Eur Respir J 2008; 31: 678–680
DOI: 10.1183/09031936.00021207

CASE STUDY

Mediastinal angiomyolipomas in a male patient affected by tuberous sclerosis

A. Warth*, E. Herpel*, A. Schmähl#, H. Hoffmann¶, F.J.F. Herth+, P. Schirmacher*, H. Dienemann¶ and P.A. Schnabel*

ABSTRACT: Classical angiomyolipomas are benign tumours composed of various tissues, including components of fat, abnormal blood vessels and smooth muscle cells. They are often found in association with tuberous sclerosis complex (TSC).

The present study reports a male patient affected by TSC with intermittent, massive chylous pleural effusions, who developed recurrent mediastinal angiomyolipomas. The tumours were characterised *via* histological and immunohistochemical methods.

Although angiomyolipomas frequently occur in the kidneys of TSC patients, this case is the first report of mediastinal angiomyolipomas associated with TSC.

Besides lymphangioleiomyomatosis, this differential diagnosis has to be taken into account in the case of chylous pleural effusions and mediastinal masses in tuberous sclerosis complex patients.

KEYWORDS: Angiomyolipoma, chylothorax, mediastinum, pleural effusion, tuberous sclerosis complex

AFFILIATIONS
*Institute of Pathology, University Hospital Heidelberg, and Depts of #Radiology, ¶Thoracic Surgery, and +Pneumonology and Critical Care Medicine, Thoraxklinik Heidelberg, University of Heidelberg, Heidelberg, Germany.

CORRESPONDENCE
P.A. Schnabel
Institute of Pathology
University of Heidelberg
Im Neuenheimer Feld 220/221
D-69120 Heidelberg
Germany
Fax: 49 62213961672
E-mail: philipp.schnabel@med.uni-heidelberg.de

Received:
February 21 2007
Accepted after revision:
July 27 2007

STATEMENT OF INTEREST
None declared.

At 5 yrs of age the male patient was diagnosed with tuberous sclerosis complex (TSC; Bourneville's disease, M. Bourneville-Pringle), presenting with multiple characteristic cutaneous angiofibromas (adenoma sebaceum) on his back and legs. The patient was admitted to the hospital 2 yrs later due to a large tumour of the left kidney. A nephrectomy was performed and the histopathological evaluation revealed an angiomyolipoma, a tumour classically associated with TSC [1]. Additionally, the following examinations and computed tomography (CT) scans revealed multiple hamartomas in the right kidney, liver, left ventricular endomyocardium of the posterior wall and in the fundi of both eyes (not shown). The consecutive neurological and ophthalmological examinations revealed no further cerebral abnormalities and the patient's history was negative for seizure disorders.

During the further course of illness, the patient was continuously admitted to the hospital with symptoms of dyspnoea, chest pain, nausea and vomiting. In addition to extensive fat- and soft tissue-equivalent extensive masses of the retroperitoneum (putative recurrence of the resected renal angiomyolipoma), radiological and subsequent interventional diagnostics revealed massive chylous pleural effusions that were treated by intercostal drainage. The laboratory values for the pleural effusions were as follows with the normal serum values in parentheses: triglycerides >2,700 $mg \cdot dL^{-1}$ (0–200 $mg \cdot dL^{-1}$), cholesterol 169 $mg \cdot dL^{-1}$ (0–200 $mg \cdot dL^{-1}$), total proteins 6.1 $g \cdot dL^{-1}$ (6.6–8.7 $g \cdot dL^{-1}$), lactatedehydrogenase 386 $U \cdot L^{-1}$ (135–225 $U \cdot L^{-1}$). Subsequent diagnostics further revealed a mediastinal mass of uncertain origin in the dorsal mediastinum close to the oesophagus. At this point, the patient was 27 yrs old. In order to specify the tumour, the patient was subjected to a biopsy. Histology revealed a classical angiomyolipoma, which was completely surgically resected. The patient's symptoms and chylous pleural effusions were recurrent 5 yrs after the first resection. Therefore, further diagnostics were performed, which demonstrated a new mediastinal mass (fig. 1). The histology of the $15 \times 8 \times 3$-cm specimen again revealed a classical mediastinal angiomyolipoma (figs 1–3), suggesting local recurrence of the previously resected mass. However, a second angiomyolipoma cannot be definitively excluded without reference to the original. Abdominal and thoracic CT scans could not demonstrate an extension between the previously diagnosed abdominal mass (putative recurrence of the renal angiomyolipoma) and the

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

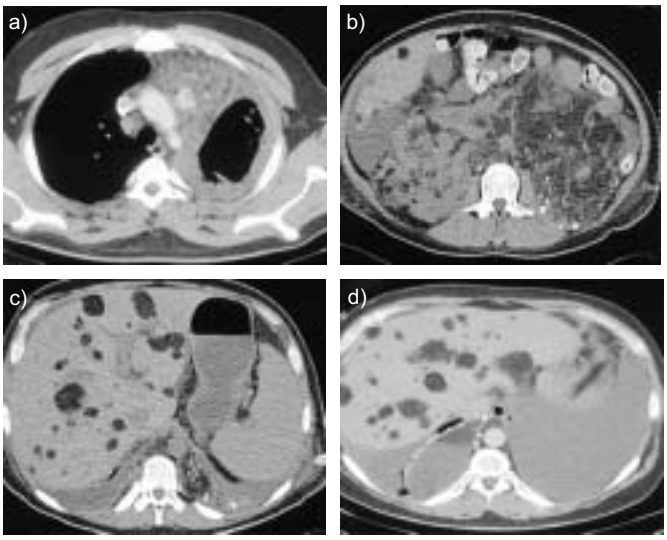

FIGURE 1. Computed tomography (CT) scans of the patient immediately prior to resection of the second mediastinal angiomyolipoma. a) With *i.v.* contrast in the mediastinal vessels, the anterior mediastinum is filled out with fat- and soft tissue-equivalent, inhomogenous masses, which broaden the mediastinum. Additionally, pleural thickening and effusions are apparent, including focal callosities with accentuation of the left side. b and c) Abdominal scans demonstrate multiple, hypodense and fat-equivalent hepatic lesions. Additionally, an extensive mass showing the same CT appearance is apparent in the left retroperitoneum. d) The intra-abdominal white spots represent inclusions of contrast agents following lymphography. However, the basal lung scans do not reveal any tumour manifestation, thereby implying that a continuous tumour extension from the retroperitoneum to the mediastinum is rather unlikely.

prevalent mediastinal masses (fig. 1), thereby implying a *de novo* genesis of the mediastinal tumour. Immunohistochemistry demonstrated the classical composition of angiomyolipomas with positivity of the tumour cells for melanoma (HMB45) and melan-A, muscle actin-specific (HHF35) as well as desmin positivity of the smooth muscle component. Adipocytes stained for S-100 protein and capillary and venous vessels stained positively for CD31 and C34 (fig. 3). The proliferation rate varied between 1 and 10% (Ki67). Lymph nodes encircled by the tumour formation showed regularly distributed lymphoid cell aggregates that were positive for CD3, CD5, CD20, CD138 and

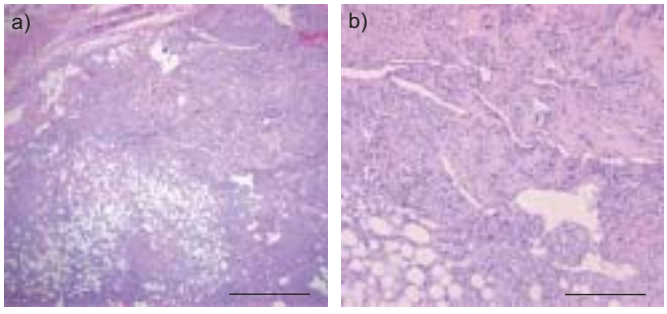

FIGURE 2. a) Overview and b) detail of the mediastinal angiomyolipoma after conventional haematoxylin and eosin staining demonstrating the tumour characteristics, including fat, abnormal blood vessels and smooth muscle components. Scale bars= a) 100 μm and b) 50 μm.

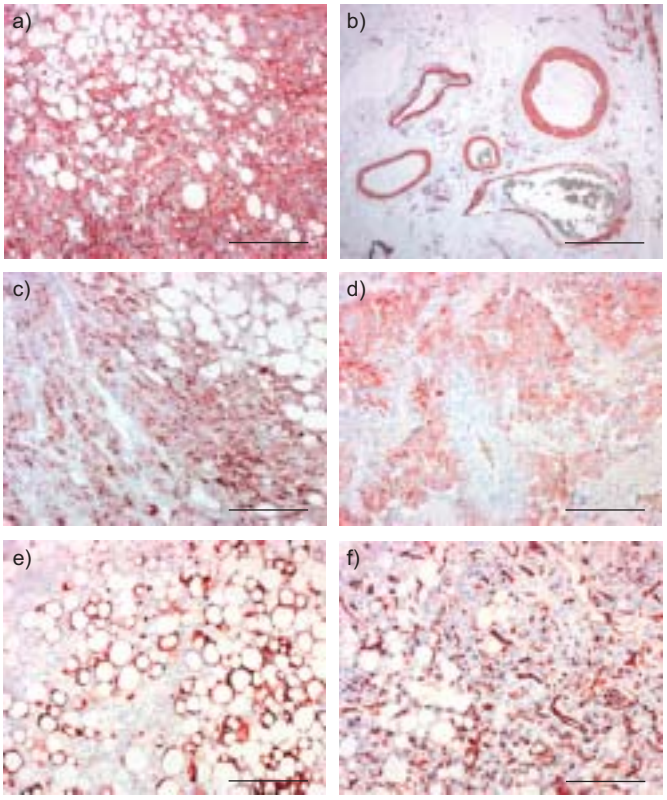

FIGURE 3. Immunohistochemical staining of the mediastinal angiomyolipoma. Staining against muscle actin-specific antibody marked a) the smooth muscle components of the tumour and b) the smooth muscles of vessels. c) Melanoma staining of the tumour cells, which were also focally positive for d) melan-A. e) Staining against S-100 revealed the fat components of the tumour. f) Immunohistochemistry against CD31 resulted in staining of tumour vessels. Scale bars=50 μm (a, c and f) and 100 μm (b, d and e).

CD68 (not shown). Although intensive histological evaluation was performed, no features of lymphangioleiomyomatosis (LAM) could be detected.

DISCUSSION

Among other clinical symptoms, such as skeletal sclerosis, epilepsy and mental retardation, TSC is characterised by multiple tumour manifestations in various organs, including the typical so-called adenoma sebaceum (angiofibroma) of the skin, giant cell astrocytoma, high-grade glioma, chordoma, glioneuronal hamartoma, angiomyolipoma and cysts of the kidneys, renal cell carcinoma, cardiac rhabdomyoma, retinal glioma and others [1–3]. An involvement of the lungs is uncommon (<1–3% of all patients in different series), but when present, pulmonary manifestation dominates the clinical course of the patient, with dyspnoea and fatigue as the cardinal symptoms [2, 4, 5]. Besides LAM, symptoms of spontaneous pneumothorax due to honeycombing and the formation of cysts in the lung parenchyma, cor pulmonale and chronic cough or hemoptysis occur frequently [2], but pulmonary symptoms appear later in life compared with cutaneous and neurological manifestations, with an average presentation age of 34 yrs [6]. Chylous pleural effusions in TSC patients are uncommon and raise suspicions about LAM, but

this disorder is almost exclusively found in female patients of childbearing age [7] and there are < 10 case reports worldwide of LAM occurring in male patients. LAM is the main cause of chylous pleural effusion in TSC patients. In the current case, the finding of massive tumour growth around mediastinal lymph nodes may explain the recurrent chylous effusions.

Descriptions of mediastinal angiomyolipomas are rare and <10 cases have been described in the literature to date [8]. None of the reported cases were related to patients affected by TSC and none of the patients suffered from chylous pleural effusions. Additionally, two cases of an intrapulmonary angiomyolipoma in a TSC patient have been reported [9, 10]. Moreover, there is a recent description of a 35-yr-old female patient with LAM and a history of a renal angiomyolipoma, who presented with intermittent palpitations and arrhythmias caused by cardiac compression by a posterior mediastinal angiomyolipoma. However, this mediastinal angiomyolipoma was theorised to represent a direct extension from the retroperitoneum [11]. In the present case, thoracic and abdominal CT scans could not identify a retroperitoneal tumour extension from the putative recurrence of the renal angiomyolipoma and, additionally, the second or assumed recurrent mediastinal angiomyolipoma was located in the anterior mediastinum (fig. 1). Nevertheless, this possibility has to be taken into account since small tumour extensions might not be detectable by CT. Extrarenal angiomyolipomas are generally considered to be due to multicentricity and not metastasis [12, 13].

In summary, angiomyolipomas are frequently found in the kidney, but angiomyolipomas in the mediastinum are exceedingly rare with less than a dozen cases reported to date. The present case is the first description of mediastinal angiomyolipomas in association with tuberous sclerosis complex. Of clinical importance is this demonstration that mediastinal angiomyolipomas and not only lymphangioleiomyomatosis have to be considered as a reason for chylous pleural effusions in patients with tuberous sclerosis complex. Furthermore, angiomyolipomas should be included in the differential diagnosis of pulmonary manifestations and tumours arising in the mediastinum in tuberous sclerosis complex patients.

REFERENCES

1 Rakowski SK, Winterkorn EB, Paul E, Steele DJ, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. *Kidney Int* 2006; 70: 1777–1782.

2 Aughenbaugh GL. Thoracic manifestations of neurocutaneous disease. *Radiol Clin North Am* 1984; 22: 741–756.

3 O'Callaghan FJ, Osborne JP. Advances in the understanding of tuberous sclerosis. *Arch Dis Child* 2000; 83: 140–142.

4 Pallisa E, Sanz P, Roman A, Majo J, Andreu J, Caceres J. Lymphangioleiomyomatosis: pulmonary and abdominal findings with pathologic correlation. *Radiographics* 2002; 22: 185–198.

5 Cohen MM, Pollock-BarZiv S, Johnson SR. Emerging clinical picture of lymphangioleiomyomatosis. *Thorax* 2005; 60; 875–879.

6 Dwyer J, Hickie JB, Garvan J. Pulmonary tuberous sclerosis: report of three patients and a review of the literature. *Q J Med* 1971; 40: 115–125.

7 Ryu JH, Doerr CH, Fisher SD, Olson EJ, Sahn SA. Chylothorax in lymphangioleiomyomatosis. *Chest* 2003; 123: 623–627.

8 Amir AMI, Zeebregts CJ, Mulder HJ. Anterior mediastinal presentation of a giant angiomyolipoma. *Ann Thorac Surg* 2004; 78: 2161–2163.

9 Marcheix B, Brouchet L, Lamarche Y, *et al*. Pulmonary angiomyolipoma. *Ann Thorac Surg* 2006; 82: 1504–1506.

10 Wu K, Tazelaar HD. Pulmonary angiomyolipoma and multifocal micronodular pneumocyte hyperplasia associated with tuberous sclerosis. *Hum Pathol* 1999; 30: 1266–1268.

11 Torigian DA, Kaiser LR, Soma LA, Tomaszewski JE, Kotloff R, Siegelman ES. Symptomatic dysrhythmia caused by a posterior mediastinal angiomyolipoma. *AJR Am J Roentgenol* 2002; 178: 93–96.

12 Bloom DA, Scardino PT, Ehrlich RM, Waisman J. The significance of lymph nodal involvement in renal angiomyolipoma. *J Urol* 1982; 128: 1292–1295.

13 Eble JN. Angiomyolipoma of kidney. *Semin Diagn Pathol* 1998; 15: 21–40.