Causes of severe pulmonary impairment in a young patient

Cauze de afectare pulmonară severă la un pacient tânăr

Abstract

There are countless diagnostic possibilities when treating a patient with a pulmonary impairment, and the most obvious causes are not always the real ones. We present the case of a 41-year-old patient, with six previous episodes of pulmonary tuberculosis (with no sufficient clinical and bacteriologic diagnostic arguments in all cases), diagnosed with type I Gaucher disease, on substitutive enzymatic treatment. When registered, the patient presented severe mixed ventilatory defect, with severe alteration of the alveolo-capillary diffusion, being severely hypoxemic and hypercapnic, severely desaturating at small efforts, and the CT exam revealed significant pulmonary alterations, including lung cysts, diffuse interstitial fibrosis, areas of ground-glass opacities, and cystic bronchiectasis. The patient received treatment with two bronchodilators from different classes and inhaled corticoid, oxygenotherapy, and non-invasive ventilation (BiPAP), considering the blood gas analysis. The evolution under therapy was favorable, with stable disease for six months, after which the patient dying as a result of a massive hemoptysis (probably due to an aspergilloma revealed by the last CT scan). We intend to discuss the causes for such a severe pulmonary impairment, respectively the extensive post-tuberculosis sequelae versus a possible pulmonary impairment due to Gaucher disease.

Keywords: ***Gaucher disease, severe pulmonary impairment, post-tuberculosis sequelae, non-invasive ventilation***

Rezumat

Când un pacient tânăr prezintă o afectare pulmonară severă, posibilitățile diagnostice sunt nelimitate. Nu întotdeauna cauzele cele mai evidente se dovedesc a fi și cele reale. Prezentăm cazul unui bărbat în vârstă de 41 de ani, cu șase episoade anterioare de tuberculoză pulmonară (nu toate cu argumente suficiente de diagnostic clinic și bacteriologic), diagnosticat cu boală Gaucher de tip I, pentru care este în tratament substitutiv enzimatic. La luarea în evidență, pacientul prezenta disfuncție ventilatorie mixtă severă, cu alterarea importantă a difuziunii alveolo-capilare, fiind hipoxemic și hipercapnic, desaturând sever la eforturi mici, iar examenul computer tomografic a evidențiat o importantă remaniere pulmonară, cu chisturi pulmonare, fibroză interstițială difuză, zone de geam mat și bronșiectazii chistice. Pacientul a primit tratament cu două bronhodilatatoare din clase diferite, corticoid inhalator, oxigenoterapie, dar și ventilație non-invazivă (BiPAP), având în vedere analiza gazelor sangvine. Evoluția sub tratament a fost bună, cu stabilizarea bolii pe o perioadă de 6 ani, după care pacientul a decedat în urma unei hemoptizii masive (probabil din cauza unui aspergilom constatat la ultima tomografie efectuată). Ne propunem să discutăm motivele acestei afectări pulmonare atât de grave, respectiv sechele post-tuberculoase extinse sau o posibilă afectare pulmonară în cadrul bolii Gaucher.

Cuvinte-cheie: ***boală Gaucher, afectare pulmonară severă, sechele post-tuberculoase, ventilație non-invazivă***

Oana Claudia Deleanu[1,2], Ana-Maria Zaharie[3], Andra Elena Mălăuț[4], Florin Dumitru Mihălțan[1,2]

1. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. "Marius Nasta" National Institute of Pneumophthisiology, Bucharest, Department of Pulmonology III, Romania

3. "Marius Nasta" National Institute of Pneumophthisiology, Bucharest, Sector IV Dispensary Department, Romania

4. Medicover Clinic, Pulmonology, Bucharest, Romania

Corresponding author:
Ana-Maria Zaharie
E-mail: ana_neb@yahoo.com

Introduction

Severe pulmonary impairment in young patients is particularly important because of its impact on the quality of life, its significant economic burden, as well as due to the limited therapeutic options available. The most common causes include alpha-1 antitrypsin deficiency, idiopathic pulmonary fibrosis, and pulmonary manifestations associated with systemic diseases.

Gaucher disease (GD) is an autosomal recessive disease characterized by a deficiency of lysosomal enzyme glucocerebrosidase, which results in glucocerebroside accumulation in macrophages and reticuloendothelium of various organs (primarily the liver and spleen, but also bones and lungs)[(1)].

We present the case of a patient with a severe pulmonary condition, labeled as a post-tuberculosis syndrome, who also has GD with possible pulmonary damage. This case motivated us to discuss the pulmonary manifestations of GD.

Case presentation

We present the case of a 41-year-old man who presented with dyspnea and cyanosis with minimal effort, and a weight loss of approximately 3 kilograms in the last four months. The patient was known to have a long history of pulmonary disorders, beginning with the age of 2 years old. At this age, he was diagnosed with miliary tuberculosis, based on suggestive radiological signs, hyperergic intradermal reaction (IDR) to PPD test, and a positive family history (mother and brother with pulmonary tuberculosis). He received treatment and later, at the ages of 4 and 6 years old, based on the same radiological image, he was diagnosed with tuberculosis relapse and he received repeated treatment. We must mention that none of the three episodes was bacteriologically confirmed. Following these episodes, based on X-ray features and a restrictive ventilatory dysfunction, at the age of 13, he was diagnosed with pulmonary fibrosis. At the age of 25, the patient was consulted at a pneumology clinic during an episode of respiratory symptoms exacerbation associated with fever. The diagnostic tests revealed biological inflammatory syndrome, moderate thrombocytopenia, and moderate anemia. The patient had marked restrictive syndrome and distal obstructive syndrome (as reported in the discharge letter, without other details). At bronchoscopy it was

Table 1 The evolution of functional parameters over time

Parameter	First assessment	1 year	3 years	4 years (exacerbation)
FEV1	0.68L (16.6%)	0.80L (20.4%)	0.72L (18.1%)	0.76L (19.3%)
FVC	0.95L (19%)	1.38L (28.8%)	1.27L (26.1%)	1.31L (27.1%)
TLCplet	5.06L (70%)	5.49L (77.8%)	4.62L (64.0%)	4.62L (64.0%)
RV	4L (198%)	4.05L (203.3%)	3.35L (164.2%)	3.36L (163%)
Raw	200%	169%	176%	194%
TLCO	9.3%	27.5%	23.1%	27.6%,
KCO	27%	64.1%	49.0%	51.9%
pH*	7.39	7.43	7.39	7.39
PaO_2*	45.9	59.4	57.9	40.7
$PaCO_2$*	57.5	46.3	49.5	47.8-64

Abbreviations – FEV1: forced expiratory volume in the first second; **FVC:** forced vital capacity; **CPTplet:** total lung capacity at plethysmography; **RV:** residual volume; **Raw:** airway resistance; **TLCO:** diffusing capacity of the lungs for carbon monoxide, also known as transfer factor for carbon monoxide; **KCO:** the rate constant for carbon monoxide uptake from alveolar gas; **PaO_2:** partial pressure of arterial oxygen; **$PaCO_2$:** partial pressure of carbon dioxide in arterial blood.
* results are obtained from arterial blood gas test performed without oxygen or noninvasive ventilation

Table 2 Oxygen saturation values (SaO2) during overnight pulse oximetry

SaO_2 value	Percentage of the recording period spent at this value
SaO_2 >90%	3%
SaO_2 85-90%	43%
SaO_2 80-85%	40%
SaO_2 75-80%	9%
SaO_2 70-75%	4%
SaO_2 <70%	0.5%

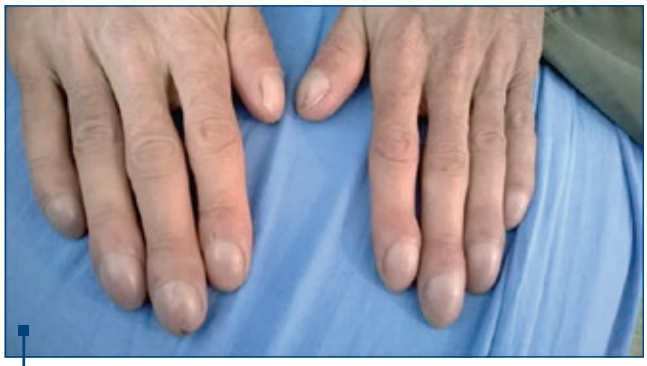

Figure 1. *Nail clubbing*

detected a transversal scar at the opening of upper lobe bronchus, otherwise pale mucous membranes and few secretions. Bronchoalveolar lavage showed a number of normal cells, with lymphocyte predominance. A level of 59.9 UI of ACE was determined. Sputum and aspirate microscopy were negative (culture results were not available to us). The patient was diagnosed with stage III sarcoidosis, but it was decided to prescribe both corticosteroid and anti-tuberculosis treatment. In-hospital evolution was favorable, with decreased ACE levels. At discharge, after two months of anti-tuberculosis treatment, it was recommended tuberculosis chemoprophylaxis with hydrazide and ethambutol twice a week (according to the discharge letter). A year on from the onset of corticosteroid therapy, a diagnosis of pulmonary tuberculosis was established, with positive microscopy and cultures, with rifampicin and isoniazid susceptibility on antibiogram, and also constrictive pericarditis requiring pericardiotomy. Three years later, another episode of tuberculosis was diagnosed (the last one), with positive microscopy and culture.

At four years after this last visit to the pulmonology clinic, a needle bone biopsy was performed in order to determine the cause of hematological changes (i.e., anemia and thrombocytopenia), leading to a diagnosis of Gaucher disease type I. The diagnosis was subsequently confirmed by a low level of beta-glucocerebrosidase (2.1 nmol/h/mg protein – the normal range being 6-25) and an increased level of chitotriosidase (40500 nmol/h/mL plasma – while the normal range is 170-5700). Other symptoms of the disease included organomegaly (enlarged spleen with the lower pole located at 8 cm below the costal margin with a total volume of 680 ml, which is seven times larger than normal, and firm, enlarged liver with the inferior margin 2 cm below the costal margin), bone-related symptoms (intermittent pain in the knees, significant femoral neck osteoporosis bilaterally), cachexia and abnormal blood count values (anemia and thrombocytopenia). At the age of 37, the patient was started on intravenous imiglucerase every two weeks, which resulted in partial improvement of anemia and thrombocytopenia.

At 41 years old, he had his first assessment at our clinic. The patient was cachectic (body mass index: 14.8 kg/m^2), in poor general condition, with digital clubbing (Figure 1), cyanosis, dyspnea at minimal exertion, significant hepatosplenomegaly, pale skin, alar chest, normal percussion sounds and normal symmetrical breathing sounds on auscultation, bilateral basal crackles, SaO_2 at rest, while breathing ambient air 91% (desaturating at minimal exertion), respiratory rate 18 breaths/minute, no apparent cardiac changes. Chest

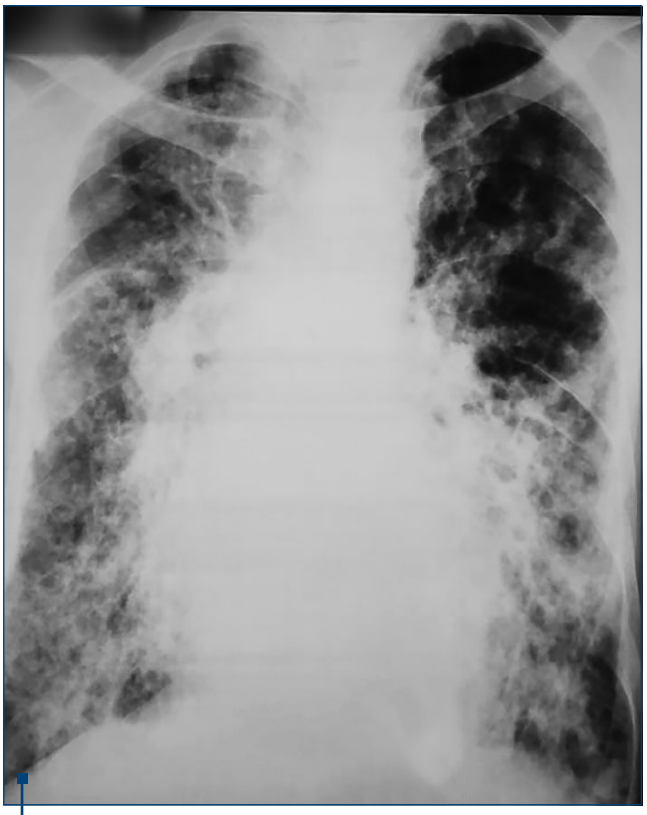

Figure 2. *Posteroanterior chest X-ray: significant bilateral fibrous changes, predominantly found in the basal areas*

X-ray revealed extensive high density nodular and reticulonodular opacities bilaterally, more evident in the lower lung fields (features suggestive of pulmonary fibrosis) – Figure 2. Sputum microscopy tests for tuberculosis were repeatedly negative, as were subsequent culture results. Other tests showed thrombocytopenia (75000/mm^2) and inflammatory biological syndrome, with erythrocyte sedimentation rate =30 mm/h. Functional tests revealed severe mixed ventilatory dysfunction with FEV1 of approximately 17% of predicted value, reduced total lung capacity on plethysmography, with central airway resistance, severely impaired alveolar-capillary diffusion, with reduced transfer constant. Arterial blood gas test results showed severe hypoxemia and mild hypercapnia (detailed results of functional tests and arterial blood gas tests are presented in Table 1). Hypoxemia improved with supplemental oxygen at supply flow of 4 liters per minute. The ECG revealed a minor right bundle branch block. The patient had severe desaturation during the walk test, from 94% to 77%, with significant worsening of dyspnea (5 to 9) and fatigue (5 to 8) on the Borg scale, after walking 72% of the predicted distance in 6 minutes. Chest CT scan revealed extensive lung architectural distortion, scar retractions, cysts with subpleural, basal predominance, diffuse interstitial fibrosis, as well as ground-glass opacities and cystic bronchiectasis (Figure 3). Overnight

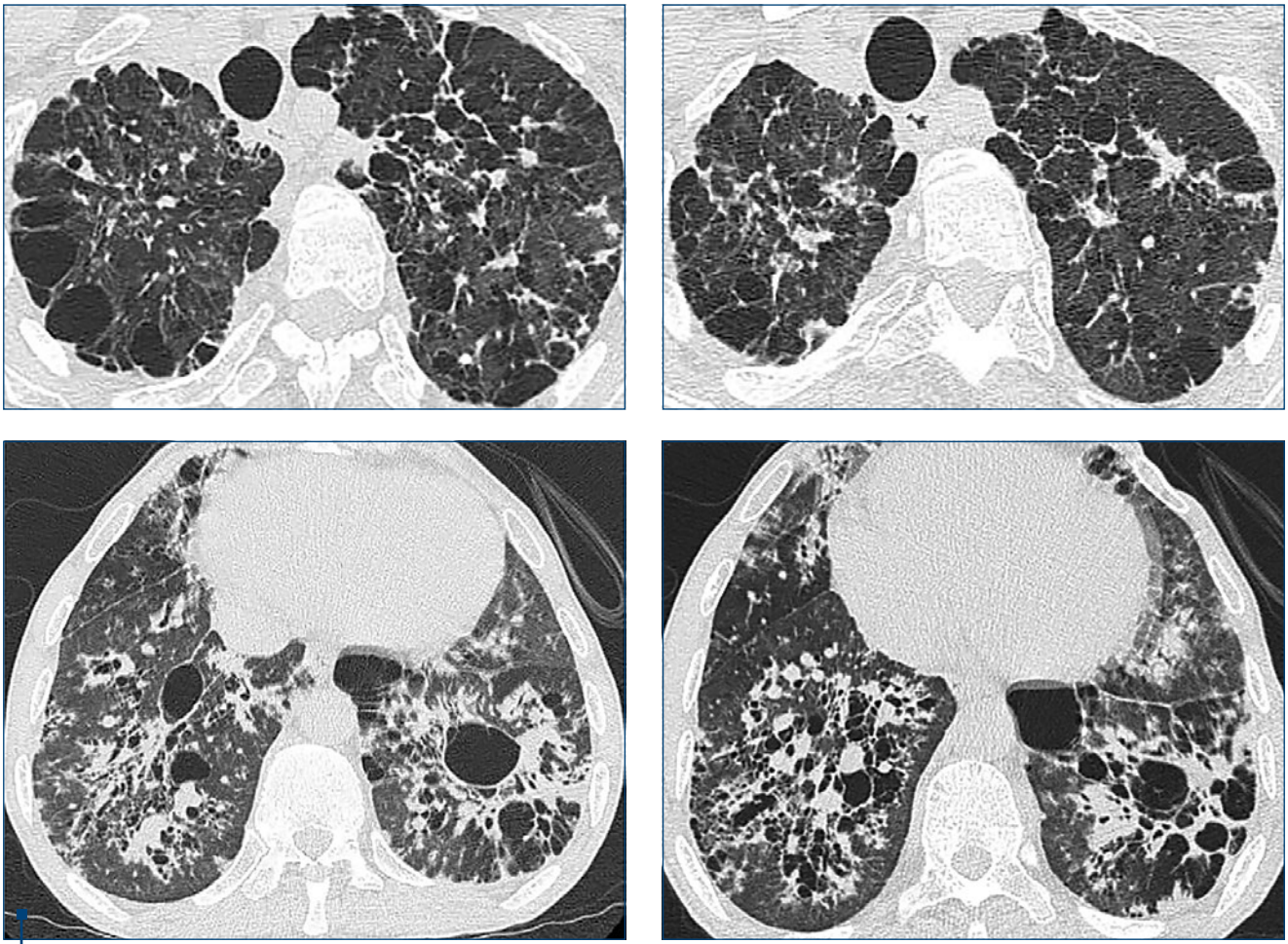

Figure 3 a, b, c, d. *CT scan: diffuse interstitial fibrosis, pulmonary cysts, bronchiectasis, and ground-glass opacities.*

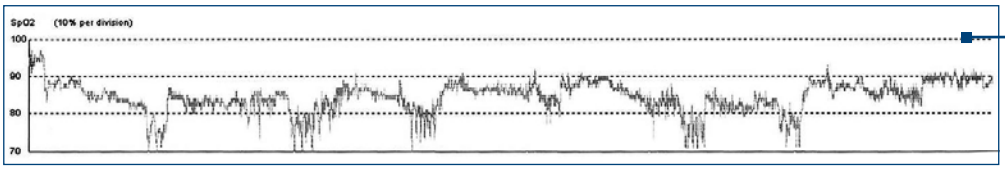

Figure 4: *Overnight pulse oximetry: persistent hypoxemia despite oxygen supplementation*

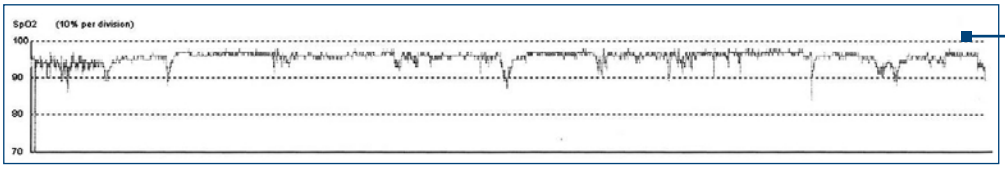

Figure 5. *Overnight pulse oximetry: hypoxemia improvement with NIV BiPAP 8/4 cm H_2O*

pulse oximetry with an oxygen supply flow at 4 liters per minute showed persistent hypoxemia throughout the night, with SaO_2 values almost exclusively below 90% (Figure 4, Table 2). Considering the severity of hypoxemia and the symptoms, it was decided on noninvasive ventilation, which had a significant positive effect on hypoxemia (Figure 5).

Consequently, the patient received the following diagnoses: interstitial pulmonary fibrosis, chronic global respiratory failure requiring oxygen therapy and noninvasive ventilation at home, bilateral bronchiectasis, Gaucher disease type I, extensive bilateral fibrocavitary sequelae post-tuberculosis, severe protein-calorie malnutrition, secondary thrombocytopenia, minor right bundle branch block. The recommendations at hospital discharge included triple therapy (tiotropium bromide 18 mcg/day in combination with budesonide/formoterol 320/9 mcg, 1 puff twice a day), oxygen therapy at home, 2-4 L/min, minimum 18 hours/day, and noninvasive ventilation with BiPAP 8/4 cm H_2O during the night and as needed, pneumococcal vaccine every 5 years and seasonal flu vaccination.

After this first assessment at our clinic, the patient had several more scheduled visits, as well as a few episodes of infectious exacerbation (only once was identified *Streptococcus pyogenes*). The initial evolution was favorable (after the initiation of noninvasive ventilation), with improved plethysmography and blood gas tests results (Table 1). Four years later, the patient had a severe exacerbation episode, presenting to the emergency room with a sudden worsening of dyspnea, tachypnea, marked hypoxemia (at admission SaO_2 74%, corrected with oxygen 4 L/min up to 87%), and hemoptysis. The patient was suspected to have pulmonary thromboembolism, which was not confirmed by emergency CT scan, the symptoms being attributed to an infectious non-tuberculosis exacerbation (based on negative sputum microscopy). However, an increased diameter of the pulmonary artery trunk and an intracavity mycetoma caused by aspergilloma were noted on CT (Figure 6). Subsequent echocardiography did not confirm the presence of pulmonary hypertension. After empirical antibiotic treatment, the evolution started to improve slowly. The patient continued the previously recommended treatment. Pulmonary rehabilitation program enrollment was suggested, but the patient (who lived in a rural environment) could not participate. In

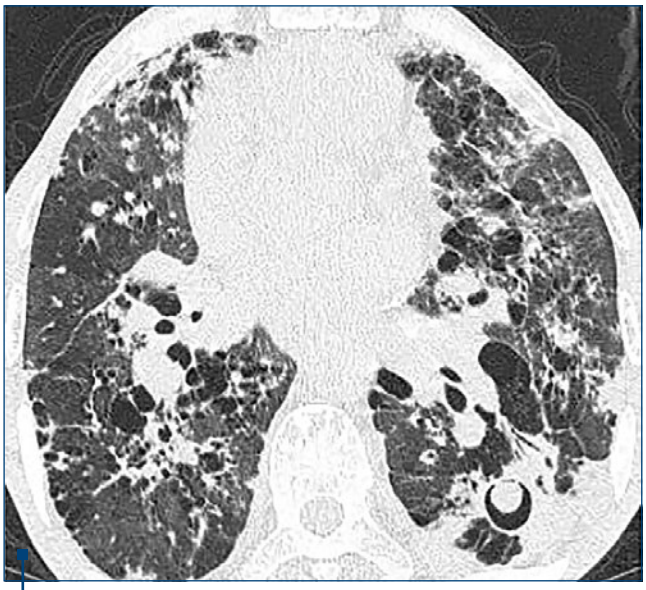

Figure 6. *CT scan: intracavity mycetoma caused by aspergilloma*

hospital, the patient received physical therapy whenever possible, and also recommendations regarding a home exercise program. Also, the patient personally requested an assessment of medical records for lung transplantation, but the answer from the transplantation clinic was negative because the transplantation surgery was deemed unfeasible due to a history of multiple episodes of tuberculosis, as well as the unfavorable nutritional status. Throughout the described period the patient received enzyme replacement therapy.

Six years after the first full pulmonary assessment, at the age of 47 years, the patient died at home, following massive hemoptysis.

Discussion

We presented the case of a patient with an extensive history of lung disease (and not only). The patient had six episodes of pulmonary tuberculosis (of which only two had been bacteriologically confirmed), and each time he received anti-tuberculosis treatment. We do not have records on the administration of anti-tuberculosis drugs, but considering the patient's consistency during the monitoring period, as well as the rigorously presented medical records, we believe that the patient was compliant and adherent to treatment. Looking back, and

knowing the diagnosis of Gaucher disease, we wonder if it is possible that glucocerebroside accumulation in lungs in childhood could have been interpreted as a tuberculosis recurrence (since the arguments for the diagnosis of the episodes at 4 and 6 years, respectively, were not convincing).

The pulmonary manifestations of Gaucher disease (GD) include interstitial, alveolar and perivascular infiltration of lipid-loaded macrophages. Lungs involvement begins early in childhood, sometimes with discrete symptoms (coughing, dyspnea on exertion), as an interstitial syndrome, which is visible on X-ray and presents as ground-glass opacities on CT, sometimes with interlobular septal thickening. With adequate coloring, bronchoalveolar lavage performed during bronchoscopy may reveal lipid-loaded macrophages[1]. It is estimated that less than 5% of GD patients have pulmonary involvement[2], and the literature is usually limited to case presentations. Certain genotypes (homozygous L444P) predispose to pulmonary involvement in GD patients[3]. The patient had genetic testing, but unfortunately, the results were not available to us. The well-known pulmonary complications in patients with GD who don't receive enzyme replacement therapy are pulmonary arterial hypertension and hepatopulmonary syndrome. Splenectomy is essential for the evolution of the pulmonary vascular disease[4]. Our patient did not have a splenectomy. Pulmonary hypertension was suspected, but was not confirmed at ultrasound examination. On CT, the presence of intrapulmonary shunts was not confirmed (although this is not sufficient to exclude this diagnosis). We would like to mention that a possible specific feature of Gaucher disease, known since the '80s, is an increased level of serum angiotensin-converting enzyme[5]. Our patient had an increased ACE level, while bronchoalveolar lavage showed a normal number of cells, although with lymphocyte predominance. A decrease of ACE levels following a test treatment is not confirmatory for sarcoidosis, given the nonspecific anti-inflammatory action of corticosteroids. Thus, it may be possible that these manifestations labeled as sarcoidosis could have been related to Gaucher disease.

The evolution of disease after enzyme replacement therapy can vary; usually, hypersplenism, hematology values, and organomegaly improve following treatment, while pulmonary symptoms respond variably[6], sometimes without noticeable improvement. Transplantation is possible, but not commonly performed. Cases with no disease recurrence after transplantation were previously reported[7].

On the other hand, pulmonary sequelae following six episodes of tuberculosis are normal. Most of the times, the extended post-tuberculosis sequelae symptoms are mixed ventilatory dysfunction, sometimes in association with severe hypoxemia[8]. It is, however, peculiar that X-ray changes in our patient were more pronounced basally, not apically, as could be expected with post-tuberculosis sequelae. Thus, the severe changes could be explained by two completely different causes (a very common infectious disease – tuberculosis, and a very rare pulmonary disorder associated with a systemic disease, which is also rare). Possibly, the diagnosis could have been established based on bronchoscopy with bronchoalveolar lavage, but considering the patient's severe functional status, we decided that the benefits of this test did not exceed the risks (fatal in this case).

Regardless of the cause, treatment (chiefly palliative) of both hypoxemic and hypercapnic severe respiratory failure with noninvasive ventilation (NIV) has proved beneficial. For that reason, in case of post-tuberculosis sequelae, NIV can be used both in exacerbations[9], as well as chronically[10]. In our opinion, the fact that a patient with such severe impairment survived for 6 years, having a relatively decent life, is an important achievement. A remarkable feature is the absence of pulmonary hypertension (on echocardiography) on the background of a severe prolonged hypoxemia. However, we do not exclude the possibility of ultrasound examination difficulties, considering the considerably narrowed intercostal spaces.

The cause of death is probably hemoptysis associated with an intracavity *Aspergillus*-related mycetoma. Even if it were not for a mycetoma, given the significant structural changes, we cannot exclude the possible presence of intrapulmonary shunts that could rupture.

Conclusions

We believe that this case is worth presenting, due to its distinctive characteristics: a rare disease, with comorbidities and possible pulmonary involvement, with multiple episodes of tuberculosis, difficult evolution leading to severe respiratory failure, and relatively favorable evolution with palliative NIV. ■

References

1. Gülhan B, Ozçelik U, Gürakan F, et al. Different features of lung involvement in Niemann-Pick disease and Gaucher disease. Respir Med 2012; 106(9):1278–85.
2. Miller A, Brown LK, Pastores GM, et al. Pulmonary involvement in type 1 Gaucher disease: functional and exercise findings in patients with and without clinical interstitial lung disease. Clin Genet 2003; 63(5):368–76.
3. Santamaria F, Parenti G, Guidi G, et al. Pulmonary Manifestations of Gaucher Disease. Am J Respir Crit Care Med 1998; 157(3):985–9.
4. Lo SM, Liu J, Chen F, et al. Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. J Inherit Metab Dis 2011; 34(3):643–50.
5. Lieberman J, Beutler E. Elevation of Serum Angiotensin-Converting Enzyme in Gaucher's Disease. N Engl J Med 1976; 294(26):1442–4.
6. Goitein O, Elstein D, Abrahamov A, et al. Lung involvement and enzyme replacement therapy in Gaucher's disease. QJM 2001; 94(8):407–15.
7. Rao AR, Parakininkas D, Hintermeyer M, et al. Bilateral lung transplant in Gauchers type-1 disease. Pediatr Transplant. 2005; 9(2):239–43
8. Ramos LMM, Sulmonett N, Ferreira CS, Henriques JF, Miranda SS de. Functional profile of patients with tuberculosis sequelae in a university hospital. J Bras Pneumol; 2006; 32(1):43–7.
9. Aso H, Kondoh Y, Taniguchi H, et al. Noninvasive Ventilation in Patients with Acute Exacerbation of Pulmonary Tuberculosis Sequelae. Intern Med 2010; 49(19):2077–83.
10. Esquinas AM, Egbert Pravinkumar S, Scala R, et al. Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. Eur Respir Rev 2014; 23(134):427–38.