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Bacteriologically confirmed pulmonary tuberculosis in a patient with lymphangioleiomyomatosis accompanying tuberous sclerosis syndrome

Gruźlica płuc potwierdzona bakteriologicznie u chorej na limfangioleiomiomatozę w przebiegu stwardnienia guzowatego

Abstract

Lymphangioleiomyomatosis (LAM) is a rare disease of unknown origin, that may be sporadic or develop in the course of tuberous sclerosis (TS). Patients do not present immune deficiency, but structural changes in the lung parenchyma (cysts) may encourage various infections, for example tuberculosis. Radiologic findings are often difficult to interpret, because of changes related to LAM itself. We present a young women with a history of TS and LAM in whom protracted respiratory tract infection was finally diagnosed as tuberculosis. Initial diagnosis was based primarily on clinical signs and symptoms and treatment was started despite a negative result of sputum microscopy for acid-fast bacilli. In the course of treatment, the diagnosis was supported by genetic test for *M. tuberculosis* in bronchoalveolar lavage fluid, positive tuberculin skin test, interferon-gamma release assay and finally, positive sputum culture in liquid media.

Key words: lymphangioleiomyomatosis, tuberous sclerosis, tuberculosis, diagnostics

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Introduction

Lymphangioleiomyomatosis (LAM) is a rare lung disease with unknown aetiology, usually developing alone (sporadic LAM, found only in women in procreative age, with a prevalence of 1:1 000 000) or as a unit associating TS (tuberous sclerosis) [1]. The American register of LAM patients from the years 1998–2001 included 243 cases [2], the Japanese one — 173 cases [3], while the Spanish one — 72 cases [4]. There is no such a register in Poland.

Lymphangioleiomyomatosis leads to multiplication of smooth muscle cells in the bronchial walls, as well as in blood and lymphatic vessels of the lungs, mediastinum, and retroperitoneal space, followed by a destruction of the lung parenchyma and formation of the cysts [5]. Tuberous sclerosis is a autosomal dominant genetic disorder. Its prevalence amounts to 1:6000. It is caused by a mutation of *TSC1* and *TSC2* genes encoding proteins which suppress the development of tumours: tuberin and hamartin. The mutation results in an

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abnormal production of these proteins, and thus leads to the development of multiple, mostly benign tumours (hamartomas, angiomyolipomas, astrocytomas, angiofibromas, rhabdomyomas, lymphangiomyomas) in different organs. Especially important for the diagnosis are the angiomyolipomas of the kidneys. Changes of the central nervous system may cause epilepsy or mental retardation [6]. In approx. 40% of women with TS, there may be lesions of the lungs, morphologically consistent with LAM [7, 8]. LAM treatment is mainly symptomatic. Nowadays, the administration of progesterone and other gonadal hormones is not advised. Clinical tests involve the use of sirolimus. In case of advanced functional disorders of the respiratory system, the patients should be qualified for lung transplantation [8].

Tuberculosis is an infectious disease, with an incidence of over 8000 new cases a year in Poland [9]. The incidence rate is caused by a recent transmission from individuals coughing up *Mycobacterium tuberculosis* with sputum and by reactivation of past infections with a decreased immunity. According to the latest epidemiological studies, about 20% of the Polish population is infected with *Mycobacterium tuberculosis*. The incidence amounts to over 12% in the groups of 25–45 years and it rises with age (Kuś, unpublished data).

Structural abnormalities of the respiratory system encourage the development of tuberculosis. We present a case report of a patient with LAM in the course of TS, who was diagnosed with bacteriologically confirmed lung tuberculosis at the age of 30.

Case report

A 30-year-old patient with LAM in the course of tuberous sclerosis followed up in of the Institute of Tuberculosis and Lung Diseases (ITLD) since 1997. Tuberous sclerosis was diagnosed when she was 2 years old, on the basis of characteristic somatic features (Pringl's mark on the forehead skin) and calcifications in deep brain structures, visible on CT (computed tomography). Since the year 1997, there were a few recurrences of pneumothorax. In 1999, the patient underwent a right-sided pleurodesis during which a lung specimen was taken for histopathological examination which showed lesions of LAM type. In the same year, tumour of the left kidney was diagnosed and resected in kidney-saving procedure. Histopathological examination showed a structure of angiomyolipoma, with prevailing muscular component, foci of fat tissue and quite numerous vessels. In the observation period, the patient's health state was good, her functional parameters of the respiratory system (both the volumetric ones and the diffusion capacity) were within the normal ranges. Mental development was not significantly affected and the patient graduated from economic secondary school and worked as economist for a few years. At the age of 22, she was diagnosed with reduced lung diffusion capacity (up to 60% of the predicted value) for the first time in her life and her functional parameters started deteriorating since then. In the last tests, i.e. from 2010, there was a moderate obturation with features of pulmonary hyperinflation (RV, residual volume of 2.49 l — 176% of the predicted value) and a severely impaired diffusion capacity (30% of the predicted value). HRCT (high-resolution CT) showed very numerous small cysts and air spaces of different size in the pulmonary parenchyma, as well as pleural thickening on the right side. Image of the mediastinum and hili was normal (Fig. 1, Fig. 2 A–D). The lesions did not show any significant changes with time, starting from 2002.

With the age of 25, the patient deteriorated neurologically, starting with visual disturbances, vertigo and from 2009, progressing disturbances of sensation of the left side of the body, with muscle paresis. There was also an increasing number of small lesions, most probably of choristoma type, in the liver, and of angiomyolipoma type, in both kidneys. As far as respiratory symptoms were concerned, the patient complained of persistent cough with scanty expectoration. Sputum was sampled several times for bacteriological examinations, including the presence of *Mycobacterium tuberculo-*

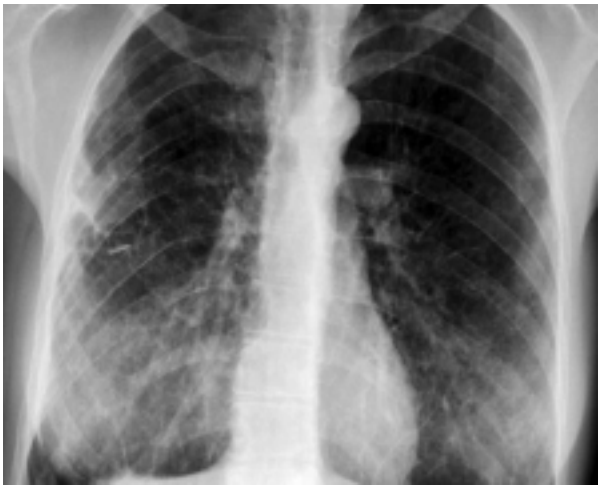

Figure 1. Postero-anterior X-ray of the chest (2010): disseminated changes in both lungs - small air spaces. Normal picture of both hili and mediastinum

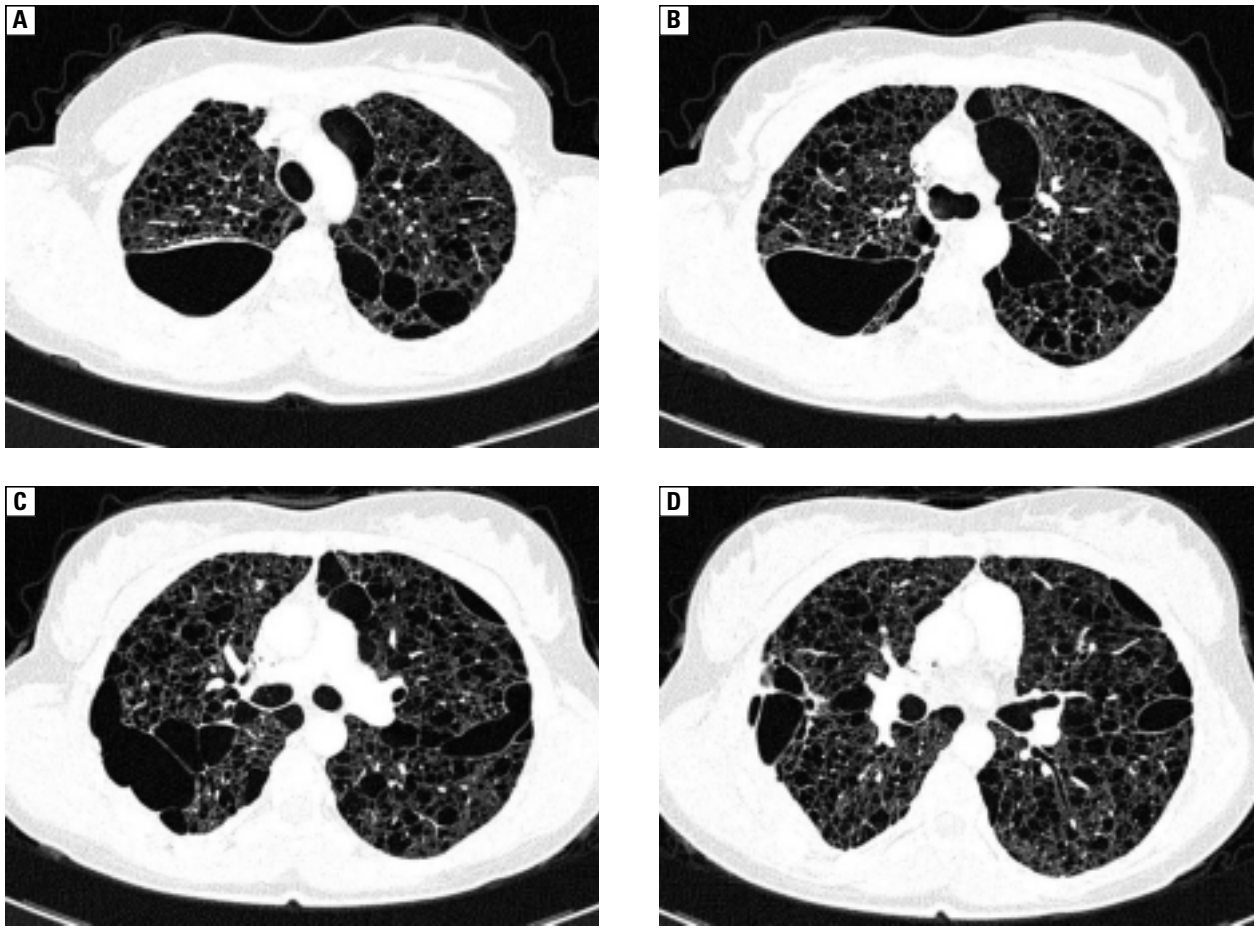

Figure 2 A–D. High resolution computed tomography of the lungs (2010). In both lungs numerous air spaces of different size. Bigger, subpleural air spaces may correspond with residual pneumothorax. No enlarged lymph nodes of hili nor mediastinum visible

sis. The results of cultures were negative. In February 2011, the patient presented to ITLD due to a two-month history (approximately) of upper airway infection with increased cough, fever of 39°C, sweating and loss of body mass (approx. 5 kg in one month). The patient was taking antibiotics (amoxicillin with clavulonic acid and clarithromycin) without a significant improvement. Deficient respiratory murmur was found on auscultation over the whole lung fields and quite numerous gentle crackles over the middle field of the left lung, absent in previous examinations. The increased body temperature (of up to 38°C) persisted. Laboratory tests showed a moderate increase in the number of leukocytes, with a higher rate of neutrophils, a significantly raised ESR, and a slight increase in CRP (C-reactive protein). Chest X-ray showed patchy opacities of the parenchyma in the upper lobe of the left lung (Fig. 3). HRCT was performed, which confirmed the presence of patchy opacities in the upper lobe of the left lung overlapping lesions that developed in the course of LAM (Fig. 4 A–D). Radiological changes were described as inflammatory, and the radiologists did not suggest tuberculosis as aetiological factor. Sputum was obtained to examine the presence of MTB

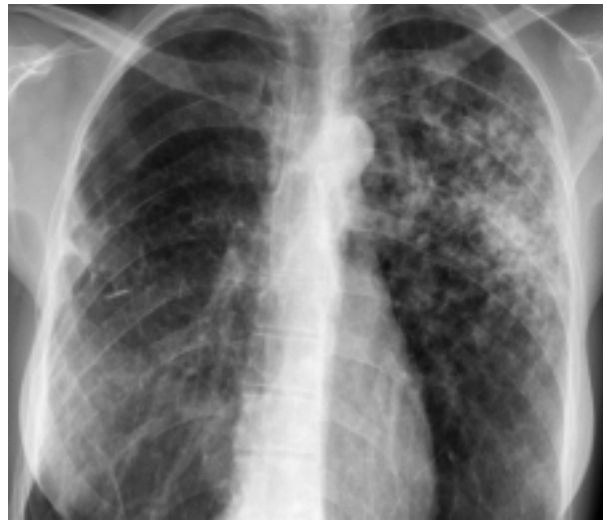

Figure 3. Postero-anterior X-ray of the chest (2011): In the left upper lobe large area of patchy opacities

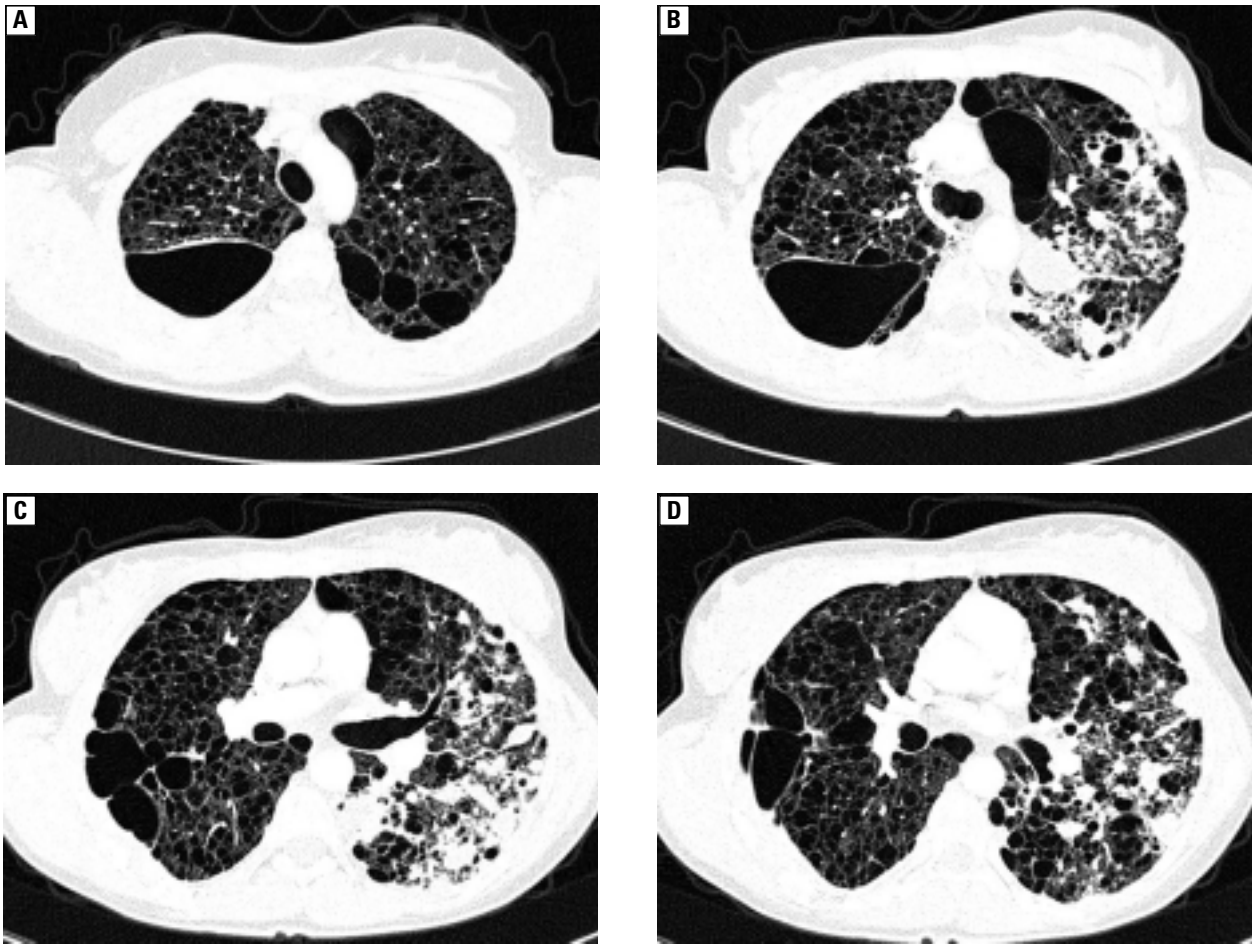

Figure 4 A–D. High resolution computed tomography of the lungs (2011). In the left upper lobe massive, patchy opacities, accompanying prior radiologic changes related to lymphangioleiomyomatosis

— direct samples did not contain acid-fast bacilli. Bronchoscopy was carried out and showed multiple anthracotic incrustations of the bronchial mucosa. On the basis of the clinical picture (protracted fever, with no response to antibiotic treatment, sweating, and loss of the body mass), and despite the fact that the radiological picture was not too characteristic, lung tuberculosis was diagnosed and antimycobacterial therapy was immediately introduced. A direct examination of the BAL fluid revealed no acid-fast bacilli, but a genetic test for MTB gave a positive result after 3 days (BD ProbeTec™). At the same time, tuberculin skin test was carried out, and the size of the reaction amounted to 16 mm. Interferon-gamma release assay (IGRA, QuantiFERON®-TB Gold In Tube) was negative at first, but gave positive results when repeated after a week. After 9 days, MTB from sputum was grown in liquid media. The strain was sensitive to basic antimycobacterial drugs. Due to ophthalmological contraindications to ethambutol (changes in the eye in the course of tuberous sclerosis) rifampicin, isoniazid, streptomycin and pyrazinamide were used. The first three drugs were well tolerated with no clinical or laboratory symptoms of toxicity. The administration of pyrazinamide was followed by dyspeptic symptoms, abdominal distension, aversion to food, vomiting and loose stools. Laboratory tests showed an increased activity of liver enzymes (ALT — 12 times above the upper limit of reference value, AST — 20 times above the upper limit of reference value) and hyperbilirubinaemia. All antimycobacterial drugs were withdrawn. Clinical symptoms subsided but laboratory parameters still remained abnormal. According to the previous arrangements, the patient was transferred to the Mazovian Center of Lung Diseases and Tuberculosis, for treatment continuation. After over 10 days, liver function parameters regained their normal values; antimycobacterial treatment was gradually introduced again, with pyrazinamide being replaced by ofloxacin.

Discussion

Poland belongs to countries with a medium incidence of tuberculosis, but the epidemiological

indices improve systematically, approaching rates found in countries with a low incidence (i.e. below 20/100 000/year, according to the WHO) [9, 10]. Lower incidence of tuberculosis leads to a higher number of diagnostic difficulties and to a situation in which the disease is not considered in the differential diagnosis of respiratory infections. Active tuberculosis is usually a result of activation of a latent infection. Approximately 5–10% of infected individuals will develop the disease in the course of their life [11]. The risk of tuberculosis increases in individuals with deficiency of cellular immunity. The most significant factor increasing the risk of disease development is the HIV infection, but other diseases decreasing the cellular immunity (such as renal insufficiency, diabetes) are of importance as well [12]. Immunosuppression, e.g. after organ transplantation, or in individuals with autoimmune diseases (especially those treated with TNF-alpha inhibitors), is also a risk factor [13]. Korean studies have shown a higher incidence of tuberculosis in patients with interstitial pulmonary fibrosis [14].

So far, no disturbances of cellular immunity have been observed in patients with LAM or tuberous sclerosis [15]. There are no reports on a higher incidence of respiratory infections (including tuberculosis) among those patients. However, it is known that changes in the parenchymal structure (e.g. the presence of bronchiectasis or bronchial cysts) favour the colonisation with mycobacteria. The presented patient had multiple air spaces in the lungs, which could favour mycobacterial infection. The clinical course was initially suggestive of bacterial infection (e.g. of pneumococcal aetiology), found mostly in out-hospital pneumonia. However, no response to treatment with amoxicillin, loss of body mass, increasing weakness, and night sweating, suggested a different cause. Moreover, in a case with a chronic disease of the respiratory system, persisting symptoms of infection should induce the physician to refer the patient for chest X-ray. Unfortunately, this examination was performed in this case as late as during consultation at ITLD and showed patchy opacities in the upper lobe of the left lung. The description was not suggestive of a TB infection. A more detailed evaluation was performed with HRCT, which showed consolidations and nodular lesions. However, there were no typical opacities of *"tree in bud"* [16]. A significant role of HRCT (in combination with clinical data) in the diagnostics of active tuberculosis and in differentiation between inactive and active lesions had been suggested for a long time [17, 18]. A slight increase in the parameters of inflammation was also an evidence against an acute bacterial infection [19]. A positive result of IGRA test and of tuberculin skin test were suggestive of infection with *Mycobacterium tuberculosis*. In combination with clinical and radiological symptoms, they may bring the diagnosis closer [20]. There was a positive result of genetic test for MTB, despite the absence of acid-fast bacilli in the sputum or BAL fluid in the presented patient. This was one more evidence in favour of the diagnosis of tuberculosis [21]. The final diagnosis was confirmed by positive results of cultures in liquid media.

The presented case showed that tuberculosis is a disease which should be taken into consideration when long-term infections of the respiratory system are diagnosed, especially in combination with different injuries of the pulmonary parenchyma.

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