Neurofibromatosis type 1 with interstitial pulmonary lesions diagnosed in an adult patient. A case study and literature review

Nerwiakółkniakowatość typu 1 ze zmianami śródmiąższowymi w płucach, rozpoznana u osoby dorosłej. Opis przypadku i przegląd piśmiennictwa

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Abstract

A case of a 43-year-old man with clinically diagnosed neurofibromatosis type I (NF-1, von Recklinghausen disease) was referred to a lung disease unit for investigation of worsening tolerance of physical effort and of aetiology of radiological cystic lung lesions, seen in high-resolution computed tomography (HRCT). The patient had been treated for epilepsy since childhood, and had third degree tricuspid valve incompetence, with no pulmonary hypertension detected during right heart catheterization. Interstitial pulmonary lesions were finally attributed to his primary disease, and further clinical observation is required in order to determine their dynamics. The observed deterioration in the patient’s tolerance to physical effort was connected to the accompanying respiratory tract infection with Klebsiella oxytoca and Staphylococcus aureus, in a subject with cystic lung lesions and tricuspid valve incompetence. The report describes the criteria for NF1 diagnosis and points out the controversies of coexistence of interstitial pulmonary lesions in the clinical picture of the disease.

Key words: neurofibromatosis type 1, cystic lung disease, pulmonary fibrosis, high-resolution computed tomography, interstitial lung diseases

Introduction

Neurofibromatosis type I (NF1, von Recklinghausen disease) is a genetically determined disease with complex symptomatology concerning multiple organs of neuroectodermal origin. This group of diseases is also commonly called phakomatoses, from the Greek phakos meaning “stigmatized at birth”. The main symptoms concern skin, nervous system, and eyes, with abnormalities of many other organs, including the lungs [1, 2]. Neurofibromatosis type 1 has autosomal dominant inheritance and an incidence of 1:3,500 live births, with variable expression in different subjects and ages. The disease is caused by mutation in the NF1 gene on chromosome 17q11.2. Given the gene’s complexity, size, and numerous exons that can be affected, clinical pictures are variable, with different intensity and age of symptom onset. The probability of disease in a child of an affected parent is 50%. Nearly half of all cases are the result of new (spontaneous) mutations, and do not have family context [2]. Molecular diagnostics is not routinely applied, and diagnosis is made mainly based on the clinical picture using the consensus criteria described in 1997 [3]. Clinical criteria were not modified in the new consensus from 2007 [4]. Most cases are diagnosed by paediatricians, especially in patients with multiple skin lesions. In some patients, however, the disease is diagnosed in adult life or remains undetec-
neurofibromatosis type 1 with interstitial pulmonary lesions diagnosed in an adult patient.

Case report

A 43-year-old male gardener was treated for epilepsy since 9 years of age. Currently, he has grand mal fits several times a year, despite medication. The patient never smoked cigarettes and negated alcohol consumption. He was admitted to hospital for diagnostics of pulmonary lesions visualized in high-resolution computed tomography (HRCT). The lesions were identified in the course of cardiologic evaluation for pulmonary hypertension, to which he had been referred due to worsening tolerance of physical effort for the previous 2-3 years. Five months earlier the patient was hospitalized due to pneumonia. At that time, he experienced dyspnoea, mild cough, and was subfebrile. His general condition improved following administration of antibiotics but after a short time his dyspnoea resumed, and he became weaker. He was then referred to the department of cardiology, where many imaging and functional tests were performed to give reasons for his effort dyspnoea. Echocardiography showed dilated right ventricle, 3rd degree insufficiency of the tricuspid valve, and 1st degree insufficiency of the mitral valve. Mean right ventricular systolic pressure (RVSP) was 54 mmHg. Ejection fraction, morphology of other valves, and heart muscle contractility was normal. Resting ECG revealed flat to negative T waves in inferior leads. Twenty-four ECG registration gave normal readings. Exercise test (with the patient walking on treadmill) was clinically and electrocardiographically negative. Chest CT and perfusion lung scintigraphy were performed in an attempt to find the cause of the pulmonary hypertension. Computed tomography scanning revealed no embolism in pulmonary arteries or their branches. Multiple small cystic lesions were, however, visualized in both lungs, mainly in peripheral areas, with single larger bullae up to 2 cm in diameter in apical segments (fig. 1), alongside thickened interlobular septae (fig. 2). Mediastinal and hilar lymph nodes were moderately enlarged. Scintigraphy revealed decreased perfusion in peripheral segments. However, no segmental perfusion deficits suggestive of embolism were detected. Catheterization of the right heart chambers was performed, revealing normal pressure and resistance values in pulmonary circulation. No significant shunt in the right heart chambers was noted. Coronarography and magnetic resonance imaging (MRI) of the heart were also performed, both revealing normal muscle blood supply and contractility. Six-minute marching test was performed, revealing a significant drop in arterial blood saturation from 99% at baseline to 77% at the end; heart rate increased from 67/min to 113/min. The covered march distance was 330 m. Final conclusion from cardiologic investigation was tricuspid valve insufficiency, with recommendation of further diagnostics of pulmonary lesions.

Figure 1. Fine cystic lesions situated mainly in the peripheral parts of lungs, and single larger bullae (up to 2 cm) in apical segments

Figure 2. Thickening of interlobular septae and multiple cystic lesions in lower parts of both lungs
On the day of admission to hospital, the patient was in good general condition. His fine, almost child-like constitution, with body height of 155 cm and weight of 51 kg, was noteworthy. The patient complained of mild effort dyspnoea but had no cough or fever. Physical examination revealed multiple scattered skin lesions in form of soft, elevated, slightly discoloured nodules (fig. 3), with several beige discolorations of the café-au-lait spot-type (fig. 4) and numerous freckles in the armpits (fig. 5). The patient claimed he had skin lesions since childhood but they seemed to increase in number during puberty and further multiplied with age. Lung auscultation revealed normal vesicular sound. March test was repeated as the patient claimed that his effort tolerance improved. The patient could walk for 350 m, and saturation changed from baseline 97% to 94%, with heart rate increasing from 69/min to 103/min. Bronchoscopy revealed no pathology of the bronchial tree. Sampled material included bronchial mucosa, bronchialalveolar lavage (BAL) for bacteriological mycological tests as well as for tuberculosis testing (BACTEC). Histopathological examination disclosed normal respiratory-type mucosa. Cultures of BAL fluid gave positive results for *Klebsiella oxytoca* (multiple colonies) and *Staphylococcus aureus MSS* (single colonies). Both kinds of bacteria were sensitive to amoxicillin with clavulanic acid (among others); therefore, this antibiotic was administered. Direct examination and culture of BAL fluid were negative for *Mycobacteria*. Plethysmography showed no ventilation abnormalities. Taking into account the specific skin lesions and history of epilepsy since childhood, tentative diagnosis of neurofibromatosis type 1 was made. Magnetic resonance imaging of the brain showed pathological lesions in the right hippocampus, frontal gyrus of the frontal lobe, and convexity of the right cerebral hemisphere as well as in the right cerebellar hemisphere. The largest lesion was 17 × 21 mm. Lesions were heterogeneously enhanced by contrast medium and were described as probable foci of glial hyperplasia/dysplasia (*haemartoma*). The describing consultant concluded that the lesions might be radiologically consistent with the suggested diagnosis of von Recklinghausen disease. Laboratory investigations showed increased level of C-reactive protein (CRP; 43 mg/l), which was clinically interpreted as a sign of bacterial respiratory tract infection. Taking into account the results of all the investigations performed in the departments of cardiology and lung diseases, a final diagnosis of neurofibromatosis type 1 was made, with associated cystic lung lesions, moderate lung fibrosis, and concomitant respiratory tract infection with *K.oxytoca* and *S.aureus*. The worsened tolerance to physical effort with decreasing...
saturation, as observed during cardiological diagnostic procedures, was attributed to the current respiratory tract infection superimposed on NF1-related lung lesions. Effort dyspnoea decreased following antibiotic therapy. The patient was discharged home, with antibiotics to be continued for up to 14 days. Follow-up hospital admission was planned after 4 months in order to perform functional tests of the respiratory tract and ophthalmological examination. Neurological medication was continued, and a neurosurgical consultation was planned alongside follow-up in the outpatient service of the department of lung diseases. On the day of next admission to hospital the patient again complained of effort dyspnoea, moderate pain, and oedema of the right ankle, which appeared several weeks earlier; the patient is currently scheduled for admission to the rheumatology department. The patient also complained of dry cough and mild fever (up to 37.4%) in the evenings. Laboratory investigations were also performed this time, revealing leukocyturia, mild proteinuria, as well as increased CRP. The patient negated, however, urinary tract complaints. Plethysmography was normal, but a mild decrease in forced expiratory volume in first second (FEV1) and forced vital capacity (FVC) of 200 ml as compared to previous investigation were noted. During the march test, the patient could walk for 400 m, despite pain in his right leg. Saturation decreased then from 96% at baseline to 91%. Resting arterial blood gasometry was normal. Ophthalmological consultation disclosed multiple Lisch nodules in both irises, demonstrated in slit lamp examination; the lesions were typical for NF1 (fig. 6).

Considering the signs of urinary tract infection, an oral antibiotic was prescribed for 7 days, with control urine testing at follow-up in the outpatient clinic. Follow-up with hospital admission was scheduled 8 months later, with planned echocardiography and chest HRCT for investigation of lung lesion evolution and potential progression of lung fibrosis.

**Discussion**

Clinical criteria of NF1 diagnosis were published in 1997 [3] and complemented in 2007 [4]: These include features detectable on physical examination. The disease can be diagnosed if at least two major criteria can be found in a patient. These include: [2]:

- presence of at least six **cafe-au-lait** spots of more than 5 mm in diameter in children and 15 mm in adults;
- presence of at least two neurofibromas or one plexiform neurofibroma;
- presence of freckles and/or discolorations in sun-protected areas (armpits, pubic area);
- optic glioma;
- presence of at least two iris nodules (Lisch nodules);
- specific skeletal abnormalities;
- at least one first degree relative fulfilling the above-mentioned criteria.

Minor criteria, including macrocephaly and short stature, are also mentioned in the classification. Many authors describe also plexiform neurofibromas affecting in sheaths of multiple peripheral nerves, and cerebral gliomas. Many patients experience symptoms and signs from the central nervous system (CNS), including epilepsy, intellectual impairment, as well as short stature, which is attributed to a specific location of a glial neoplasm thus resulting in secondary growth hormone deficiency. Growth hormone treatment for short stature is not routinely administered. Approximately 30% of NF1-patients suffer from various orthopaedic problems, particularly scoliosis, bone deformities, or dysplasia [6].

The presented patient had four out of seven NF1 diagnostic criteria: several skin lesions macroscopically consistent with neurofibromas, multiple freckles and larger discolorations in the armpits, at least 6 **café au lait** spots of more than 15 mm, alongside Lisch nodules of the iris, CNS symptoms radiologically consistent with **haematomata** with secondary epilepsy, short stature, and skeletal deformities with decreased mobility of the right ankle. Chest HRCT showed multiple cystic lung lesions of less than 20 mm in diameter, located mostly in the upper lobes as well as ground glass pattern, with thickening of interlobular septae.

**Figure 6.** Numerous brown Lisch nodules in the iris
The first description of coexisting NF1 and interstitial lung disease was published in 1963 by Davies, based on interpretation of radiological pictures [7]. The author followed several NF1 patients and claimed that interstitial lung disease with effort dyspnoea occurred in 10–20% of them. He suggested inclusion of interstitial lung disease to clinical criteria of NF1. Webb and Goodman later described the presence of thin-walled and nodular lung lesions, located mostly in subpleural areas [8]. With the introduction of HRCT reports of interstitial lung disease in NF1, patients began to emerge [9–11]. The relationship between the occurrence of interstitial disease and cystic lung lesions and NF1 is questioned by some authors. Some publications correlate the presence of these lesions with the clinical course of NF1 [9, 12], whereas others believe that it is smoking habit that induces development of lung lesions [10]. Oikonomau et al. described six adult NF1 non-smoking patients, all of whom had lung lesions in HRCT, including cysts (from several to more than 100), measuring up to 18 mm, situated particularly in upper lobes. All the patients also had ground glass pattern. The currently described patient was a non-smoker and had multiple lesions of less than 20 mm (fig. 1). He also had ground glass pattern, mainly in posterior lung regions (fig. 2). Radiological findings of this type can be found in histiocytosis X, lymphangioleiomyomatosis, and some cases of lymphocytic interstitial pneumonia (LIP) associated with immunosuppression or in cases of Sjögren syndrome. The presented patients had no clinical symptoms or signs of any of the mentioned entities. Pathogenesis of cystic lung lesions in NF1 patients is unclear. Biopsy material from lung parenchyma shows lymphocytic infiltrates in alveolar septae and peribronchial tissue, which may contribute to obturation of the smallest bronchioles and development of cysts. Amyloid deposition was also described histopathologically [7, 13]. No lung tissue sampling has been performed yet, but the procedure may be indicated if functional and radiological signs of interstitial lung disease point to disease progression. The aim of this case presentation was to recall diagnostic criteria of von Recklinghausen disease as well as to describe the unusual radiological presentation with clinically overt effort dyspnoea.

Despite the presence of clinically detectable signs and symptoms, diagnosis of NF type 1 was made in our patient at the age of 43 years. Prognosis is difficult to assess, as dynamics of lung lesion development cannot be foreseen, and only a long-term follow-up may be contributory. Evolution of CNS lesions cannot be foreseen either. Approximately 20% of NF1 patients develop CNS malignancies.

Patients with NF1 require continuous multidisciplinary medical care.

Conflict of interests

The authors declare no conflicts of interest

References