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CASE REPORT

Lymphangiomyomatosis in Bourneville's Tuberous Sclerosis

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Abstract

Lymphangiomyomatosis is a rare disease characterized by a proliferation of abnormal smooth muscle cells responsible for infiltration with destruction of tissue architecture and genesis of cystic lung and lymphatic lesions.

In addition to lung damage, Bourneville's tuberous sclerosis (BTS) affects also the skin, brain, retina, kidneys and, less frequently, the heart and bone. We report the case of a young patient with bilateral pneumothorax revealing pulmonary lymphangiomyomatosis in the context of BTS.

Keywords: Bilateral Pneumothorax; Lymphangiomyomatosis; Bourneville's Tuberous Sclerosis

Introduction

There is a genetic relationship with BTS and lymphangiomyomatosis, including the participation of the TSC2 gene, that's why clinicians need to be conscious of the association and to make a STB assessment in the face of any suspicion of lymphangiomyomatosis (namely bilateral pneumothorax). Lymphangiomyomatosis is a young woman's disease, often revealed by recurrent pneumothorax, with or without exertional dyspnea. The analysis of molecular mechanisms during BTS and lymphangiomyomatosis and the demonstration of migratory properties of smooth muscle cells reveal specific antiproliferative therapeutic prospects.

Observation/ Results

She is a patient aged 25 yo, mentally retarded, followed for an undocumented kidney problem for the last 4 years.

Since 4 months, she reports dyspnea of effort with aggravation of the bilateral lumbar pain. the symptomatology increased one month ago by a dyspnea of rest with a dry cough without chest pain or hemoptysis, which prompted her to go to the emergency, the clinical examination found a polypneic patient at 32 c/ min sao2 at 79%, intercostal draught with a bilateral air epilepticus syndrome. A chest X-ray was taken, showing a bilateral pneumothorax of great abundance on the right and a partial pneumothorax on the left.

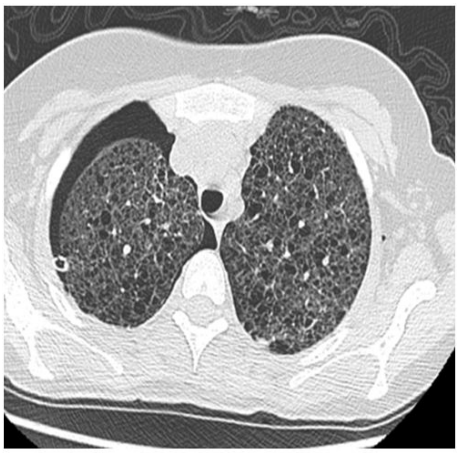

Figure 1: CT scan showing a bilateral cystic pulmonary lesion and a right pneumothorax in the context of tuberous bourneville sclerosis

The patient was drained on both sides with good evolution. Elsewhere, skin examination found fibrous plaques on the forehead, papular lesions on both cheeks and on the wings of the nose, acromic plaques on the external surface of the left thigh, 2 hypochromic macules on the left thigh, and a small number of fibrous plaques on the right thigh. Abdominal examination found bilateral lumbar tenderness and neurological examination is without peculiarities cranial and thoraco abdominal scan (done after an accidental fall of the left drain) objectified a bilateral cystic pulmonary lesion and a right pneumothorax (Figure 1).

In addition to the chest abnormalities, the scan showed subependymal cerebral nodules (Figure 2) and renal mass on both sides (angiomyolipoma) (Figure 3).

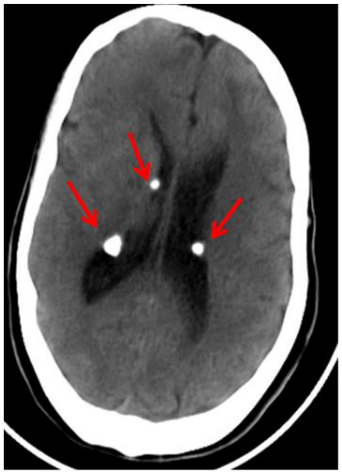

Figure 2: Cranial scan showing a subependymal cerebral nodules in the context of tuberous bourneville sclerosis

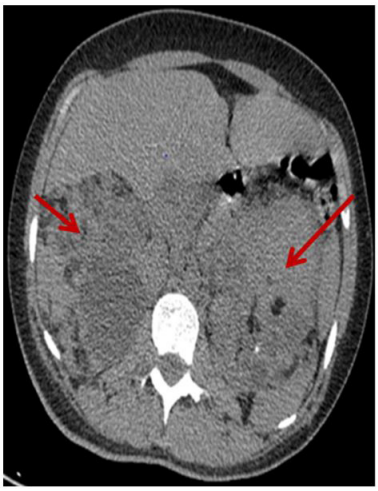

Figure 3: Abdominal scan showing renal angiomyolipoma in the context of tuberous bourneville sclerosis

The diagnosis of Bourneville's tubular sclerosis was retained. In search of other abnormalities a cardiology consult with cardiac echography ruled out a heart condition as well as an ophthalmological examination.

A surgical pleurodesis was proposed, but the patient was recused by the anaesthetist because of the major risk of ventilating pathological lungs. The evolution was marked by the return of the lung to the wall, mTOR inhibitors were prescribed to the patient at her discharge from hospital.

Discussion

Lymphangiomymatosis is a rare disease in young women, in period of genital activity, the average age of diagnosis varies between 30 and 45 years [1]. During the course of the Bourneville's tubular sclerosis, the physiopathology implies the mutation of the tumour suppressor genes TSC1 and TSC2. Pulmonary lymphangiomyomatosis is often discovered in the course of a pneumothorax. The Suspicion of tuberous bourneville sclerosis requires a complete systematic review in search of other systemic disorders, the diagnosis of BTS is based on clinical, radiological and sometimes genetic criteria (Table 1) [2]. It is the identification of the two genes responsible for the disease which, by making it possible to understand how these tumors were forming, paved the way for treatment medical. A crucial discovery was that proteins encoded by these two genes form a complex that physiologically inhibits the mTOR signaling pathway (for mammalian Target of Rapamycin), which has a role central to the physiological control of proliferation cell phone.

Genetic Diagnostic Criteria	Clinical Diagnostic Criteria
Identification of a pathogenic mutation in the TSC1 or TSC2 gene in DNA extracted from normal tissues is sufficient to make a definite diagnosis of Bourneville's tubular sclerosis In 10 to 25% of people with Bourneville's tubular sclerosis, conventional genetic tests do not reveal a mutation. However, a normal result does not rule out the diagnosis.	Major criteria : 1- Hypomelanic spots (>3), minimum 5mm in diameter 2- Angiofibromas (>3) or cephalic fibrous ©. 3- Nail fibroids 4- Grief Skin Plates 5- Multiple retinal hamartomes 6- Cortical dysplasia (cortical tubers or lines of radial migration in the white matter) 7- Subependymal Nodules 8- Subependymal giant cell tumor 9- Cardiac rhabdomyoma 10- Lymphangioleiomyomatosis* 11- Angiomyolipomas* Minor criteria : 1- "Confetti" skin lesions 2- Wells in dental enamel (>3) 3- Intra-oral fibroids (>2) 4- Achromic retinal spots 5- Multiple renal cysts 6- Non-renal Hamartomes
Definite diagnosis: 2 major criteria or 1 major and 2 minor criteria Possible diagnosis: 1 major criteria or more than 2 minor criteria	
A combination of the two major clinical criteria which are Lymphangioleiomyomatosis and Angiomyolipomas, without other features of tuberous bourneville sclerosis, is not considered for definitive diagnosis.	

Table 1: Diagnostic criteria of Bourneville's tubular sclerosis [2]

It appeared that when one of these proteins is deficient due to a mutation of TSC1 or TSC2, the excessive activation of this signaling channel mTOR conducts, in tissues where a second somatic mutation, to the tumor proliferation that goes constitute the hamartome. Hence the use of mTOR inhibitors (already used in organ transplantation): sirolimus or rapamycin (Rapamune®) or everolimus (Certican®). The effect of these drugs was first tested in animal models and then in a few patients with large cerebral or renal hamartoma. The results being favourable, clinical trials were conducted in patients with renal manifestations [3], pulmonary [3], and cerebral [4]. The results are impressive and consistent: after 6 months of treatment, the size of the tumors in these various organs is reduced by more than 30% in 75% of cases of patients [5]. In two recent clinical trialsn reported using everolimus in 117 patients treated for cerebral astrocytoma (84% under the age of 18 years of age) and 118 treated for renal.

Angiomyolipoma, a reduction of size of more than 50% of the targeted tumours is obtained, at the After one year, in 35 and 42% of patients, respectively [6,7]. At the end of the current follow-up (19-33 months; mean 28 months), the lesions continue to decrease or in any case stabilize. However, these drugs do cause enough often some side effects, including the main are stomatitis and respiratory tract infections [8,9]. Rapamycin has also been tested in topical use. At concentrations ranging from 0.003% to 1% for the treatment of angiofibromas of the face, with results very encouraging both in size and appearance. Other treatments can be offered: recurrent pneumothorax may warrant pleural symphysis, avoiding talcum powder or chemical symphyses which can complicate transplant surgery, in favor of partial pleurectomies by video surgery [10]. The iterative punctures have not proved to be effective, pleurodesis with or without ligation of the thoracic duct may be justified in case of recurrent symptomatic forms.

Conservative surgical removal and/or selective embolisation of renal angiomyolipoma and considered in case of haemorrhagic complication or angiomyolipoma measuring more than 4 cm [11]. For the lung damage, although there are mild forms, lymphangiomyomatosis most often progresses to chronic respiratory failure within a few years or decades. Hormone therapy has not been shown to be effective in the absence of controlled clinical trials. Lung transplantation is the last therapeutic option, with rare recurrences on transplanted lungs having been reported.

Conclusion

Pulmonary lymphangiomymatosis most often progresses to chronic respiratory failure within a few years or decades. Hormonal therapy has not been shown to be effective in the absence of controlled clinical trials. Lung transplantation is the last therapeutic resort; rare recurrences of transplanted lungs have been reported.

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