



Lymphangioleiomyomatosis-Tuberous Sclerosis Complex. Contraindication For Lung Transplantation? A Case Report

Complejo linfangioleiomiomatosis-esclerosis tuberosa, ¿contraindicación para el trasplante pulmonar? Presentación de un caso



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Transplantation



Palabras clave (DeCS)

Esclerosis tuberosa
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Trasplante

Summary

The lymphangioleiomyomatosis (LAM) - Tuberous Sclerosis (TS) Complex is a rare disease with multisystem involvement affecting mainly lung and brain. We present the case of a 25-year-old female patient with pulmonary LAM. During the work-up studies for the lung transplantation protocol, the systemic extrapulmonary involvement of the LAM-TS complex is documented. From this case, a literature review of the systemic radiological manifestations of the disease and of the diagnosis and management recommendations of these patients was made. Special focus was made on the indications and contraindications of lung transplantation.

Resumen

El complejo linfangioleiomiomatosis (LAM)-esclerosis tuberosa (ET) es una enfermedad rara, con compromiso multisistémico que afecta principalmente pulmón y cerebro. Se presenta el caso de una paciente de 25 años con LAM pulmonar que ingresa a la institución para protocolo de trasplante pulmonar. Durante los estudios de extensión se documenta compromiso extrapulmonar sistémico del complejo LAM-ET. A partir de este caso, se realizó una revisión de la literatura de las manifestaciones radiológicas sistémicas de la enfermedad y las recomendaciones de diagnóstico y manejo de estos pacientes; en especial, las indicaciones y contraindicaciones del trasplante pulmonar.

Introduction

Lymphangioleiomyomatosis (LAM) is an interstitial lung disease caused by interstitial smooth muscle proliferation that produces cystic changes of the parenchyma. Classically, this disease affects women of reproductive age; the most frequent symptoms are chronic cough, progressive decrease in functional status, occasional spontaneous recurrent chest pain due to pneumothorax and quillothorax. LAM may appear as a sporadic or inherited autosomal dominant disease associated with tuberous sclerosis complex (TS) (1). The case of a patient with LAM-TS complex with multisystem involvement is presented below and the possibilities of lung transplantation in these patients are discussed.

Case report

A 24 year old female patient who is admitted to a pulmonary LAM lung transplant protocol with repeated episodes of pneumothorax and progressive decrease in functional status. Chest x-ray (Figure 1) and chest CT scan (Figure 2) show replacement of normal bilateral lung parenchyma by multiple thin-walled cysts and left basal septal pneumothorax.

As an extension study, an ultrasound of the abdomen is performed (Figure 3) showing multiple cortical echogenic lesions compatible with renal angiomyolipomas in both kidneys, a finding correlated with CT (Figures 4a and b).

The patient also has a history of childhood seizure syndrome and mild cognitive impairment. For this reason, a cerebral magnetic resonance imaging (MRI) was performed to find high signal lesions in

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sequences with cortical T2 and bilateral frontoparietal cortical and cortico-subcortical information compatible with cortical tubers (Figure 5) and linear radial bands in high signal white matter with T2 information (Figure 6). Periventricular calcified nodular lesions of less than one centimetre in relation to calcified subependymal nodules are also identified (Figure 7). All of the above findings are compatible with the manifestations of tuberous sclerosis in the central nervous system.

As an incidental finding, multiple osteoblastic lesions are found in the posterior elements of some thoracic, sacral and iliac vertebrae (Figures 8a and 8b). Alterations in lung, kidney, brain and bone were interpreted as part of the spectrum of LAM-TS disease. This raises doubts on the part of the treating team as to whether the multisystemic involvement of LAM-TS is a contraindication for lung transplantation.

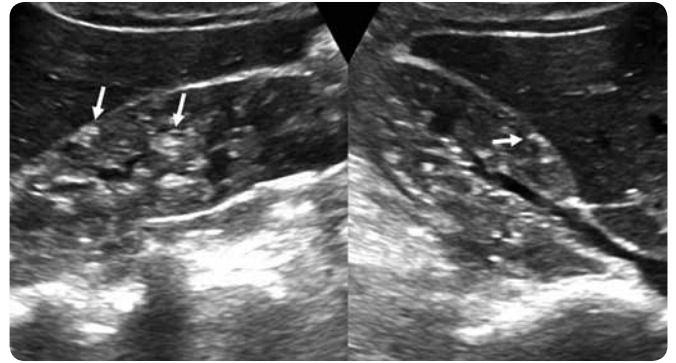


Figure 3. Ultrasound of the right kidney, longitudinal and transverse cuts. Multiple ecogenic cortical lesions that do not deform the renal contours and cause loss of corticomedullary differentiation by bilateral renal angiomyolipomas (arrows).



Figure 1. Chest x-ray, posterior anterior. Increased lung volume with diffuse bilateral reticular interstitial opacities and a radiolucent image at the base of the left hemithorax suggestive of bull or septate pneumothorax.

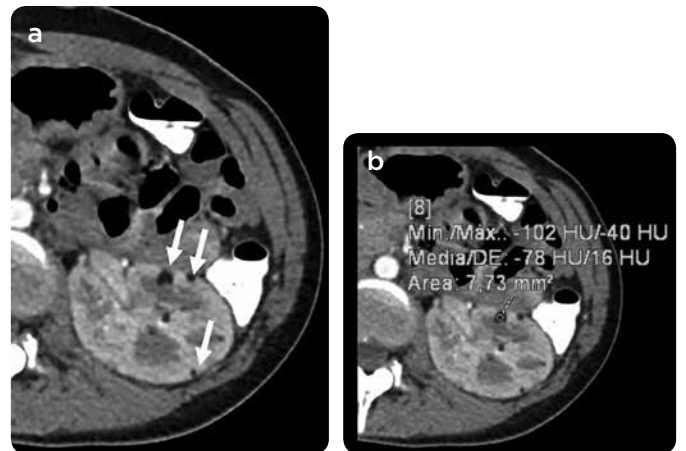


Figure 4. a and b). CT scan of the abdomen with contrast dye, axial cuts. Bilateral cortical focal lesions with fat density by renal angiomyolipomas (arrows).



Figure 2. Chest CT, axial, pulmonary window. Bilateral and diffuse pulmonary parenchyma replacement by multiple thin-walled cysts. Bull/pneumothorax with associated left septal defect.

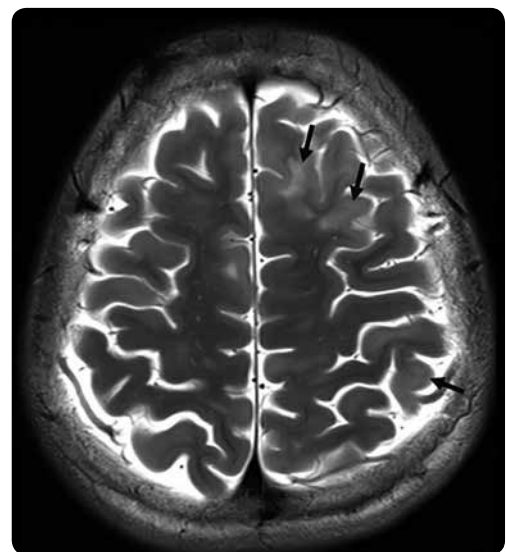


Figure 5. Brain MRI, sequence with axial T2 information. Cortical Tubers. Multiple lesions on the left frontal and parietal lobes, cortical and subcortical, high signal (arrows).

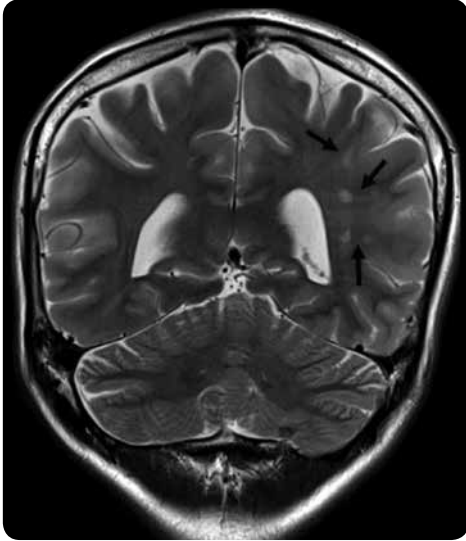


Figure 6. Brain MRI, sequence with coronal T2 information. High-signal, linear bands of white matter directed from the lateral ventricles to the cortex (arrows). Some of them are found in relation to cortical tubers.

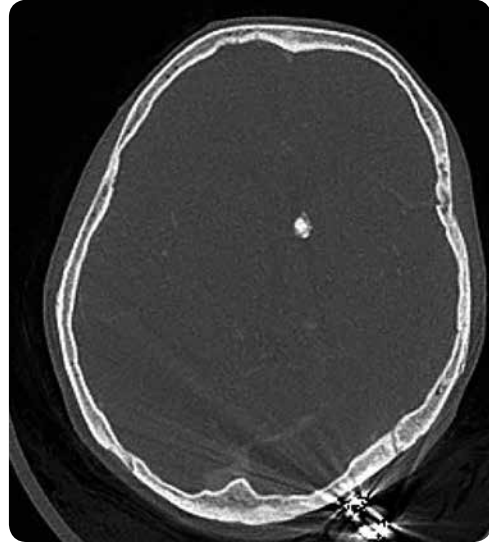


Figure 7. Skull CT scan of bone window. Calcified periventricular subependymal nodules.

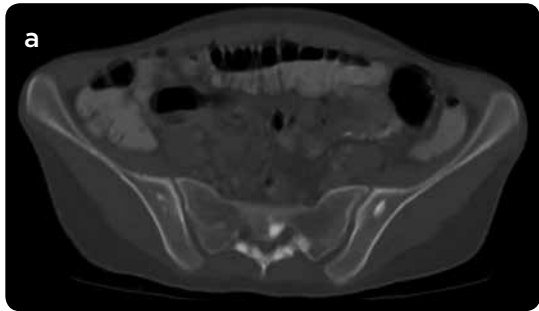


Figure 8. a and b) CT, axial cuts in bone window. Multiple osteoblastic lesions involving (a) the sacrum and both iliac bones and (b) a thoracic vertebra.

Discussion

Tuberous sclerosis (TS) is an autosomal dominant disease caused by the mutation of the TSC1 and TSC2 suppressor genes responsible for regulating cell growth and differentiation (2). The involvement of TS is multi-systemic; classically, Vogt's clinical triad of mental retardation, epilepsy and sebaceous adenomas in the skin has been described (2). LAM interstitial lung involvement may be sporadic or as part of the systemic spectrum of TS; in both cases it affects young women of reproductive age (1).

Its manifestations in the central nervous system include cortical tubers, radial migration bands, subependymal nodules and giant cell astrocytoma (3, 4). Cortical tubers are cortical epileptogenic foci typically located in the frontal lobes bilaterally; in MRI they show high signal strength in sequences with T2 spin echo and FLAIR information and do not enhance with the contrast (3). Radial migration bands are believed to represent heterotopic glia, are located perpen-

dicular to the ventricles and are directed toward the cortex, often in relation to the tubers. In MRI they are recognized as high signal bands with T2 information perpendicular to the ventricles (3). Subependymal nodules are located in the walls of the lateral ventricles, usually multiple. It is often calcified. In 10 % they can degenerate into giant cell astrocytomas (3).

Ninety-seven percent of patients with LAM-TS show abnormal findings on chest radiography, including: increased lung volume, reticular interstitial opacities, pneumothorax, or pleural effusion by chylothorax. Cysts are seen on less than 50 % of x-rays (1). Chest CT allows for better characterization of lung findings. The typical characteristic is multiple cysts between 2 and 5 mm in diameter, with thin walls less than 2 mm thick; bilateral and with diffuse compromise and slight respect for the pulmonary apexes (1, 4). When the disease is in its early stages, normal lung parenchyma can be recognized by surrounding the cysts; however, as the disease pro-



gresses, cysts can replace almost all of the healthy parenchyma (1).

The prevalence of renal angiomyolipomas in patients with sporadic LAM is less than 50 %; however, in patients with LAM-TS it increases to 80 % (5). In the latter case, they are more often symptomatic, multiple, bilateral and more likely to grow over time. They have an increased risk of rupture and bleeding (4). The most important characteristic of renal angiomyolipomas is the fat inside them (5). According to the European Respiratory Society, all patients with bilateral renal angiomyolipomas should be screened for TS and patients with renal angiomyolipomas and TS should be screened for LAM (6).

Bone involvement is variable; multiple osteoblastic lesions in the spine are more frequent in patients with LAM-TS than in patients with sporadic LAM (4, 7). Other bone changes described are: hyperostosis of the skull, scoliosis of the spine and multiple and diffuse lytic lesions (4).

Lung transplantation is a therapeutic option in patients with LAM and terminal lung disease (6); in the vast majority of transplant patients sporadic LAM is found and less than 10% corresponds to the LAM-TS complex (8); however, the different guidelines do not contraindicate lung transplantation in the latter scenario without having clear data on more complications or worse survival (6).

The need for pleurodesis and pleurectomy for complications of LAM in the pleural space has been reported in 9% to 54% of lung transplant patients (9-11). Pneumothorax occur with a frequency of 3.5 events during the disease, with an average of 5 interventions, increasing morbidity and disease costs (12). Although this does not represent a total contraindication for transplantation, some centers consider it a relative contraindication due to the increased risk of intraoperative and post-surgical complications, such as pleural adhesions and hemorrhage (10-13).

In addition to the complications inherent in lung transplantation, patients with LAM and LAM-TS may suffer from native lung pneumothorax, quillothorax and chylothorax. The prevalence of these complications varies from center to center, up to 33% of patients (8-11). Less frequent is the recurrence of LAM in the pulmonary graft; this complication is rare and its diagnosis has been made in post mortem biopsies in the vast majority of cases (14). The pathophysiology of disease recurrence is not yet clear; however, it is important to consider this possibility in patients with impaired respiratory function (13).

Drugs that inhibit the mTOR protein (sirolimus) have been shown to improve respiratory function and stabilize lung disease. In post-transplantation, the recurrence of quillothorax, extrapulmonary manifestations, such as renal angiomyolipomas, and the recurrence of lung disease decrease (8-11). However, its use is debated in the early post-surgical period due to the risk of dehiscence of bronchial anastomoses by altering the inflammatory response, fibroblastic proliferation and angiogenesis (11).

Conclusions

- » LAM is an interstitial lung disease that may be associated with the TS complex or as an isolated disease, in both cases progressively affecting lung function.

- » The LAM-TS complex is a multisystemic disease that often involves the central nervous system, lungs and kidneys.
- » The discovery of multiple and bilateral renal angiomyolipomas increases the suspicion of LAM and the LAM-TS complex.
- » There is no contraindication for lung transplantation in patients with LAM-TS.
- » It is important to know the complications associated with LAM in lung transplant patients.

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