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Recurrent pneumothorax as unusual presentation in tuberous sclerosis complex

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ABSTRACT. Tuberous sclerosis, also known as Bourneville's disease is an autosomal dominant disorder; mental retardation, seizures and facial angiofibromas represent the classic clinical triad; intelligence is sometimes preserved. Hamartomas can be found in the central nervous system, kidneys, retina and skin. Characteristically, there are hypopigmented spots on the trunk followed by wartlike lesions, known as adenoma sebaceum, distributed in a butterfly pattern over the face and cheeks. Histologically, pulmonary involvement demonstrated by lymphangioleiomyomatosis, with multiple parenchymal cysts whose walls contain proliferating smooth muscle fibers; this can lead to obstruction, air trapping, bullae formation, and pneumothorax; the presence of the latter is most uncommon. The therapeutic complexity, poor prognosis and the close follow-up required by these patients prompt our report.

Key words: Tuberous sclerosis, cystic lung disease, pneumothorax, Bourneville's disease.

RESUMEN. La esclerosis tuberosa, también conocida como enfermedad de Bourneville, es un desorden de tipo autosómico dominante caracterizado por la clásica tríada de retraso mental, convulsiones y angiofibromas faciales. En algunos pacientes, la inteligencia está conservada. Se pueden encontrar hamartomas en el sistema nervioso central, riñones, retina y piel; en ésta hay lesiones hipopigmentadas del tronco seguidas por otras faciales en forma de alas de mariposa, papiliformes, conocidas como adenomas sebáceos. Cuando se presentan lesiones pulmonares, demostradas por la linfangioleiomiomatosis, caracterizándose por numerosos quistes parenquimatosos con proliferación de músculo liso en su pared, frecuentemente existe obstrucción, atrapamiento de aire y neumotórax espontáneos, cuya presencia es aun más rara. La complejidad en el tratamiento, seguimiento y mal pronóstico motivan la presentación del caso.

Palabras clave: Esclerosis tuberosa, enfermedad pulmonar quística, neumotórax, enfermedad de Bourneville.

INTRODUCTION

Tuberous sclerosis (TS) complex, also known as Bourneville's disease, is the association of benign skin, cerebral, pulmonary and renal lesions that include a spectrum of patterns that can be associated to complications such as malignancy and pneumothorax. Here we present the case of a female admitted to our institution that presented a challenge in management and diagnosis.

CASE PRESENTATION

A 17-year-old female with a history of left nephrectomy for an angiomyolipoma a year before, received chemoradiation as adjuvant treatment due to a specimen's mistaken histological diagnosis. Four months prior to arrival she presented spontaneous bilateral pneumothoraces, more severe on left side, that resolved after 72 hours with a water seal system. The diagnosis of TS was entertained by the presence of forehead plaques and facial angiofibromas (figure 1). A brain magnetic resonance (MRI) revealed lesions compatible with TS (figures 2A and 2B); a computed tomography (CT), showed multiple well-defined lung cysts outlined by thin walls typical of lymphangioleiomyomatosis (LAM), (figures 3A and 3B) as well as renal lesions. The patient presented a second spontaneous tension left pneumothorax that did not respond to chest tube and water seal system therapy; a left video assisted thoracoscopy (VATS) achieved successful bullectomy for an apical bulla, with histological confirmation of LAM (figures 4A and 4B); a povidone-iodine (PVP-I) pleurodesis was also performed during the same procedure. A contralateral pneumothorax

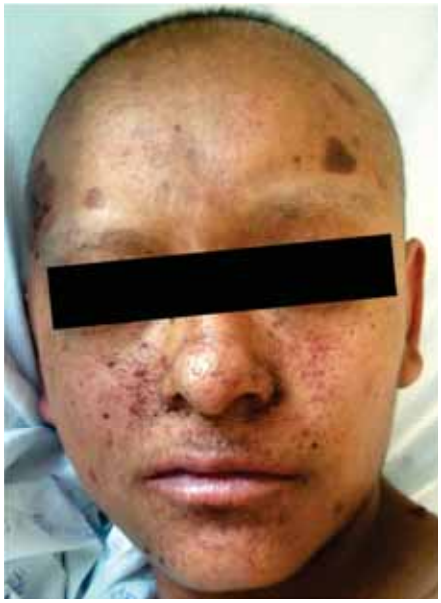

Figure 1. Forhead plaques and facial angiofibromas characteristic of TS.

appeared a few days later; VATS showed multiple parenchymal superficial cysts without a distinct site of air leak; mechanical and PVP-I pleurodesis were performed and a pneumoperitoneum was induced to reduce the size of the pleural cavity (figure 5A). A Heimlich valve was inserted for a persistent left apical pneumothorax that resolved two months after discharge from the hospital (figure 5B). She continues to be seen periodically at the Outpatient Pediatric, Thoracic Surgery and Genetics Clinics of our institution.

The Genetics and Pathology Departments concluded that tuberous sclerosis *de novo* was the definitive diagnosis.

DISCUSSION

During the patient's work-up, the diagnosis of Birt-Hogg-Dubé syndrome (BHDS) was entertained in order to explain the presence of lung cysts and pneumothorax;

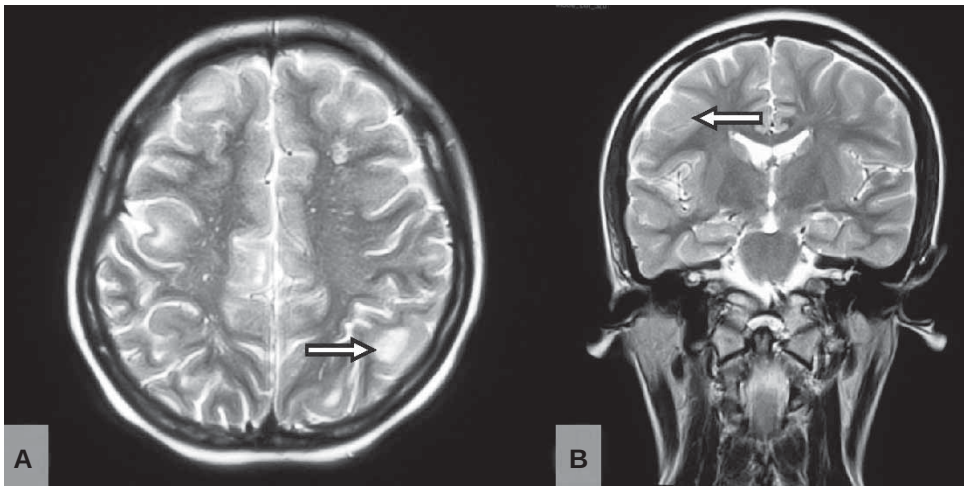

Figure 2. A) Axial and **B**) coronal T2-weighted MR image depicts cortical tubers as hyperintense lesions in the cortico-subcortical union.

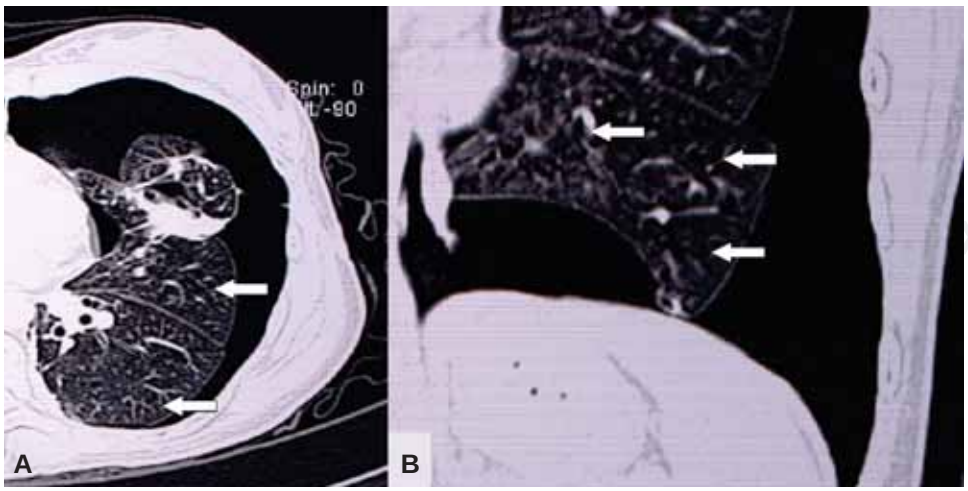

Figure 3. A) Axial and **B**) coronal computed tomography pulmonary window demonstrating the left pneumothorax, the typical finding in LAM; round, thin-walled cysts of variable size and contour.

this syndrome was originally described by Birt *et al*. in patients with multiple papular skin-colored, dome-shaped lesions on the face, neck, and trunk, histologically associated to fibrofolliculomas, trichodiscomas and soft fibromas;[1] skin lesions appear after the third decade of life. There is also a relationship to renal carcinomas, but not to brain lesions.

BHDS can be very easily confused with TS due to the close clinical relationship between them, so painstaking attention has to be made to the nonclinical details by means of high definition CT and, if possible, lung biopsy.

Other method of discrimination is by the study of the genetical inactivation of tumor suppressor genes TSC1/TSC2 for TS and mutations on the FLCN gene for BHDS.[2]

This was not necessary in our patient because the lung's different histological patterns are sufficiently different to clearly identify the two diseases; in BHDS the cystic air spaces are produced by the destruction of alveolar walls, lined by a layer of pneumocytes, surrounded by septal and/or pleural interstitial tissue in part, and are not joined by reactive stromal proliferation and inflammation, except in the case of rupture; they have their own delicate elastic framework beneath the epithelial layer, resembling normal alveoli in its basic structure. A small vein protrusion into the cystic lumen is also a characteristic of BHDS.[3] On the other hand, LAM cysts are surrounded by proliferating smooth muscle in the lung parenchyma adyacent to them, lined with numerous type II pneumocytes.[4]

Other differential diagnosis could also be entertained in a scenario with primary pneumothorax such as this, like alpha 1-antitrypsin deficiency,[5] Marfan syndrome,[6] Ehlers-Danlos syndrome,[7] primary LAM,[8] Langerhans cell histiocytosis[9] and cystic fibrosis[10] but were discarded on clinical, genetic and/or laboratory grounds.

Pulmonary involvement in TS occurs in less than 1% of patients[11] and there are few reports regarding the association of apical bullae and LAM.[12,13] LAM in TS is seen with high frequency in women because it is believed that the mutations in TSC1 and TSC2 that occur in benign cells of the lung come from the kidney angiolypomas, as the neoplastic cells are more mobile *in vitro* and estrogens stimulate their motility producing infiltrates in the muscular tissue of airways and distal entrapment of air with a subsequent cystic pattern characteristic

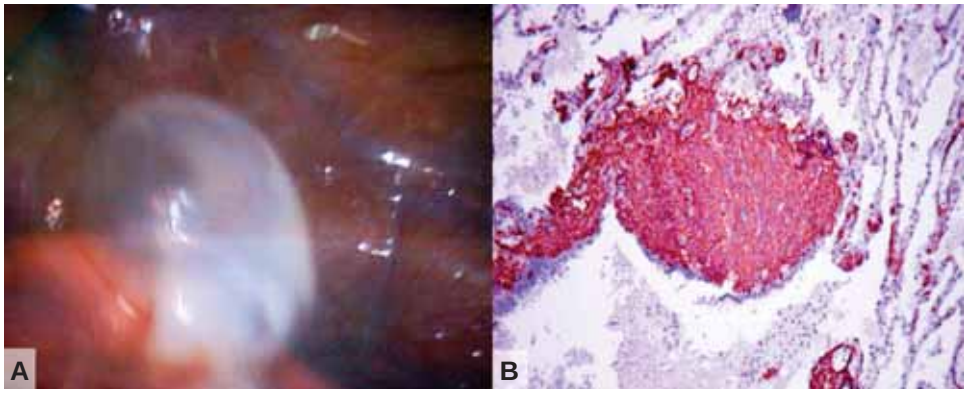

Figure 4. A) Thoracoscopy evidences apical bullae secondary to the cystic disease accompanying tuberous sclerosis. **B**) Immunostain demonstrating strong and diffuse cytoplasmic positivity for smooth muscle actin (40X).

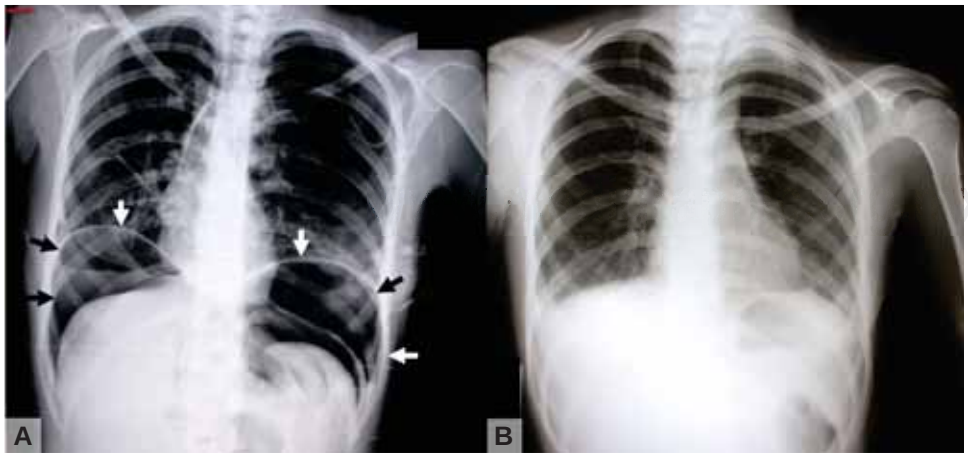

Figure 5. A) Pneumoperitoneum (*arrows*) to reduce pleural spaces. **B**) Radiographic control 2 months later, without the Heimlich valve.

of the disease.[14] We could only find 19 reported cases of pneumothorax and TS, with a reported mortality of almost 50%.[15] This association represents a challenging problem, because the relapsing pneumothoraces may difficult the patient's recovery,[16] as in our patient that had, not only relapsing, but also a persistent left sided air leak.

Although hormonal treatment has been proposed for patients with pulmonary involvement, we have not attempted it due to the lack of randomized studies.[17]

Pneumoperitoneum is a procedure originally developed for the treatment of tuberculosis in the pre-antibiotic era, its basic principle is to reduce the pleural cavities when a residual space is not occupied by lung parenchyma, allowing a complete adherence of this structure to the thoracic wall. In recent times, remains as part of the armamentarium for the thoracic surgeon when a residual space is evident during or after surgery, allowing a faster recovery. In our institute it is seldom performed, but when done, we encounter satisfactory results, such as this patient.

In conclusion, TS and spontaneous pneumothoraces represent a very rare association requiring a multidisciplinary approach in order to properly estimate the extension of the patient´s disease and offer a comprehensive and satisfactory treatment plan.

Our patient, although alive, has a poor prognosis, due to the probability of progressive respiratory failure and another pneumothorax leading to her demise.

REFERENCES

1. Birt AR, Hogg GR, Dubé WJ. *Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons*. Arch Dermatol 1977;113:1674-1677.
2. Baba M, Hong SB, Sharma N, *et al. Folliculin encoded by the BHD gene interacts with a binding protein, FNIP1, and AMPK, and is involved in AMPK and mTOR signaling*. Proc Natl Acad Sci USA 2006;103:15552-15557.
3. Koga S, Furuya M, Takahashi Y, *et al. Lung cysts in Birt-Hogg-Dubé syndrome: histopathological characteristics and aberrant sequence repeats*. Pathol Int 2009;59:720-728.
4. Kalassian KG, Doyle R, Kao P, Ruoss S, Raffin TA. *Lymphangioleiomyomatosis: new insights*. Am J Respir Crit Care Med 1997;155:1183-1186.
5. Daniel R, Teba L. *Spontaneous pneumothorax and alpha 1-antitrypsin deficiency*. Respir Care 2000;45:327-329.
6. Hall JR, Pyeritz RE, Dudgeon DL, Haller JA Jr. *Pneumothorax in the Marfan syndrome: prevalence and therapy*. Ann Thorac Surg 1984;37:500-504.
7. O'Neill S, Sweeney J, Walker F, O'Dwyer WF. *Pneumothorax in the Ehlers-Danlos syndrome*. Ir J Med Sci 1981;150:43-44.
8. Berkman N, Bloom A, Cohen P, *et al. Bilateral spontaneous pneumothorax as the presenting feature in lymphangioleiomyomatosis*. Respir Med1995;89:381-383.
9. Mendez JL, Nadrous HF, Vassallo R, Decker PA, Ryu JH. *Pneumothorax in pulmonary Langerhans cell histiocytosis*. Chest 2004;125:1028-1032.
10. Flume PA, Strange C, Ye X, Ebeling M, Hulsey T, Clark LL. *Pneumothorax in cystic fibrosis*. Chest 2005;128:720-728.
11. Dwyer JM, Hickie JB, Garvan J. *Pulmonary tuberous sclerosis. Report of three patients and a review of the literature*. Q J Med 1971;40:115-125.
12. Loh C, Sadler MA. *Pulmonary lymphangioleiomyomatosis and a solitary renal angiomyolipoma in a 26-year-old woman who presented with spontaneous pneumothorax*. Emerg Radiol 2001;8:53-54.
13. Yuko S, Takehisa O, Toshiaki W, Kiminobu A, Makoto Y, Juichi K. *Tuberous sclerosis with bilateral renal angiolypoma and repeating pneumothorax. A case report*. Nishinihon Journal of Urology 2011;63:601-603.
14. Costello LC, Hartman TE, Ryu JH. *High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex*. Mayo Clin Proc 2000;75:591-594.
15. Babcock TL, Snyder BA. *Spontaneous pneumothorax associated with tuberous sclerosis*. J Thorac Cardiovasc Surg 1982;83:100-104.
16. Narayan RL. *Images in clinical medicine. Spontaneous pneumothorax in tuberous sclerosis*. N Engl J Med 2008;358:177.
17. Castro M, Shepherd CW, Gomez MR, Lie JT, Ryu J. *Pulmonary tuberous sclerosis*. Chest 1995;107:189-195.

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