

## PEDIATRIC PULMONARY GAUCHER DISEASE: TWO PATTERNS OF LUNG INVOLVEMENT

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Gaucher disease is the most prevalent lysosomal storage disease. It is due to glucocerebrosidase deficiency with secondary visceral enlargement.<sup>1</sup> Bone marrow transplantation (BMT) was advocated as a successful treatment in the 1980s. However, the morbidity associated with BMT would seem to limit the use of this approach. Enzyme replacement by Ceredase (alglucerase injection), which catalyzes the hydrolysis of glucocerebrosidase to glucose and ceramide, could help to halt the disease process.

Pulmonary involvement in Gaucher disease is due to Gaucher cells infiltrating lung parenchyma, however, other causative agents such as infections must be excluded. Most reports on pediatric pulmonary Gaucher disease are based on radiological or post-mortem examination.<sup>2</sup> Here we present two cases of pediatric pulmonary Gaucher disease type I, with two different lung pathologies confirmed on open lung biopsy.

### Case 1

An eight-year-old male who was born at term, and was a product of a consanguineous marriage, was well until seven months of age, when he started to have diarrhea. He was diagnosed at the time at a local hospital to have *Shigella* dysentery. At nine months of age, he started to have progressive abdominal distension, weakness and weight loss. Bone marrow aspirate was suggestive of Gaucher disease. At twelve months of age he became oxygen-dependent. At twenty months, he developed hypersplenism and needed repeated blood transfusion. Splenectomy was performed and his anemia improved. A sibling of the patient died at two years of age with a similar disease.

Our eight-year-old patient presented at our hospital at

the age of two, with hepatomegaly and chest infection which responded to IV antibiotics. No HLA matching was found after typing his five siblings.  $\beta$ -glucosidase activity on cultured fibroblasts was 4.7% of control. At three years of age, he presented with bilateral lung infiltrates (Figure 1). Open lung biopsy showed Gaucher cells filling the alveolar spaces (Figure 2). These cells had centrally or eccentrically located nuclei. The cytoplasm was slightly eosinophilic with a characteristic fibrillary striated pattern. Ultrastructural examination showed numerous intracytoplasmic lysosomes containing tubular structures (Figure 3). The patient was started on Ceredase 100 U/kg/dose weekly for one month, then 60 U/kg/dose every two weeks. He showed clinical improvement with progressive weight gain, and was weaned off oxygen after six months. His liver size regressed from the right iliac fossa at presentation to 4 cm below costal margin. Liver enzymes became normal and his hemoglobin and platelet normalized. The bilateral lung infiltrates eventually cleared on x-ray. At five years of age he developed seizure, which was controlled with phenobarbital and Tegretol therapy. Due to lack of supply, the Ceredase treatment was

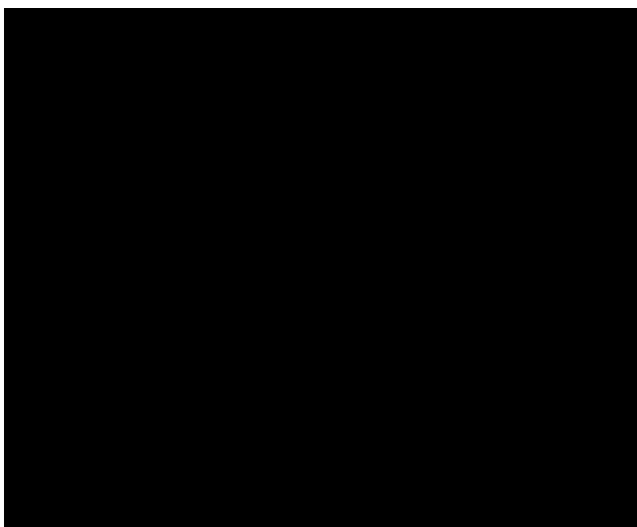


FIGURE 1. Chest x-ray, Case 1. Bilateral diffuse, interstitial and alveolar infiltrate.

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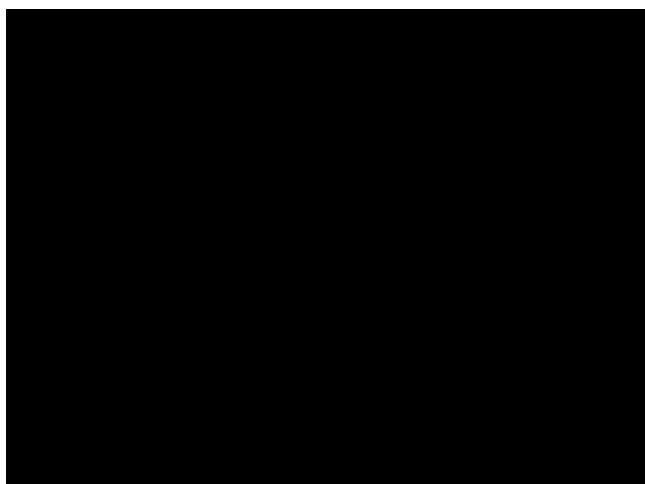


FIGURE 2. Case 1. Gaucher disease filling the alveolar spaces (H&E, 250x).

stopped, and two months later, the patient deteriorated with progressive hepatomegaly, poor feeding, and recurrence of bilateral lung infiltrates, and he subsequently became oxygen dependent. Later, Ceredase became available, and the patient markedly improved on therapy. He was weaned off oxygen, his appetite improved and he started to gain weight. Psychomotor evaluation at six years of age showed that he has normal cognitive abilities and normal motor skills. Bone changes persisted during the three-year follow-up period.

### Case 2

A three-year-old female presented at six months of age with gastroenteritis and abdominal distension. One month later, she was diagnosed as having Gaucher disease, as confirmed by BMA. She has a six-year-old brother with the same disease, but living a normal life after a successful allogenic BMT. A younger sister died at two years of age with the same disease. Our three-year-old patient presented at eighteen months of age with hepatosplenomegaly and vomiting. Her height and weight were both below 5%. At twenty months, she started to have daily epistaxis and fever. The  $\beta$ -glucosidase activity from cultured fibroblast was 3.07% of control. At two years of age, splenectomy was performed because of hypersplenism. Histological examination of the spleen showed involvement by Gaucher cells. Her CT scan of the chest showed enlarged paratracheal, carinal and subclavian lymph nodes with multiple small nodular opacities in the right upper and lower lobes. Ceredase was not available at that time, and it was decided to proceed for BMT once it became available. At three years of age the patient had BMT from a matching sibling. On the fourth postoperative day, she developed disseminated intravascular coagulation and

hypoxemia which necessitated ventilation. She also suffered from epistaxis and gastrointestinal bleeding. Chest x-ray showed scattered atelectasis and cardiomegaly. Echocardiogram showed mild pulmonary hypertension. Open lung biopsy showed occasional Gaucher cells in the interstitium, associated with fibrosis, with evidence of moderate pulmonary hypertension (Figure 4). The patient died on the 47th postoperative day.

### Discussion

Reports on pulmonary involvement with Gaucher disease are scarce, and suggest an unfavorable prognosis. Three distinct patterns of pulmonary involvement in patients with type I Gaucher disease have been described.<sup>2</sup> The first is the interstitial infiltration of Gaucher cells in the perivascular, peribronchial and septal region with fibrosis. The other pattern includes capillary plugging with Gaucher cells that occlude small capillaries and cause pulmonary hypertension.<sup>2,3</sup> The third form consists of alveolar consolidation with Gaucher cells filling air spaces which mimic "golden pneumonia." In the second pattern, chest radiograph tends to be normal and death is usually secondary to pulmonary hypertension with severe hypoxemia and cor pulmonale.<sup>3-5</sup>

To our knowledge this pattern has not been described in pediatric patients before, and our report (Case 2) is the first to describe it in a child on open lung biopsy. Both right to left shunting and a reduced pulmonary capillary volume have been postulated as the cause of the hypoxemia.<sup>2,4,6</sup> Several authors have postulated a circulating chemical or humoral substance that damages the pulmonary vasculature.<sup>2,4,6</sup> Angiotensin II has been shown to induce pulmonary hypertension in animal models, and Gaucher cells contain large amounts of angiotensin-converting enzyme.<sup>3</sup> The levels of this enzyme decrease with enzymatic replacement.<sup>6</sup> Pelini et al.<sup>7</sup> described a 42-year-old woman with type I Gaucher disease with pulmonary involvement and oxygen dependency with severe exercise limitation, normal chest radiograph and severe hypoxemia. After six months of treatment with Ceredase, she improved substantially, and was weaned completely from oxygen. Pastores et al.<sup>11</sup> described a 10-year-old pediatric patient with Gaucher disease type I who had lung involvement which persisted after twelve months of treatment with Ceredase at 60 U/kg every two weeks. Carson et al.<sup>12</sup> described a one-year-old girl with type I Gaucher disease with lung involvement who was treated with Ceredase but showed no improvement after a one year of treatment with 800 U/week. Fallet et al.<sup>10</sup> described a 15-month-old male with lung involvement at five years of age, who was treated with Ceredase 60 U/kg every two weeks and showed clinical improvement, but died of fatal idiopathic subarachnoid hemorrhage. We report a case with severe

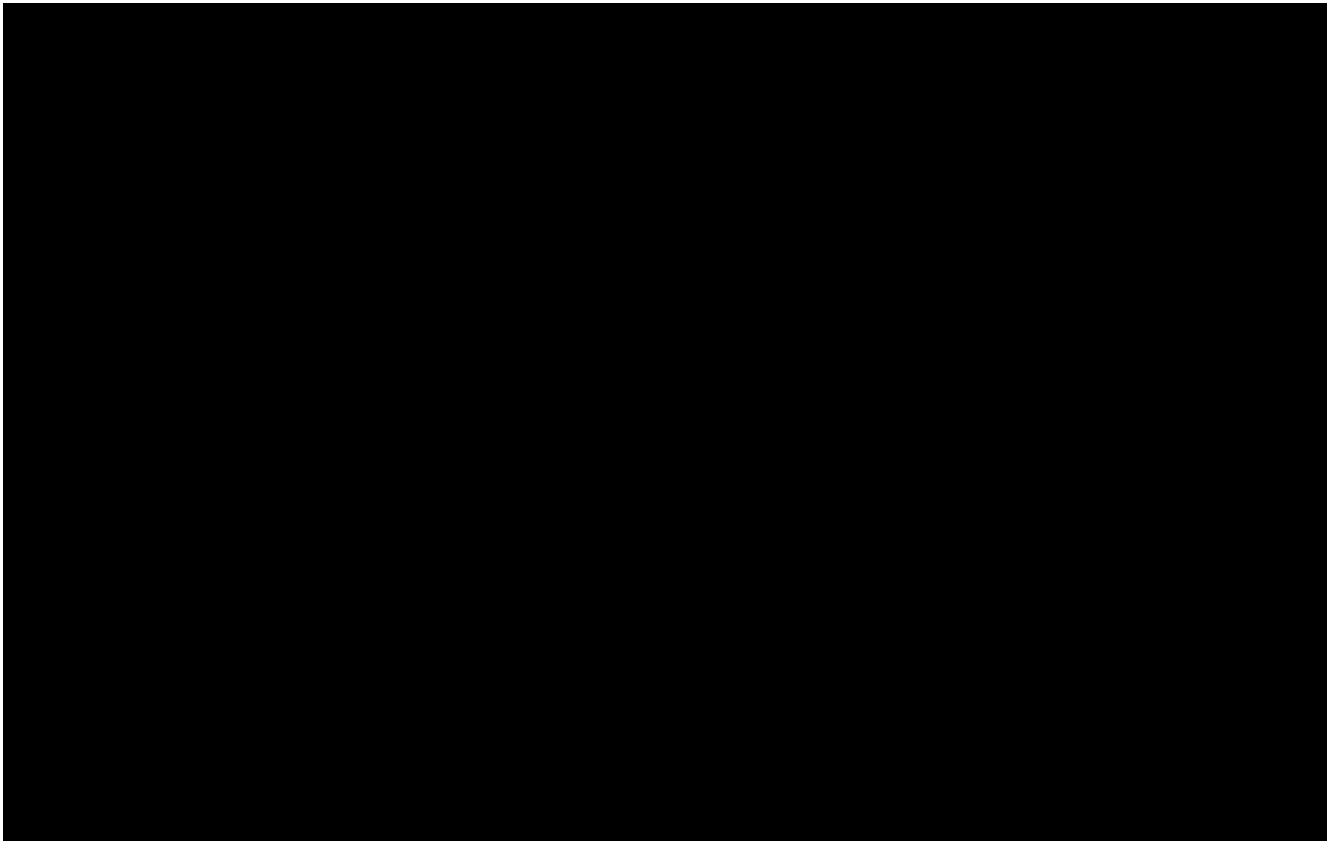


FIGURE 3. Ultrastructure of Gaucher cell in Case 1 shows numerous lysosomes in the cytoplasm (left). Higher magnification demonstrates the tubular structure of the storage material within the lysosomes (right).

pulmonary Gaucher disease with dramatic improvement on glucocerebrosidase therapy with resolution of massive chest involvement and recurrence of all symptoms once Ceredase was stopped for two months. His illness resolved upon resumption of Ceredase. Enzyme therapy was not administered for the second case while a matched bone marrow donor was awaited. Unfortunately, the patient was transplanted at a delayed stage, when her illness had progressed, possibly causing pulmonary hypertension with severe hypoxemia. Despite minimal pathology shown on open lung biopsy, pulmonary hypertension could be explained on the basis of the increased release of angiotensin II enzyme from Gaucher cells. In comparing both cases, the patient who had apparent radiological changes had a favorable prognosis once Ceredase was begun, whereas the patient with minimal x-ray changes but who had pulmonary hypertension died, as treatment was not started early. This may lead us to the conclusion that radiological findings should not be underestimated in the presence of hypoxemia and pulmonary hypertension, and treatment with Ceredase should be started immediately to prevent a fatal outcome.

Studies of the hematologic and hepatic responses to

different Ceredase dosing schedules have yielded conflicting results.<sup>6-10</sup> At our center, seven out of eleven patients with Type I Gaucher disease have lung involvement. Of the four patients with pulmonary involvement who received enzyme replacement, only two responded (unpublished data). The cost was estimated to be \$382,000 US dollars for the first year for a 70-kg patient receiving 60 U/kg every two weeks.<sup>8</sup> Our patient needed a high dose initially at 100 U/kg/week for one month, then 60 U/kg every two weeks, which seemed to be adequate to arrest the progression of the disease. Low-dose high-frequency protocol (30 U/kg/month fractionated into three infusions/week each of 2.3 U/kg) would be an alternative regimen to reduce the cost of treatment to a third of the cost of the high-dose, low-frequency protocol.<sup>6,9</sup> The former regimen was not applied to Case 1, as he lived a long distance from our hospital and careful management of his condition was not practical in his region. It should certainly be considered, however, when the application of home health care can help reduce the cost of treatment.

In summary, pulmonary involvement should be carefully evaluated in all patients with Gaucher disease. Enzyme therapy with Ceredase is beneficial in the

FIGURE 4. An interstitial blood vessel showing intimal thickening (EVG, 100x).

treatment of patients with pulmonary Gaucher disease until other modalities are available.

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