CASE REPORT

Multiple pulmonary artery aneurysms in tuberous sclerosis complex

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SUMMARY

Tuberous sclerosis complex (TSC) is a rare genetic disorder characterised by multiple hamartomas, caused by inactivating mutations of the *TSC1/TSC2* tumour suppressor genes. Classical pulmonary involvement in tuberous sclerosis complex (TSC) consists of lymphangiomyomatosis and/or multiple micronodular pneumocyte hyperplasia (MMPH). Association of TSC with pulmonary artery aneurysm (PAA) has been only exceptionally described. We report here the first case of TSC with multiple PAA in combination with MMPH, cardiac rhabdomyomas and bone, skin and brain involvement.

BACKGROUND

Tuberous sclerosis complex (TSC) is a rare genetically determined neurocutaneous syndrome caused by inactivating mutations of the *TSC1/TSC2* tumour suppressor genes and characterised by triad seizures, mental retardation and facial angiofibromas. Many other organs may, however, be involved such as the brain (tubers, subependymal nodules and astrocytomas), eyes (retinal hamartomas), kidney (angiomyolipomas), heart (rhabdomyomas) or lung. Pulmonary involvement occurs in up to ~40% of patients and is well known as lymphangiomyomatosis (LAM) and/or multifocal micronodular pneumocyte hyperplasia (MMPH). Two cases of primary pulmonary artery aneurysm (PAA) related to TSC have also been reported.^{1 2} We report here the first case of TSC presenting with multiple PAA.

CASE PRESENTATION

A female infant developed epilepsy and hypomelanotic macules in the first 4 years of life, suggesting the diagnosis of TSC. Brain MRI demonstrated subependymal nodules, cortical tubers and astrocytomas. Cardiac MRI revealed ventricular masses considered as rhabdomyomas, which spontaneously disappeared on subsequent echocardiographies. In adolescence, she developed histologically proven angiofibromas and shagreen patches. Genetic analysis demonstrated c.990insT mutation in exon 10 of the *TSC1* gene confirming the diagnosis of TSC. The patient progressively presented dyspnoea during exertion without fever, cough, weight loss, oral aphthous or genital ulcers.

INVESTIGATIONS

Laboratories showed normal serum electrolytes, C reactive protein plasma level <2 mg/l and normal leucocytes count around 5G/l. X-ray radiography showed enlargement of the right hilum (figure 1A).

Chest CT and ventilation/perfusion (V/Q) scintigraphy were performed to rule out pulmonary embolism. Neither V/Q scintigraphy nor CT showed pulmonary embolism. Chest CT demonstrated bilateral well-defined ground-glass nodules randomly scattered throughout both lungs (figure 1D,E). As TSC was genetically proven, we attributed these findings to MMPH. No pulmonary cyst was observed. Transaxial arterial phase CT images showed focal enlargement of pulmonary artery lobar branches suggesting PAA. Multiplanar arterial phase CT reconstructions confirmed fusiform aneurysms of the right middle lobe, lingula and apical branch of the left lower lobe (figure 1B,C) with segmental slight (2.2 mm) arterial wall thickening but without endoluminal or parietal thrombus and without preaneurysmal stenosis. There was no pulmonary arterial hypertension at echocardiography. In addition, multiple osteoblastic lesions of the spine were observed (figure 1F).

DIFFERENTIAL DIAGNOSIS

Pulmonary artery aneurysms can be either congenital or acquired. Congenital causes mainly include vessel wall weakness due to connective tissue abnormalities such as Ehlers-Danlos or Marfan syndrome, and left-to-right shunts leading to high pressure in the pulmonary artery such as ventricular or atrial septal defect, ductus arteriosus or sequelae after congenital cardiac heart correction. Acquired aetiologies include all causes of pulmonary arterial hypertension due to precapillary or postcapillary disease. Chronic pulmonary embolism is the first cause of pulmonary arterial hypertension that has to be ruled out since it can be easily treated. Vessel wall abnormalities can also be due to inflammatory vasculitis such as Behcet's syndrome or Hughes-Stovin syndrome or due to various infections including pyogenic bacteria, mycobacteriosis better known as Rasmussen aneurysm, candidosis or aspergillosis lung involvement. In case of inflammatory and infection causes, extrapulmonary arterial aneurysm should be carefully sought especially in the brain. Finally, mechanical aetiologies should not be forgotten especially in patients who experienced penetrating trauma or patients who benefited from intravascular procedures such as pulmonary angiography, Swan-Ganz catheterism or cardiac surgery. Rare cases of pulmonary artery tumour, such as angiosarcoma or leiomyosarcoma, have been reported.

OUTCOME AND FOLLOW-UP

PAA are followed twice a year by low-dose CT angiography and remain stable.

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Figure 1 (A) Anteroposterior chest x-ray showing enlargement of the right hilum and a pacemaker implanted for arrhythmias related to right ventricle rhabdomyomas sequelae. No pulmonary nodule is seen. (B) 14 mm thick slab CT using maximum intensity projection (MIP) reconstruction in a coronal oblique view that shows pulmonary aneurysms of medial segmental artery of the middle lobe without preaneurysmal stenosis. (C) 22 mm MIP thick slab in transverse view showing an abnormal enlargement of segmental arterial branch of the lingula. (D and E) 1.25 mm axial transverse CT scan viewed in lung window setting focused on the right lung showing multiple ground glass nodules of various sizes predominantly located at the level of the anterior segment of the right upper lobe. (F) Sagittal CT reformat viewed in bone window setting showing multifocal dense lesions of various sizes in the spine.

DISCUSSION

TSC is characterised by the presence of multiorgan hamartomas³ related to *TSC1* or *TSC2* gene mutations. *TSC1* and *TSC2* are tumour suppressor genes of the hamartin/tuberin complex known to play a central role in regulation of the mammalian target of rapamycin signalling pathway that is involved in many different human cancers.⁴ Hamartomas in TSC are more frequent in the skin, brain and kidneys but can also occur in the lung and heart. Lung involvement mainly presents as LAM with proliferation of immature smooth muscle cells (LAM cells) in the alveolar walls, bronchioles and vessels leading to formation of thin-walled cysts. MMPH can be associated with LAM, as in our case. Carette *et al*² recently reported a case of TSC with single primary PAA characterised by smooth muscle cell proliferation, disorganisation and fragmentation of elastic fibres on histological analysis, demonstrating that TSC may also affect pulmonary vessels. Burrows and Johnson¹ also reported a case of single primary PAA in TSC. In our case, common causes of pulmonary artery aneurysm such as Behçet's syndrome and Hughes-Stovin syndrome, infectious disease, lung neoplasm, Marfan syndrome and Ehlers-Danlos syndrome were ruled out in the absence of history of trauma, aphthosis, inflammation on laboratories, pulmonary embolism on V/Q scintigraphy or CT, systemic artery aneurysm on CT or pulmonary hypertension at echocardiography.⁵ Multiple fusiform PAA were thus attributed to TSC. Although smooth muscle cell proliferation was not histologically proven in our case, the presence of several fusiform aneurysms with segmental arterial wall thickening supports the hypothesis of diffuse or multifocal vascular wall abnormalities related to the dysplastic nature of TSC.² In line with this hypothesis, infiltration of vascular walls by LAM cells leading to dysplastic medial hypertrophy and wall thickening has been observed in pulmonary LAM.^{6–8} With intimal and adventitial fibrosis,^{6–9} medial dysplasia/hypertrophy could result in vascular wall embrittlement and formation of arterial aneurysm in the lung. Since the behaviour of such PAA in the TSC patient remains unclear, we decided to follow our patient twice a year.

As our patient could not undergo MRI due to pacemaker and because CT provides useful information regarding the size, number, location and extent of aneurysms,¹⁰ we decided to follow her by CT. However, low-dose multidetector-row ECG-gated CT were used to reduce patient radiation exposure while maintaining good image quality.¹¹

Learning points

- ▶ Tuberous sclerosis complex (TSC) is associated with lung involvement mainly consisting of lymphangioleiomyomatosis and/or multifocal pneumocyte hyperplasia.
- ▶ Vascular wall abnormalities due to the dysplastic nature of TSC may affect pulmonary artery leading to pulmonary artery aneurysm (PAA) formation.
- ▶ PAA should be suspected in patients with TSC and dyspnoea.
- ▶ The behaviour of TSC-related PAA is not known and justifies a follow-up by CT.

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Competing interests None.

Patient consent Obtained.

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