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Case Report

Tuberous sclerosis with severe lymphangioleiomyomatosis and chylous ascites: a case report

[1,2]Alina Habic, [1,3]Dana Crisan, [1,4]Cosmin Caraiani, [2]Mircea Grigorescu

[1] Department of Internal Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2] Gastroenterology Department, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania; [3] Vth Medical Clinic, "Iuliu Hatieganu "University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4] Radiology Department, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania.

Abstract. Tuberous sclerosis complex is a rare autosomal dominant neurocutaneous syndrome with multiple organ involvement. Pulmonary involvement occurs in only 1% of the patients with tuberous sclerosis complex and the specific lesion is lymphangioleiomyomatosis. Current paper presents the case of a young woman with tuberous sclerosis having severe lung involvement and a rare complication due to the mechanical mass effect.

Key Words: tuberous sclerosis complex, angiomyolipomas, lymphangioleiomyomatosis, chylous ascites.

Corresponding Author: D Crisan, email: crisan.dc@gmail.com.

Introduction

The tuberous sclerosis complex (TSC), also known as the Bourneville disease, is a rare autosomal dominant neurocutaneous syndrome, with variable expressivity, that causes benign tumors to grow in the brain and in other vital organs such as the kidneys, heart, eyes, lungs and skin (Cutando et al 2000). The tuberous sclerosis complex occurs in all races and ethnic groups and in both genders. Patients with TSC develop various seizure disorders in 90% of cases, while 60% develop mental retardation (Damm et al 1999; Midde et al 2013). The term TSC refers to multiple masses scattered through the cerebrum (Midde et al 2013). Dermatologic manifestations are represented by hypomelanotic macules, found in more than 90% of patients, facial angiofibromas (adenoma sebaceum), periungual fibromas (Koenen's tumors). In addition, TSC patients develop lymphangioleiomyomatosis (LAM) in the lungs, cardiac rhabdomyomas, skeletal lesions, and vascular anomalies (Valero et al 2013).

Mortality is commonly caused by cardiac lesions such as intramural rhabdomyomas.

Renal complications are the second most common cause of mortality (Valero E et al 2013). Renal cysts and angiomyolipomas (AML) are the most common abdominal findings in TSC (Crino et al 2006). Multiple hepatic AML are often found in patients with TSC and particularly in patients with bilateral diffuse renal AML. Retinal hamartomas occur in almost 50% of patients. Three types of retinal lesions have been described, including "mulberry" lesions adjacent to the optic disc, plaque-like hamartomas and "punched-out" areas of retinal hypopigmentation (Roach et al 2004). Pulmonary involvement occurs in only 1% of patients with TSC, and the specific lesion is lymphangioleiomyomatosis (Monteiro et al 2014).

TSC is caused by defects or mutations, on two genes - TSC1 and TSC2. This mutation prevents the cell from making functional hamartin or tuberin from the altered copy of the gene. Only one of the genes needs to be affected for TSC to be present (Monteiro et al 2014).

Case report

A 41 year-old female was admitted for abdominal pain and enlargement of the abdomen starting 10 days before presentation. She also presented dyspnea and weight loss with onset 2 months prior to presentation. Before we decided to publish this case report, the patient signed an informed consent.

On physical examination, periungual fibromas (Figure 1) and multiple angiofibromas (Figure 2) were observed on the face, back, hands and feet respectively. She presented also dental enamel pits. The abdomen was distended due to an ascitic fluid collection; the cardiovascular examination was normal, but mild/severe dyspnea with very diminished vesicular murmur were found at the respiratory exam.

The laboratory examinations showed mild thrombocytosis (477000 cells/dl) and a high erythrocyte sedimentation rate (111 mm at 2 h).

The abdominal ultrasound found a few hyperechoic lesions in the liver suggesting angiomyolipomas. Multiple, large heterogeneous and echogenic lesions were also present in both kidneys and the lower abdomen, as well as a large volume of ascites.

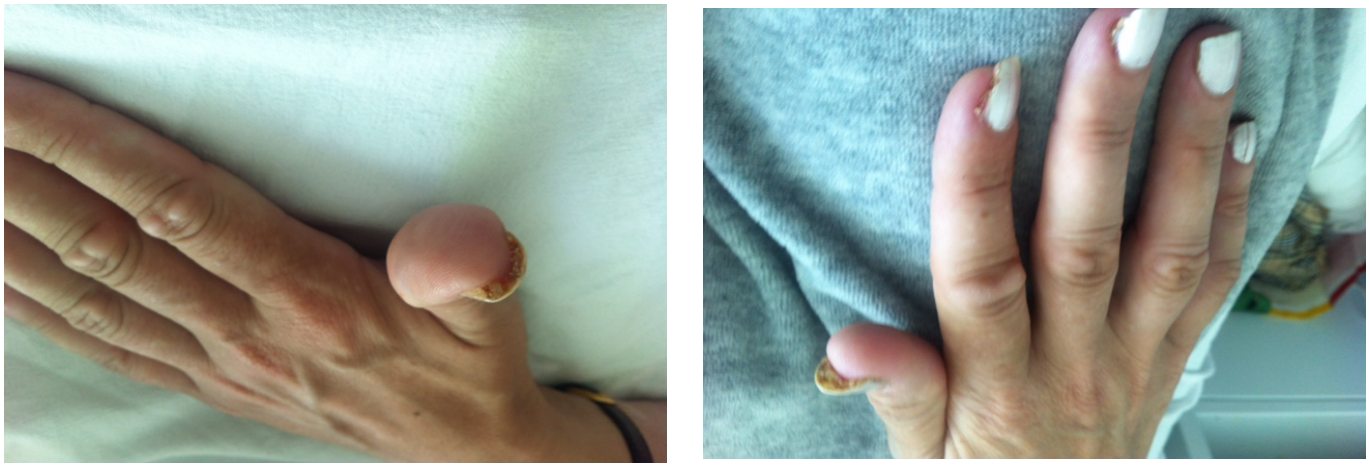


Figure 1. Multiple periungual fibromas

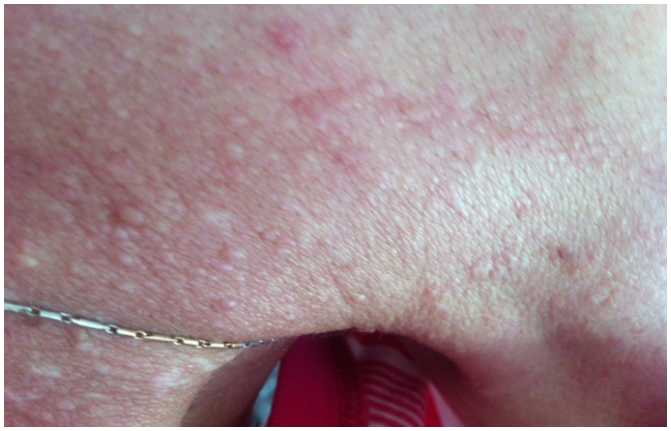


Figure 2. Angiofibromas on the back

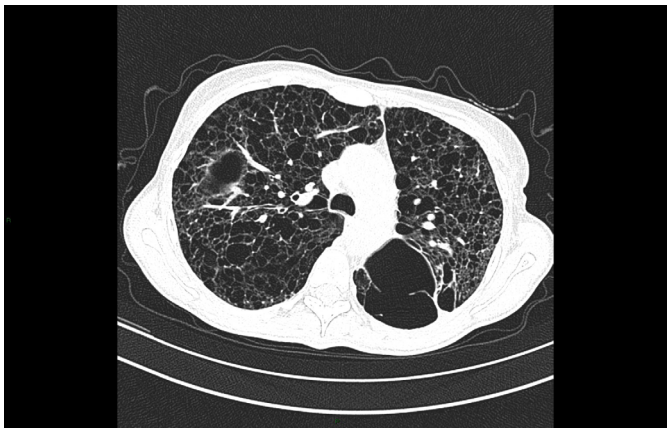


Figure 3. Thoracic CT scan: Pulmonary lymphangioleiomyomatosis, with cystic lesions and almost no normal lung tissue

We performed a diagnostic and therapeutic paracentesis, obtaining chylous ascitic fluid. The cytology of the fluid showed a high level of triglycerides (2444 mg/dl), a serum-ascites albumin gradient (SAAG) = 1, mesothelial cells, some with foamy cytoplasm, but no bacterial infection.

The computer tomography of the chest and abdomen revealed multiple bilateral thin-walled cystic lesions of varying sizes in the lungs, causing an almost complete replacement of the parenchyma (Figure 3); multiple angiomyolipomas were also found in the liver and kidneys (Figure 4.), as well as multiple angiomyolipomas in the lower abdomen. The brain MRI revealed a few subcortical tubers and subependimal nodules (Figure 5, arrows). The functional respiratory tests showed severe obstructive dysfunction (VEMS=35%, TI=0.65).

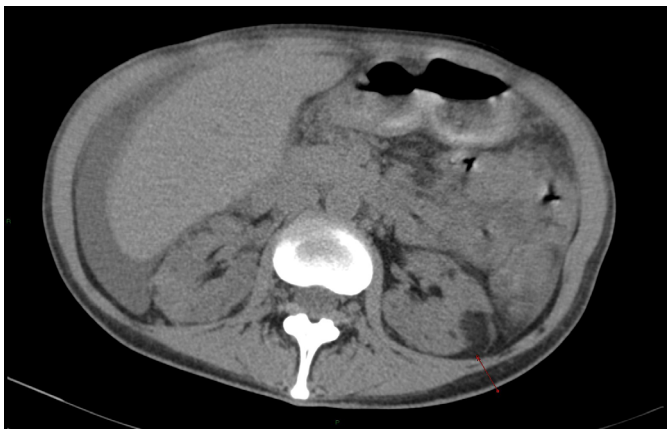


Figure 4. Abdominal CT scan: cystic lesions in the renal parenchyma and the liver

The ophthalmologic examination consisted in fundus photography and fundus autofluorescence that revealed two small spots (Figure 6, circle).

The cardiologic examination with echocardiography showed no rhabdomyomas, and the cardiac function was normal.

These features were consistent with a diagnosis of TSC with multiple organ manifestations.

The patient was referred to an oncological center where she started the treatment.

Discussion

Tuberous sclerosis is a relatively rare disease, with an incidence of approximately 1:5000 – 1:10000 live births (Leung et al 2007). Lymphangioleiomyomatosis occurs in more than 30% of women with the tuberous sclerosis complex (TSC-LAM), an inherited syndrome that is associated with seizures, cognitive impairment and benign tumors in multiple tissues. There are no pathognomonic clinical signs for tuberous sclerosis. A combination of signs, classified as major or minor, is required in order to establish a clinical diagnosis (Shrestha et al 2013). The prognosis for individuals with TSC depends on the severity of symptoms.

Seizures are the most common neurologic complication, occurring in 75%-90% of patients (Leung et al 2007). Our patient had no history of neurological manifestations, seizures or mental retardation. Despite de absence of the neurological signs, the CT examination revealed the presence of subependymal nodules and subcortical tubers – major signs for TSC.

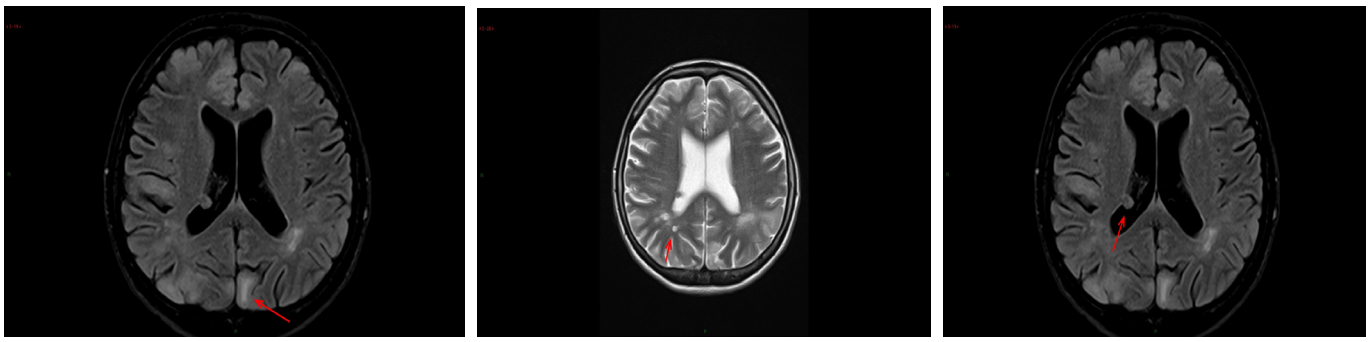
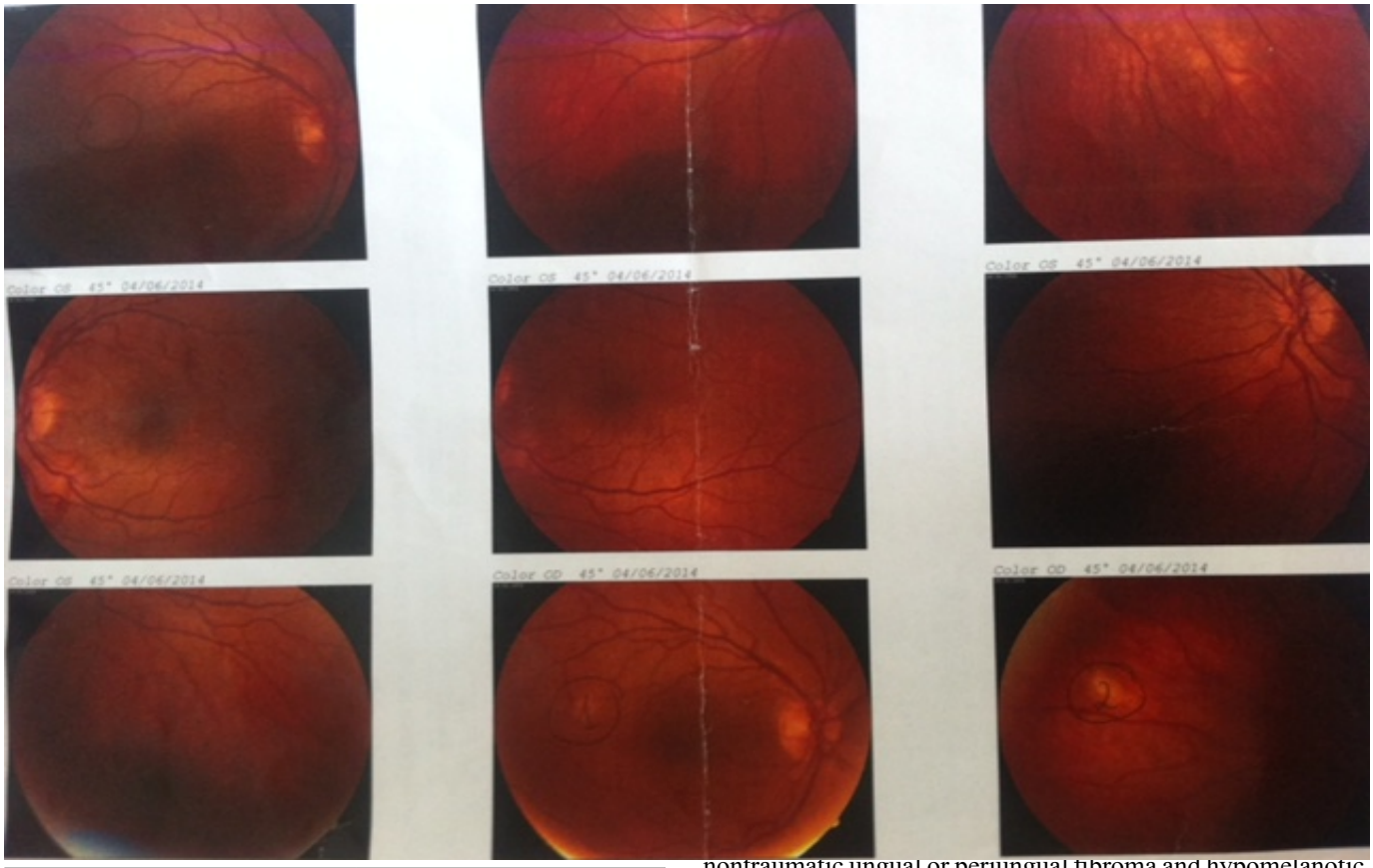


Figure 5. Brain MRI: Cortical tubers, subependymal nodule



Major criteria	Minor criteria
Cortical tuber	Cerebral white matter migration lines
Subependymal nodule	Multiple dental pits
Facial angiofibroma or forehead plaque	Gingival fibromas
Ungual or periungual fibroma (nontraumatic)	Bone cysts
Hypomelanotic macules (>3)	Retinal achromatic patch
Shagreen patch	Confetti skin lesions
Multiple retinal hamartomas	Nonrenal hamartomas
Cardiac rhabdomyoma	Multiple renal cysts
Renal angiomyolipoma	Hamartomatous rectal polyps
Pulmonary lymphangiomyomatosis	

nontraumatic ungual or periungual fibroma and hypomelanotic macules are also major signs for TSC (Roach et al 2004), and all were present in our patient.

Cardiac rhabdomyomas are present in two thirds of affected newborns, but cardiac manifestations were absent in our case. Almost all patients with TSC have enamel pitting in their permanent teeth (Franz et al 2004), and our patient was no exception. Retinal hamartomas occur in 40%-50% of patients with TSC and are bilateral in a third of cases (Franz et al 2004). Of the three types of retinal lesions, our patient had "punched-out" areas of retinal hypopigmentation.

Pulmonary manifestations are very rare, occurring in only 1% of TSC patients (Bernauer det al 2001). The classic pulmonary lesion is lymphangioleiomyomatosis, a progressive form of lung disease. Our patient had severe lung disease, functional tests revealing severe obstructive dysfunction.

Despite the renal and liver imaging abnormalities, liver and renal functions were normal. A retrospective review (Black ME et al 2012) of the clinical records and radiological images of 205 patients with tuberous sclerosis complex (TSC), that evaluated

the prevalence and progression of hepatic lesions, showed that no patient with AML had clinical symptoms or complications from hepatic lesions. Also presence of hepatic AML was associated with presence of renal AML.

Chylous ascites is a very rare condition at any age, suggesting a possible involvement of the lymphatic drainage. Our patient had multiple angiomyolipomas in the lower abdomen, with possible mass effect, impairing the lymphatic drainage and causing accumulation of ascites.

The optimal treatment for TSC is Everolimus, but only a few centers are qualified to prescribe/administrate it, which is why the patient was directed to an oncological center.

Conclusion

The tuberous sclerosis complex is a rare autosomal dominant neurocutaneous syndrome affecting multiple vital organs such as the kidneys, heart, eyes, lungs and skin. The most frequent clinical manifestations are related to the affected organ. This patient presented mild/severe dyspnea due to lymphangioleiomyomatosis, but also an uncommon symptom represented by accumulation of chylous ascites due to external compression of lymphatic ducts.

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Authors

•Alina Habic, Department of Internal Medicine, 3rd Medical Clinic, "Iuliu Hatieganu" University of Medicine and Pharmacy, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Cluj, Romania, EU, email: alina.habic@hyahoo.com

•Dana Crisan, Department of Internal Medicine, 5th Medical Clinic, "Iuliu Hatieganu" University of Medicine and Pharmacy, 11 Tabacarilor Street, 400139, Cluj-Napoca, Cluj, Romania, EU, email: crisan.dc@gmail.com

•Cosmin Caraiani, Department of Surgery, Medical Imagery, "Iuliu Hatieganu" University of Medicine and Pharmacy, 19-21 Croitorilor Street, 400162, Cluj-Napoca, Cluj, Romania, EU, email: ccaraiani@yahoo.com

•Mircea Grigorescu, Regional Institute of Gastroenterology and Hepatology, 5 Constanta Street, 400158, Cluj-Napoca, Cluj, Romania, EU, email: mdgrigorescu@yahoo.com

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