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CASE REPORT

Severe pulmonary involvement with cor pulmonale; the initial presenting feature of non-neuronopathic form of Gaucher's disease

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Abstract:
Although pulmonary involvement is a known entity in Gaucher's disease. It varies in severity from asymptomatic with only subtle radiological abnormality or abnormal finding on pulmonary function testing to severe form of interstitial lung disease with cor pulmonale. Most of severe forms of pulmonary involvement are noted in neuronopathic forms of disease and also it is rarely noted as first presentation of the disease. We report here an eight year and seven months old girl of non-neuronopathic form of gaucher's disease who intially presented with severe pulmonary involvement in form of interstitial lung disease and severe pulmonary hypertension resulting in cor pulmonale as a first presentation of disease.

Keywords: *Cor pulmonale, Non-neuronopathic, Gaucher's disease*
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Introduction

With an overall incidence of approximately 1 in 50,000 to 1 in 1,00,000 live births, Gaucher′s disease is the most prevalent lysosomal storage disorder [1,2]. An autosomal recessive disorder, Gaucher′s disease is caused by mutations in the glucocerebrosidase gene, leading to decreased enzyme activity and accumulation of glucocerebrosides within the reticuloendothelial system [1]. Three clinical forms of the disease are known--- type I non –neuronopathic form with onset in late childhood or adolescent with relatively milder course, type II is infantile form, and the type III with juvenile onset. The pulmonary involvement has been widely reported in Gaucher′s disease . It varies in severity from milder course with subtle abnormalities detected on chest radiograph or pulmonary function testing to severe form of interstitial lung disease. Cor pulmonale is a rare presentation, although reported with neuronopathic form, unlikely to occur with milder course running non-neuronopathic forms and that also as a first presentation of disease. We report a case of eight year and seven months old girl of Gaucher's disease who presented with severe pulmonary involvement in form of interstitial lung disease and pulmonary hypertension resulting in cor pulmonale as initial presentation of disease.

Case report

8.7-year-old female child presented with progressively increasing respiratory distress for the last 1 year. There was history of mild cough, but no expectoration, with no history of cyanosis, fever, noising breathing . The child′s milestones were normal for age. The girl was born out of a non-consanguineous marriage, with all the other siblings reportedly normal. Child′s weight and

height were both below the 3th percentile for his age. Pallor, engorged, and pulsatile neck veins and central cyanosis, grade 2 clubbing were present on general physical examination. Abdominal examination revealed a firm, non-tender liver having a sharp margin, and measuring 5 cm below costal margin with a span of 11 cm. The spleen measured 9 cm below costal margin along the splenic axis, with a firm consistency, and was non-tender. On respiratory system examination, fine crepitation were found to be present over the middle and lower zones of both the lungs. On cardiovascular system examination, there was loud pulmonic component of second heart sound along with a pansystolic murmur suggestive of tricuspid regurgitation at a left lower parasternal area.

Complete blood counts revealed anemia (Hb 7.9 g/dl)), leucocytopenia (total leucocyte count ranging from 1900-3600/dl), thrombocytopenia (platelet count 96000/dl). The liver enzyme levels were within normal range (serum bilirubin 1.1 mg/dl, SGOT 19 U/l, SGPT 22 U/l) with normal prothrombin and activated partial thromboplastin time (PT: control 10.7 s, test 10.1. s; aPTT: control 27.3 s, test 26.6 s). Electrolytes and renal function tests were within a normal range. Arterial blood gas analysis showed hypoxemia (pO 2 – 45.5 mmHg). Chest radiograph showed cardiomegaly (CT ratio 70%) with lung fields having pattern suggestive of interstitial lung disease (Figure 1).

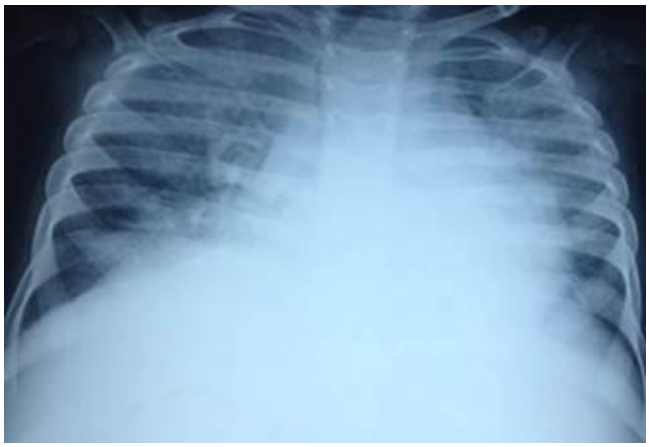

Figure 1. Cardiomegaly and features of interstitial lung disease

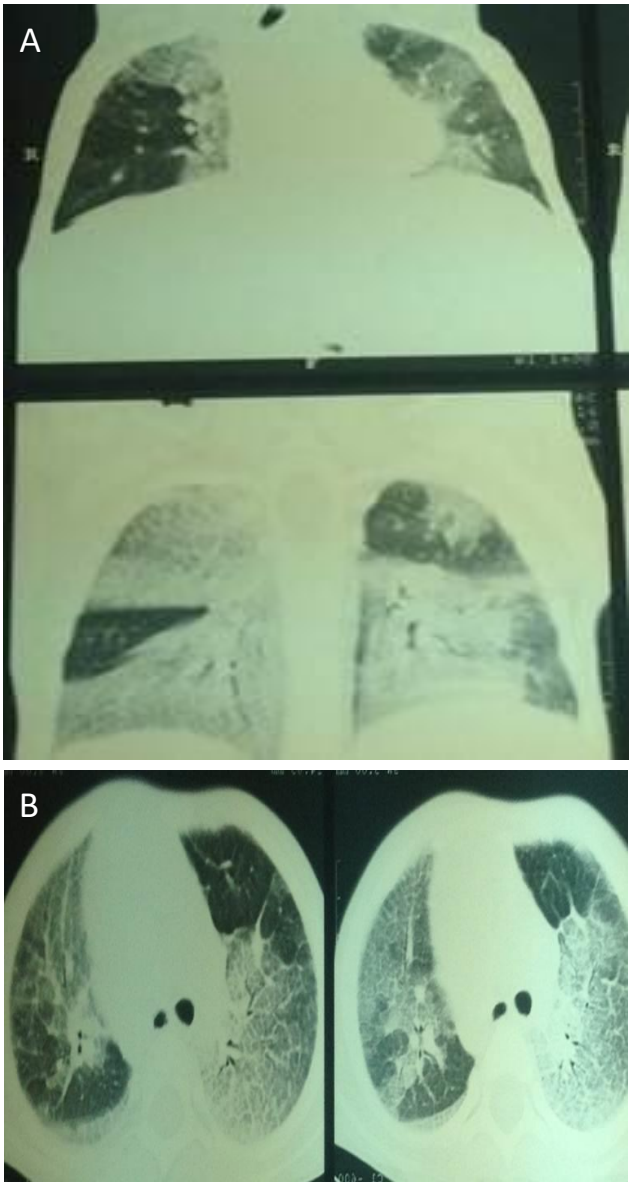

Figure 2A and B. CT scan chest showing features of interstitial lung disease

The tubercular work-up and retrovirus serology were negative. The patient underwent lung function testing and showed abnormalities consistent with interstitial lung disease (ventilatory limitation, excessive ventilation and increased dead space) as well as decreased VO2 max. The high resolution CT scan showed diffuse bilateral ground glass opacities with interlobular septal thickening (figure 2a and b). Diffuse thickening of central peribronchial vascular interstitium was present, these findings reflecting the presence of interstitial and air-space disease,

typical of interstitial lung disease. On electrocardiogram, there was right axis deviation, p-pulmonale, features of right ventricular hypertrophy. Echocardiogram showed dilated right atrium and right ventricle, severe pulmonary arterial hypertension, severe tricuspid regurgitation, and moderate pulmonary regurgitation with right ventricular systolic pressure measuring around 82 mmHg. Inter-atrial and interventricular septum was found to be bulging toward the left with paradoxical movement. Abdominal ultra-sonography revealed homogenous hepato-splenomegaly. So, in the presence of hepato-splenomegaly, cardiomegaly with murmurs suggestive of tricuspid regurgitation and presence of crepitation in chest, we have thought the possibility of storage disorder with interstitial lung disease in mind to proceed for further investigation. Bone marrow aspiration study revealed the presence of few large cells with abundant foamy cytoplasm and small round nucleus. Occasional histiocytes revealed crumpled paper like apperence of cytoplasm suggestive of Gaucher's disease. An enzyme study showed very low levels of enzyme Glucocerebrosidase (<10% of the normal level) which confirmed the diagnosis of Gaucher′s disease. The Genetic study was planned for this patient, it couldn′t be done due to non-availability. Enzyme replacement therapy planned is planned for the patient.

Discussion

Pulmonary involvement in Gaucher′s disease has been widely discussed, and reported in about one

third of the patients [3]. The medical literature, though, supports the occurrence of cor pulmonale in Gaucher′s disease; reports on such involvement are very scarce and mainly in juvenile age groups [4,5]. In our case, echocardiogram findings gave conclusive evidence of the presence of cor-pulmonale in the child. As severe pulmonary involvement is reported mainly in type II and type III Gaucher′s disease, these forms are at more risk of developing cor pulmonale. Such severe presentation is rarely noted in non- neuronopathic form of the disease which usually runs a benign course. Cor pulmonale has been reported in an already diagnosed case of gaucher's disease which later on developed interstitial lung disease. It has never been reported as initial presentation of the disease. To my best of knowledge, this has been the first case of this disease initially presented with first time as severe pulmonary involvement resulting in cor-pulmonale.

Several patho-physiological mechanisms can contribute to the occurrence of cor pulmonale in Gaucher′s disease-firstly, the infiltration of Gaucher cells in the lung interstitium and alveolar spaces leads to hypoxemia and loss of alveolo-capillary bed, thus, leading to pulmonary vasoconstriction [6]. Secondly, the plugging of the pulmonary capillary vessels by the Gaucher cells leads to pulmonary hypertension [7,8,9]. One more mechanism has been postulated for the pulmonary hypertension in Gaucher′s disease i.e. increased levels of angiotensin II [4,8]. Although the precise Pathophysiology is not known, Gaucher cells are found to be rich in angiotensin converting enzyme [5]. The above mechanisms lead to an increased pulmonary vascular resistance, which, in turn, leads to an increase in after load of the right ventricle, eventually leading to the hypertrophy of the right ventricle and later cor pulmonale.

Although the improvement in the pulmonary function tests in patients of Gaucher′s disease has been modest with the institution of the enzyme replacement therapy, [1,4] the development of cor pulmonale confers a poor prognosis on such patients as once cor pulmonale sets in the efficacy of enzyme therapy is doubtful [4]. However BEUTLER et al. [10] and PELINI et al. [11] reported that pulmonary disease was improved, as documented by amelioration in oxygenation and diffusion capacity, in patients with type I Gaucher's disease with severe pulmonary involvement (two of whom had been on continuous nasal oxygen therapy because of severe dyspnoea), upon initiation of enzyme replacement therapy.

So, we suggest that in a case of Gaucher′s disease, a detailed evaluation of pulmonary vascular

disease should be made as soon as possible, even in the absence of clinical signs and symptoms. It should primarily include imaging studies of the lungs, pulmonary function tests, and electrocardiogram and echocardiogram to evaluate pulmonary hypertension.

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