Mesenchymal cystic hamartoma of the lung in Cowden's disease

V. COTTIN*, L. THOMAS†, R. LOIRE‡, L. CHALABREYSSE‡, D. GINDRE‡ AND J.-F. CORDIER*

*Service de Pneumologie, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, France, †Service de Dermatologie, Hôpital de l'Hôtel-Dieu, France and ‡Laboratoire d'Anatomopathologie, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Université Claude Bernard, Lyon, France

INTRODUCTION

Mesenchymal cystic hamartoma of the lung is a rare clinicopathological entity (1), characterized by a cystic pulmonary lesion with typical pathological features, that slowly increases in size. Fewer than 15 cases have been reported in the literature.

Cowden's disease, or the multiple hamartoma syndrome, is an autosomal dominant tumor syndrome with involvement of various organs. Clinically, it is characterized by multiple hamartomas of ectodermal, endodermal, and mesodermal origin, a high incidence of malignant tumors of the breast, thyroid gland, and female adnexa together with gastrointestinal polyps, various mucocutaneous lesions, macrocephaly, and mild-to-moderate mental retardation (2). Our present observation suggests that Cowden's disease may include mesenchymal cystic hamartoma of the lung.

CASE REPORT

A 46-year-old woman was referred in 1994 for a cystic pulmonary lesion of the lung on chest X-ray. She had smoked for less than a year at age 19. She had a history of Cowden's disease diagnosed at age 11, and a family history remarkable for cancer of the pleura and scrotal tongue in her mother. The patient had conspicuous mucocutaneous lesions, including facial trichilemmomas, acral keratosis, oral papillomas, scrotal tongue, macroglossia, papillomas of the skin in the peribuccal, cervical, and thoracic areas, and small scattered vitiligo. Dysmorphic manifestations included macrocephaly, turricephaly, bilateral frontal humps, and low implantation of ears and hair. Her height was 158 cm and her weight 72 kg. She had undergone surgery for bilateral benign breast cysts in 1989 and 1991, hysterectomy for multiple hamartomas of the uterus in 1988, surgery for fibromas of the uterine cervix in 1991, and resection of thyroid nodules in 1975 and 1980. In 1992, a history of recurrent headache had revealed a tumor of the cerebellar area, which was radiologically diagnosed as non-resectable benign meningioma. Systematic gastroscopy and colonoscopy disclosed benign hamartomatous polyps of the gastrointestinal tract.

In 1978, a cystic lesion of the right lung was discovered on a chest radiograph. In May 1994, the patient complained of grade 1 dyspnea at exercise and slight mucous bronchorrhea. Physical examination revealed wheezing in the right upper pulmonary lobe. The chest radiograph showed a thin-walled cyst in the right upper lobe, which had increased in size since 1978. No air-fluid level was seen on this occasion, although it had been occasionally noted previously. CT-scan of the chest showed a thin-walled air cyst in the anterior segment of the right upper lobe, 7 cm in diameter (Fig. 1). A thin dividing wall was present within the cyst and accentuated after intravenous injection of iodinated contrast material. A second cyst, 15 mm in diameter, was also present beneath the larger cyst. Magnetic resonance imaging of the lung with intravenous injection of gadolinium confirmed that the dividing wall was vascularized. Lung scintigraphy showed that the cyst was neither ventilated nor perfused. Fiberoptic bronchoscopy showed normal airways. Pulmonary function tests showed a restrictive and obstructive pattern, with forced vital capacity (FVC) 2.03 l (68% predicted), forced expiratory volume in one second (FEV_1) 1.28 l/s (51%), FEV_1/FVC 63% (78%), total lung capacity (by helium diffusion) 3.21 l (69%). The CO diffusion coefficient and PaO_2 were normal. Routine blood biochemical and hematological studies, and urine analysis were normal. Sedimentation rate was 16 mm/h.

A mesenchymal cystic hamartoma of the lung was suspected. The patient underwent thoracotomy and upper right lobectomy in November 1994. On gross pathological examination, the lesion consisted of a thin-walled cyst which measured $50 \times 40 \times 40\ mm^3$. Numerous small cysts were present within the wall of

Received 8 April 2002, accepted in revised form 8 August 2002.
Correspondence should be addressed to: Dr. Jean-François Cordier, Service de Pneumologie, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, 69394 Lyon Cedex 03, France. Fax: +33 472 3576 53; e-mail: germop@univ-lyon1.fr

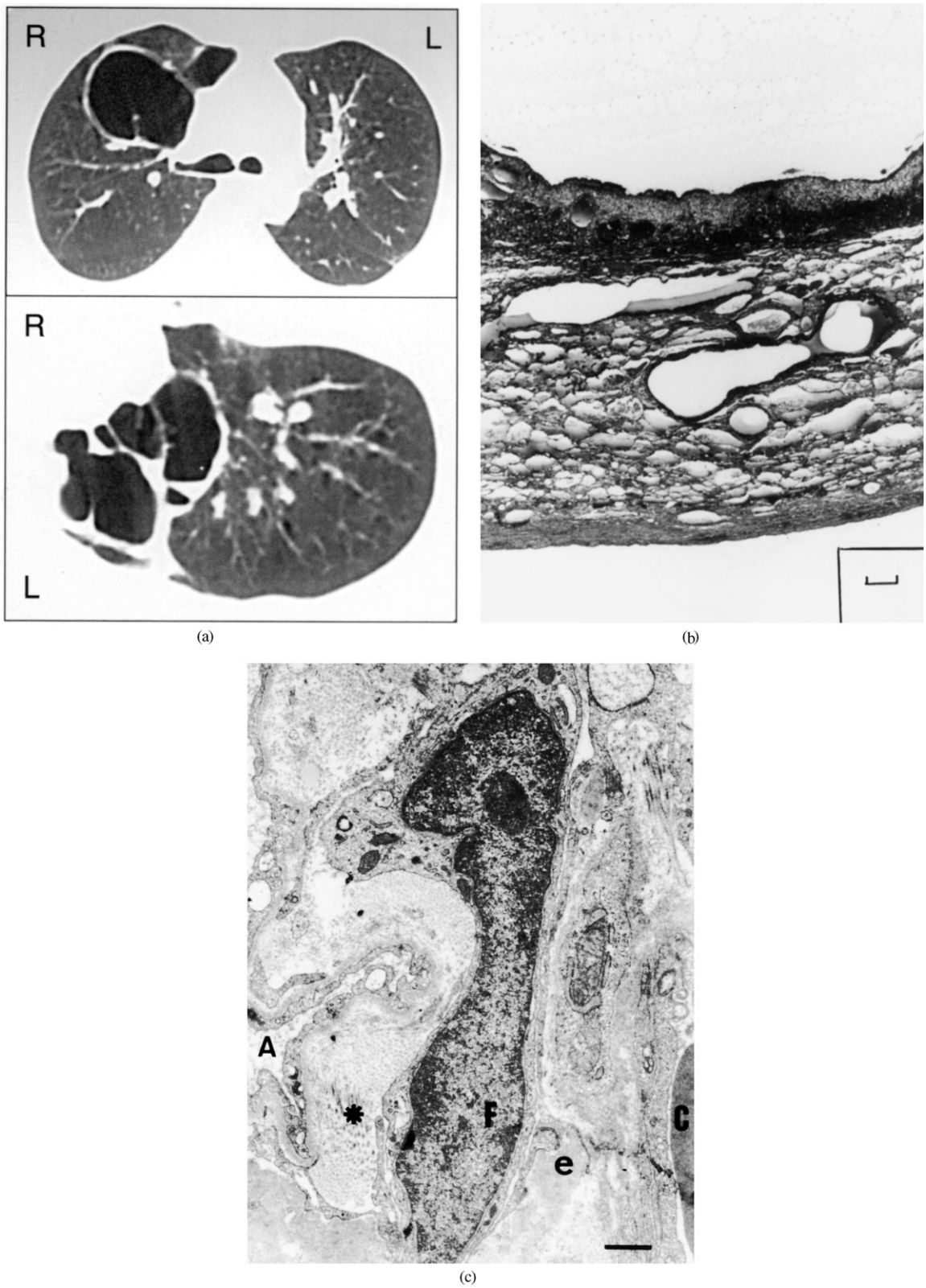

Fig. 1. (a) (Upper panel) Appearance of the lesion on CT-scan of the chest (5-mm sections); (lower panel) CT-scan of the chest performed on left lateral decubitus showing the dividing wall within the cyst and an air-fluid level; R, right, L, left. (b) Light microscopy showing the thin wall of the cyst, with the presence of a thin cambium layer underneath the respiratory epithelium; small mucus cysts are entrapped in the cambium layer (× 2.5, scale bar: 200 μm). (c) Electron microscopy of the mesenchymal cystic hamartoma, showing a fibroblast (F) with little cytoplasm and a large nucleus, close to an alveolar epithelial cell (A), a capillary vessel (C), and abundant collagen (*) and elastin (e) fibers (scale bar: 1 μm).

the large cyst, and were filled with coagulated blood. No connection was seen between the lumen of the cyst and that of the bronchi. Microscopically, the walls of the cysts were thin, and lined with respiratory epithelium. Beneath the epithelium, the large cyst was rimmed by a thin band-like layer of cells (cambium layer) composed of primitive mesenchymal-like cells with dark nuclei. Small mucous cysts were enclosed in the cambium layer, and small nodules of mesenchymal cells were also present. Immunostaining of the respiratory epithelium was positive for cytokeratin; staining of the fibroblasts was positive for α-actin and vimentin. Ultrastructural examination showed that both endodermal (alveolar epithelial cells) and mesodermal (fibroblasts, endothelial cells) components of lung parenchyma were present within the lesion, a finding consistent with hamartoma. The fibroblasts showed no ultrastructural differentiation toward myofibroblasts. The mesenchymal matrix showed abundant elastin accumulation (microfibrils and elastin fibers), and loose collagen bundles. These findings were consistent with a diagnosis of mesenchymal cystic hamartoma of the lung.

Since 1994, the patient has undergone several surgical procedures for Cowden-related lesions, including nodular papilloma of the breast, bilateral cystadenofibroma of the ovaries, and multinodular heterogeneous hyperplasia of the thyroid gland. In 1999, obstructive sleep apnea syndrome was diagnosed, and the patient was treated with continuous positive airway pressure ventilation. In January 2001, chest radiography showed no evidence of recurrence.

DISCUSSION

The diagnosis of Cowden's disease is based on the association of macrocephaly, facial trichilemmomas, oral papillomas or scrotal tongue, and hamartomas of various origins (2), all of which were present in our patient who met the diagnostic criteria of the International Cowden Consortium (3). The family history also suggests this diagnosis, since the mother of our patient had a history of scrotal tongue and neoplasia (information about any mucocutaneous lesions was lacking). Therefore, the diagnosis of Cowden's disease may be considered definite in our patient. In addition, the presence of a tumor of the cerebellum of unknown histopathology might suggest Lhermitte–Duclos disease (dysplastic gangliocytoma of the cerebellum), since an association between this condition and Cowden's disease has been reported (4).

The occurrence of a cystic pulmonary lesion in a patient with multiple hamartoma syndrome led us to suspect a cystic mesenchymatous hamartoma; indeed, both the clinico-radiological and the histological appearances of the pulmonary lesion were typical of this diagnosis. The cyst grew slowly over many years, and only became symptomatic latterly. The intermittent air-fluid level was suggestive of bleeding. This was confirmed by pathological analysis, which showed that numerous small cysts present within the wall of the large cyst were filled with coagulated blood. Hemorrhage from large systemic arteries into a cystic mesenchymatous hamartoma of the lung has been described (1), and may even be lethal (5). Other serious complications include pneumothorax or hemothorax from rupture of a subpleural cyst into the pleura, and malignant transformation of the cyst (1,6–8). Although surgical resection of asymptomatic cysts is usually not recommended, it may be performed to establish the diagnosis and to prevent complications. However, new nodules and cysts may continue to appear after surgery.

Cystic mesenchymatous hamartoma has been reported neither in Cowden's disease, nor in pulmonary hamartoma syndrome, another entity in which pulmonary hamartomas, developmental abnormalities and benign tumors are associated (9). However, a case of classical pulmonary hamartoma has been reported in a patient with Cowden's disease; the lesion was not cystic (10).

Mutations of the recently discovered tumor suppressor PTEN gene have been detected in a proportion of, but not all patients with Cowden's disease (11,12), and in various primary tumors. Such mutations are likely to influence the development of various tumors in Cowden's syndrome. Thus, it may be hypothesized that germline or somatic mutations of PTEN (or of other genes adjacent to PTEN on chromosome 10q22–23) may be involved in the development of mesenchymal cystic hamartoma in patients with or without history of Cowden's disease. In our patient, a screening test for mutations of the PTEN gene was performed on peripheral leukocytes as well as on the lung hamartoma by denaturating gradient gel electrophoresis, and was negative. Since the genetic screening of the PTEN gene is negative in about 25% of patients with Cowden's disease, such findings do not question the clinical diagnosis. We speculate that the disease in our patient might be related to a mutation in a regulatory region of the PTEN gene, to a large deletion or a mutation leading to aberrant splicing (12), or to epigenetic alterations of the wild-type PTEN gene, which are not detected by the genetic screening.

CONCLUSION

Since it is extremely unlikely that a very rare hamartoma would occur by coincidence in a patient with Cowden's disease (a condition known to predispose to multiple hamartomas), we suggest that mesenchymal cystic hamartoma of the lung may be included in the spectrum of Cowden's disease.

Acknowledgements

We are endebted to Dr E.J. Mark, MD (Boston, USA) who confirmed the pathological diagnosis of mesenchy-

mal cystic hamartoma of the lung in our patient; to Dr M. Longy (Bordeaux, France) who performed the genetic analysis; and to Drs T. Greenland and E. Chan who reviewed the manuscript.

REFERENCES

1. Mark EJ. Mesenchymal cystic hamartoma of the lung. *N Engl J Med* 1986; **315:** 1255–1259.
2. Hanssen AMN, Fryns JP. Cowden syndrome. *J Med Genet* 1995; **32:** 117–119.
3. Nelen MR, Padberg GW, Peeters EA, *et al*. Localization of the gene for Cowden disease to chromosome 10q22–23. *Nat Genet* 1996; **13:** 114–146.
4. Padberg GW, Schot JD, Vielvoye GJ, *et al*. Lhermitte–Duclos disease and Cowden disease: a single phakomatosis. *Ann Neurol* 1991; **29:** 517–523.
5. Chadwick SL, Corrin B, Hansell DM, *et al*. Fatal haemorrhage from mesenchymal cystic hamartoma of the lung. *Eur Respir J* 1995; **8:** 2182–2184.
6. van Klaveren RJ, Hassing HHM, Wiersma-van Tilburg JM, *et al*. Mesenchymal cystic hamartoma of the lung: a rare cause of relapsing pneumothorax. *Thorax* 1994; **49:** 1175–1176.
7. Becroft DMO, Jagush MF. Pulmonary sarcomas arising in mesenchymal cystic hamartomas. *Pediatric Pathol* 1987; **7:** 478.
8. Hedlund GL, Bisset GSd, Bove KE. Malignant neoplasms arising in cystic hamartomas of the lung in childhood. *Radiology* 1989; **173:** 77–79.
9. Gabrail NY, Zara BY. Pulmonary hamartoma syndrome. *Chest* 1990; **97:** 962–965.
10. Sasaki M, Hakozaki H, Ishihara T. Cowden's disease with pulmonary hamartoma. *Intern Med* 1993; **32:** 39–41.
11. Liaw D, Marsh DJ, Li J, *et al*. Germline mutations in the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. *Nat Genet* 1997; **16:** 64–67.
12. Nelen MR, van Staveren WC, Peeters EA, *et al*. Germline mutations in the PTEN/MMAC1 gene in patients with Cowden disease. *Hum Mol Genet* 1997; **6:** 1383–1387.