles per minute, SpO2 of 95% with hyper-resonance on percussion and diminished breath sounds in both lung zones. Her cardiovascular examination, pulse rate -90 beats per minute, Blood pressure- 130/70mmHg, Apex beat-5 left intercostal space, mid-clavicular line, and heart sounds; first and second. Her abdominal and Neurologic examinations were normal. Her presumptive diagnosis was diffuse lung disease with possible bronchiectasis. Her follow-up Chest computer tomography scan showed bilateral diffuse widespread thin-walled cysts of varying sizes with suspicion of Lymphangioleiomyomatosis (Fig 2).

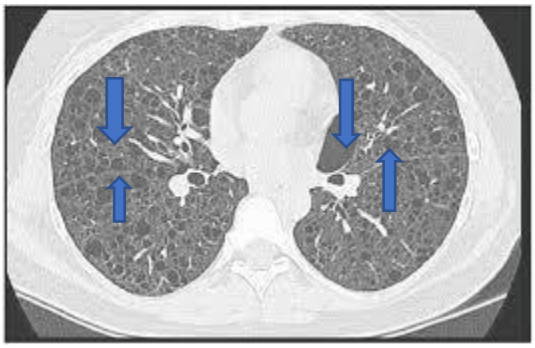

Figure 2: Sagittal section of Chest computer tomography scan showing bilateral diffuse widespread thin-walled cysts of varying sizes

Her abdominopelvic CT scan shows tiny renal calculi in both kidneys. Also noted was a hemangioma of 15x16mm in segment V of the liver. Her spirometry showed an obstructive pattern; PRE-FEV1 was 1.62 (62%), PRE- FVC was 2.04(77%), PRE-FEV1/FVC was 68(80%), PRE-PEF was 193(58%), PRE-FEF25-75 was 0,86(27%). Her Echocardiography showed normal left ventricular function and no evidence of pulmonary hypertension. A lung biopsy was

not done to avoid a repeat pneumothorax because she has just had repeated pneumothoraces before being referred to the specialist clinic. She was placed on twice-weekly Azithromycin, a Long-acting beta-agonist/inhaled corticosteroid (salmeterol/fluticasone), and intermittent SABA(Salbutamol). She had a stat dose of pneumococcal conjugate 13 and was commenced on pulmonary rehabilitation. The patient sought treatment abroad and had a repeat Chest computer tomography scan done, which showed a similar pattern to the previous chest computer tomography scan. Fig 3.

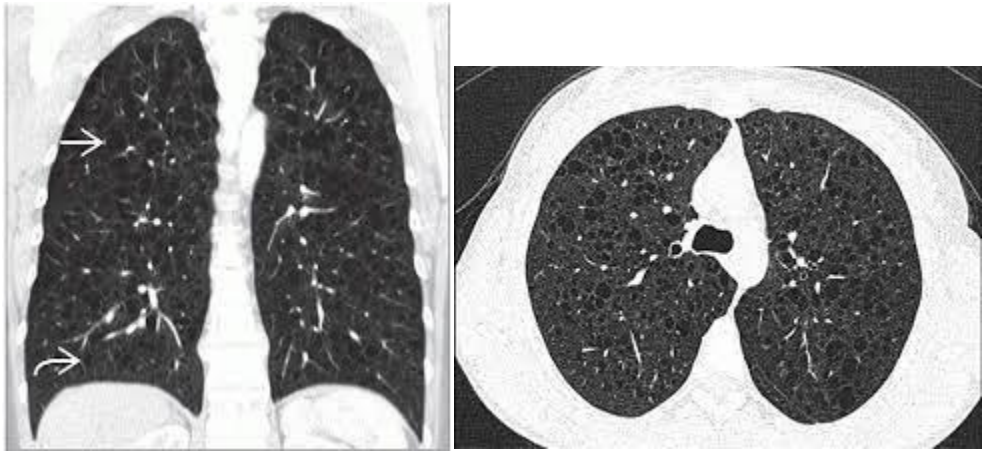

Figure 3: Coronal and Sagittal sections: Chest computer tomography scan showing bilateral diffuse widespread thin-walled cysts of varying sizes

She also had full lung function tests done. Her repeat spirometry about six months after the previous one showed a mixed pattern with significant reversibility; PRE-FEV1 was 0.80 (34%), PRE-FVC was 1.82(63%), PRE-FEV1/FVC was 44(53%), PRE-PEF was 1.45(23%), PRE-FEF25-75 was 0.37(14%), POST-FEV1 was 0.93, POST-FVC was 2.11, Her Vascular endothelial growth factor (VGEF) - D was elevated-800pg/mL(Normal value<800pg/mL) (7). She was commenced on sirolimus 2mg daily to maintain a level of 5-15ng/mL. This is being monitored serially. Her last serum sirolimus level was 4.73 ng/mL

POST FEF25-75 was 0.42 and reversibility was 17%. Her diffusion lung capacity of carbon monoxide (DLCO) was low 6.7l(31%) indicating poor gaseous exchange. Her lung capacities were also reduced (Total lung capacity-2.19(50%<), Functional residual capacity-1.36(59%<), and vital capacity 2.06(70%<)) done.

Presently, she has improved exercise tolerance and no episode of hemoptysis or a new pneumothorax. Her saturation level was >96% on room air.

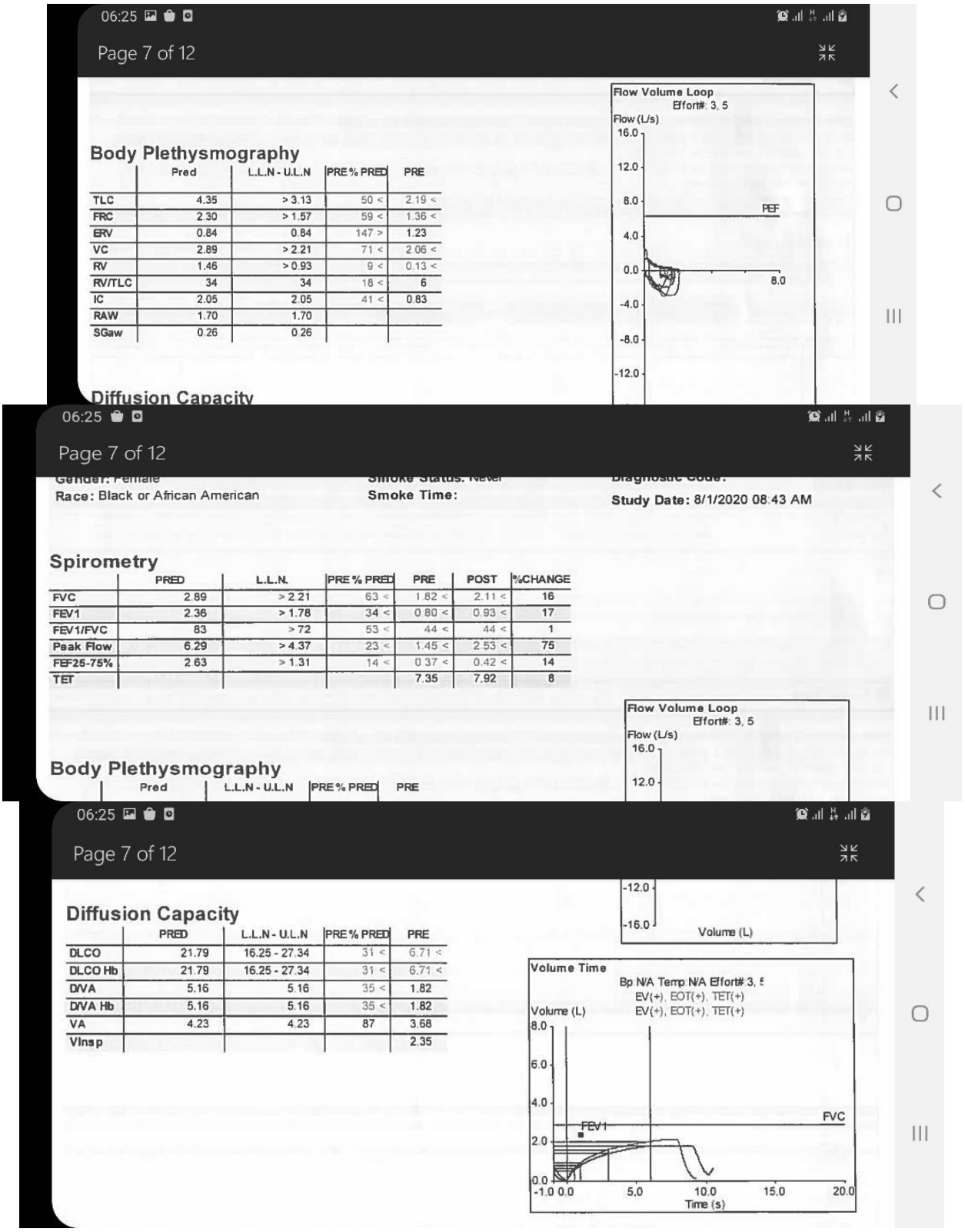

Figure 4: Spirometry showing a mixed pattern with significant reversibility. Her lung capacities were reduced (Total lung capacity, functional residual capacity, and vital capacity). The diffusion lung capacity of carbon monoxide (DLCO) was low.

Discussion

Lymphangioleiomyomatosis is a rare disorder that presents in women. The prevalence of diagnosed LAM is 4.9 cases per million females(range 3.35-7.76) in Europe and North America, and this varies between regions (1). There is poor epidemiological data about the prevalence in Africa. The mean age at presentation is 37 years (range, 18–89 years). Many authors described it as a disease of women of childbearing age (5). However, LAM is now considered to be a chronic disease that can affect both pre and postmenopausal women (8). The age of our patient falls within the range in the literature. There are two forms of LAM; the sporadic form which occurs in a nonheritable form that involves only the lung, lymphatics, and kidney and is estimated to have a prevalence of approximately 3.3-7.7 per 1,000,000 (8). This second form is the tuberous sclerosis-associated form that occurs in up to 40% of women with the tuberous sclerosis complex. (9). There is the suggestion of a genetic link to the tuberous form of the disease (10). This case shows lung involvement with renal calculi in both kidneys and liver hemangiomas and may suggest a sporadic form. The classical histology of LAM shows a proliferation of smooth muscle arranged in fascicular, trabecular, and papillary patterns associated with slit-like vascular channels (11). However, lung biopsy wasn't done in this case because of the classical features of the disease demonstrated on the imaging and elevated VEGF-D. Lung biopsy is often used to confirm the diagnosis, but recent clinical guidelines specify that a definitive diagnosis can be made without lung biopsy in the presence of lung cysts, plus evidence of either angiolipomas, chylous collections, or tuberous sclerosis (7, 12). In addition, the Application of European Respiratory allowed a definite diagnosis without biopsy in 69%, and adding VEGF-D measurements to ERS criteria further reduces the need for biopsy by 10% (7, 12). VEGF-D is a lymphangiogenic growth factor that is increased in most patients with lymphangioleiomyomatosis (13). Serum VEGF is a biomarker that can distinguish sporadic lymphangioleiomyomatosis from other cystic and chylous lung diseases, potentially decreasing the need for lung biopsy (9). Crino et al reported that with a cutoff value for VEGF-D of 574 pg/mL, the test sensitivity for sporadic lymphangioleiomyomatosis was 86%, and the specificity was 91%, and the positive likelihood ratio was 9.6 (9).

The differential diagnoses considered based on the radiologic findings were interstitial lung disease and bronchiectasis. However, all the serologic and infectious screening for the differentials were negative in this patient.

The exact pathogenesis of LAM is unclear. It is characterized by abnormal smooth muscle-like cell (LAM cell) proliferation and infiltration. The proliferating LAM cells exhibit features of co-expressing contractile proteins (smooth muscle actin and desmin) and melanocytic markers (HMB-45, HMSA-1, Melan-A, or MART-1, and microphthalmia transcription factor). These features mean this lesion can be considered one of the perivascular epithelioid cell tumor family members. Matsui et al demonstrated the presence of estrogen receptors and progesterone receptors in the epithelioid cells of patients with LAM who never received hormonal therapy but later became negative after treatment with progesterone and tamoxifen (14). A hormonal cause has been suggested since the disease is often preceded by pregnancy or hormonal therapy (15). There was no history of use of hormonal therapy for hormonal imbalance in our patient.

Treatment options include hormonal therapy with (tamoxifen and progesterone), oophorectomy, and sirolimus. (16, 17, 18, 19). A lung transplant seems to offer better survival benefits for patients with pulmonary LAM (20, 21). The consideration for our patient was sirolimus with other forms of supportive therapies. Katsutoshi et al reported that low-dose sirolimus (trough level, 5 ng/mL or less) performed as well as the higher doses used previously for improving pulmonary function and decreasing chylous effusion in patients with LAM (13, 22).

The average survival of patients with LAM is reported to be about 9.4 years (2). Silverstein et al. found that death from respiratory insufficiency usually occurred within four years of the onset of lung disease. Currently, there is no report from Nigeria about the burden and prognosis of the disease.

Our limitations in the evaluation of the patient include unavailability of access to VEGF assay and lung volumes/capacities locally. These tests were however done albeit abroad.

Conclusion

In conclusion, we present one of the rare lung diseases, a case of pulmonary LAM in a 43-year-old woman who presented with progressive shortness of breath with recurrent hemoptysis

and pneumothorax. The typical features in the current case include the patient's age, gender, radiologic features, and VEGF- D value. There is a need for a high index of suspicion for LAM in women of child-bearing age with cystic lung diseases.

List of abbreviations

LAM	Lymphangioleiomyomatosis,
VEGF- D	Vascular endothelial growth factor
TB	Tuberculosis
CXR	Chest x-ray
RR	Respiratory rate
PR	Pulse rate
BP	Blood pressure
HS	Heart sound
LICMCL	Left intercostal space midclavicular line
CT	Computer tomography
PRE-FEV1	Pre-forced expiratory volume in the first second
PRE- FVC	Pre-forced vital capacity
PRE-PEF	Pre-peak expiratory flow
PRE-FEF25-75	Pre-forced expiratory flow between 25-75%
POST-FEV1	Post- forced expiratory volume in the first second
POST-FVC	Post-forced vital capacity
POST FEF25-75	Post forced expiratory flow in 25-75%
ECHO	Echocardiography
LABA/ICS	Long-acting beta-agonist/Inhaled corticosteroid
DLCO	Diffusion lung capacity of carbon monoxide
mmHg	millimeters of mercury
pg/mL	picogram per milliliter
ng/ml	nanogram per milliliter
SABA	Short-acting beta-agonist

Declarations

Ethics consideration
Written informed consent for publication was obtained from the patient whose management is being reported.

Consent for publication
The authors hereby give consent for the publication of this work under the Creative Commons CC Attribution. Non-commercial 4.0 license.

Availability of data and materials
All data generated or analyzed in this study are included in this article and are available on request.

Competing interests
The authors declare no competing interest in the publication of this case report.

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