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Case report

Pleural tuberculosis in a patient with untreated type 1 Gaucher disease

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ABSTRACT

Gaucher disease (GD) is an autosomal recessive glycolipid storage disorder, due to deficiency of the lysosomal enzyme glucocerebrosidase, leading to accumulation of the substrate glucocerebroside in the cells of the macrophage-monocyte system. Patients with GD have alteration in their immune system and impaired microbicidal capacity of mononuclear phagocytes. It has also been demonstrated that monocyte dysfunction may correlate with the plasma glucocerebrosidase concentrations. Tuberculosis (TB) is a major public health problem in developing countries. Pleural TB is one of the most common forms of extra-pulmonary TB. Since immune system can be impaired due to the deficiency of glucocerebrosidase in various ways, TB can be observed in patients with GD especially when left untreated. Cytopenia(s) is also general finding in untreated Gaucher patients, and they may be observed most frequently due to the infiltration of the bone marrow with Gaucher cells together with the additional factor of splenomegaly. We herein present a case of an adult patient with heterozygous untreated GD1, who developed pleural TB complicated by ipsilateral pulmonary fibrosis. Before his admission to our clinic, pleurectomy operation was performed and 4-drug combination anti-TB therapy was initiated including isoniazid, rifampicin, ethambutol and pyrazinamide. Fever complaint was disappeared with anti-TB treatment but he also had fatigue and pain. After initiation of enzyme replacement therapy in addition to anti-TB treatment, clinical and hematological improvement was observed. To our knowledge, this is the first reported case of GD1 with pleural TB.

1. Introduction

Gaucher disease (GD) is an autosomal recessive glycolipid storage disorder, due to deficiency of the lysosomal enzyme glucocerebrosidase, leading to accumulation of the substrate glucocerebroside in the cells of the macrophage-monocyte system [1]. GD has been distinguished into 3 clinical forms, based on the absence (type 1) or presence (types 2 and 3) of neurologic involvement. Type 1 GD (GD1), is also known as chronic non-neuropathic and late onset form [1]. Patients with GD have alteration in their immune system due to the (1) abnormalities in macrophage function, (2) hypersplenism leading to lymphopenia and neutropenia, (3) abnormalities in humoral immunity, (4) impaired superoxide production by the monocytes, or (5) impaired response to some mitogens [2–7]. It has also been demonstrated that monocyte dysfunction may correlate with the plasma glucocerebrosidase concentrations [2]. For these reasons untreated GD patients may have a predisposition to bacterial infections [2–7]. Tuberculosis (TB) is a major public health problem in developing countries. Pleural TB is one of the most common forms of extra-pulmonary TB [8]. Macrophages and T-cells have a direct impact on the control of TB infection. CD4+ T-cells produce interferon (IFN)-γ, which can activate macrophages. Activated marcophages can inhibit or kill organisms through two paths, the major path is the activated marcophages producing nitric oxide and related reactive nitrogen intermediates (RNIs), and the other

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antimycobacterial activity of macrophages is the fusion of the lysosome with a phagosome-containing ingested bacteria [9,10]. Since immune system can be impaired due to the deficiency of glucocerebrosidase in various ways, TB can be observed in patients with GD especially when left untreated. Cytopenia(s) is also general finding in untreated Gaucher patients, and they may be observed most frequently due to the infiltration of the bone marrow with Gaucher cells together with the additional factor of splenomegaly [11,12].

We herein present a case of an adult patient with heterozygous untreated GD1, who developed pleural TB complicated by ipsilateral pulmonary fibrosis. To our knowledge, this is the first reported case of GD1 with pleural TB.

2. Case report

A 35-year-old man was admitted to our outpatient clinic with fatigue and left upper quadrant abdominal pain in October 2013. He also had a fever of 38.5 °C, dyspnea, hacking cough and right chest pain for the past 20 days. He lost 4 kgs within the past 6 months. The patient had GD1 which was diagnosed 5 years ago while examined at the age of 30 due to organomegaly and thrombocytopenia of 74 $\times$ 10^9/L. The glucosylceramidase activity was found to be low (1.52 nmol/h/mg protein, range; 9.4 $\pm$ 3.2 nmol/h/mg protein) in leukocytes and heterozygous mutation of N370S in the GBA1 gene was present. He had refused enzyme replacement therapy (ERT). In his medical history, he had pulmonary TB in 1998 for which he received 6 months of anti-TB treatment. His elderly brother had also pulmonary TB, and his parents were consanguineous, and his other brother and two sisters were also diagnosed as GD.

In the medical history, he had pulmonary infection, pneumothorax and recurrent pleural effusion for the past 6 months (Fig. 1). The blood cultures, and pleural fluid examinations, which were performed while the fever persisted, revealed no infectious pathogens. Due to his recurrent pulmonary infection and right-sided pleural effusion, he had received various antibiotics and tube thoracostomy. Since the pulmonary complications did not recover, a right-sided thoracotomy, decortication and pleurectomy operation was performed. The pathological examination of pleura biopsy revealed multi focal caseous necrosis surrounded by palisading epitheloid histiocytes and langhans giant cells, non-necrotising and necrotizing granulomas, and fibrosis in the adjacent alveolus were also present (Fig. 2). Acid fast bacteria was not determined by EZN stain, and Mantoux tuberculin skin test remained anergic after 48 and 72 h of placement. Despite a negative pleural fluid culture for M. tuberculosis, pleural TB was diagnosed 20 days prior to his admission and 4-drug combination anti-TB therapy was initiated including isoniazid (H) 300 mg/day, rifampicin (R) 600 mg/day, ethambutol (E) 1500 mg/day and pyrazinamide (Z) 1500 mg/day (HRZE) in September 2013.

On admission, the patient was cachectic and pale, and in physical examination breath sounds were diminished especially at the bases of right lung. There were no peripheral enlarged lymph nodes, and liver was palpated 10 cm below the right costal margin with a massive splenomegaly, which was palpated in left inguinal region. His vital signs and fever were within normal limits.

Complete blood count revealed pancytopenia, and the leukocyte count was 2.5 $\times$ 10^9/L (neutrophil count was 1.2 $\times$ 10^9/L), hemoglobin level was 11.8 g/dL, and the platelet count was 107 $\times$ 10^9/L. In peripheral blood smear, there were 54% segmented neutrophils, 2% eosinophils, 34% lymphocytes and 10% monocytes in the differential leukocyte count, the erythrocytes were normocytic and normochromic, and platelets were around 80–100 $\times$ 10^9/L. The erythrocyte sedimentation rate was 50 mm/h, and C-reactive protein (CRP) 13.4 mg/dL (range, 0–5 mg/dL). Serum total protein and albumin levels were 8.13 g/dL and 3.5 g/dL, respectively. There was a polyclonal gammopathy in the serum protein electrophoresis (Immunoglobulin (Ig)A: 566 mg/dL, IgG: 2500 mg/dL, IgM: 524 mg/dL). Liver function tests, and blood urea nitrogen and creatinine levels were within the normal range. Serum iron, total iron binding capacity, and ferritin levels were 54 μg/dL, 214 μg/dL, and 1266 ng/mL, respectively. Serum vitamin B12, folic acid and thyroid stimulating hormone levels were within the normal limits. Serum lactate dehydrogenase was slightly elevated (380 U/L), but haptoglobin and indirect bilirubin levels and reticulocyte count were normal. Direct and indirect Coombs tests were negative. Viral serology including hepatitis B&C with human immunodeficiency virus were

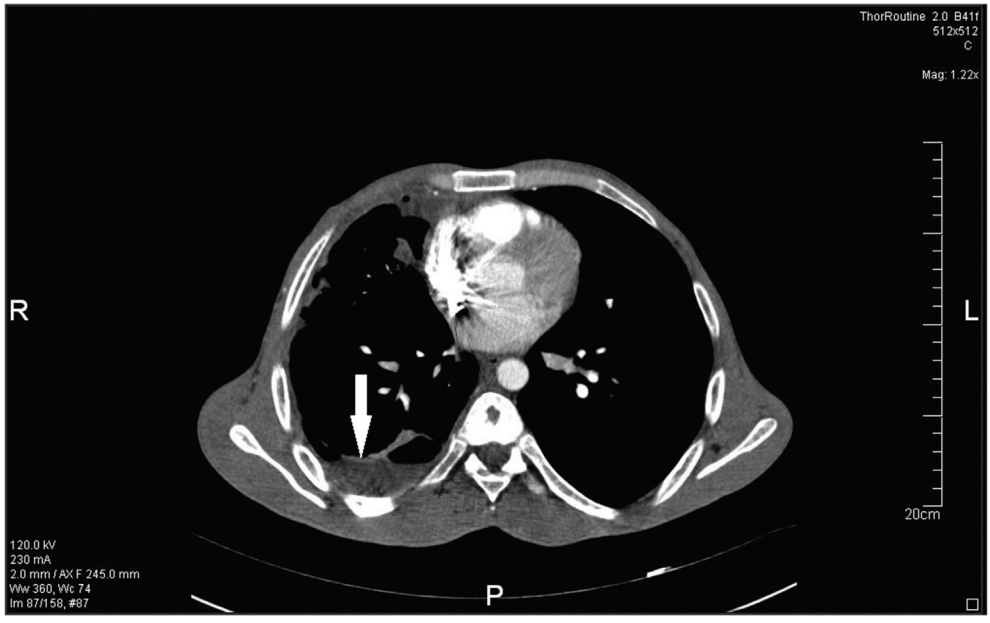

Fig. 1. Right-sided pleural effusion in thorax CT (white arrow).