

Pulmonary hemorrhage in type 3 Gaucher disease: a case report

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Abstract A 2-year-old boy with type 3 Gaucher disease (GD) on treatment with enzyme replacement therapy (ERT) was found dead in bed having been apparently well the night before. At the time of diagnosis, he had significant respiratory symptoms (severe and persistent bouts of coughing) that had been attributed to Gaucher lung infiltration and that were controlled by inhaled and orally administered steroids. These symptoms had begun to reappear just prior to death. Postmortem revealed extensive pulmonary hemorrhage and intra-alveolar collections of Gaucher cells. There was very little evidence of GD elsewhere. Death was ascribed to pulmonary hemorrhage secondary to GD. The pathogenesis was unclear. To the best of our knowledge, this is the first case of isolated pulmonary hemorrhage secondary to GD and may represent a hitherto unrecognized complication of this condition. Given the apparent temporal relationship, we propose that it represented a severe, terminal event in the course of Gaucher lung disease.

Introduction

Gaucher disease (GD) is an autosomal recessively inherited liposomal storage disorder. It is characterized by deficient activity of the lysosomal enzyme β -glucosidase (OMIM #606463), resulting in accumulation of its substrate, glucosylceramide. This leads to multisystem disease in-

volving enlargement and dysfunction of the spleen and liver, destruction of bone, and pulmonary infiltration in severe cases. In some patients, there is also involvement of the central nervous system (CNS) (Beutler and Grabowski 2001). This has led to the traditional subtyping of GD into three groups:

1. GD-1: adult, nonneuronopathic (OMIM #230800), in which there is an absence of CNS involvement.
2. GD-2: acute infantile (OMIM #230900), in which there is a rapid relentless neurological progression leading to death, usually by 2 years of age.
3. GD-3: subacute neuronopathic (OMIM #231000), in which there is slower and more variable neurological progression.

Somatic disease is seen in all three types and tends to be particularly severe in GD-3. It can affect different organs, including the lungs. We report a patient with GD-3 who had particularly severe lung disease.

Case report

A 3-year-old boy was referred for examination with his identical twin brother. They were born by lower-segment Caesarean section at 36 weeks' gestation (the indication was possible twin-twin transfusion syndrome). The patient's birth weight was 2.3 kg. No immediate perinatal problems were reported. At the age of 3, he developed a chest infection. Routine examination revealed the presence of hepatosplenomegaly, and he was referred for further investigations. The leukocyte enzyme assay confirmed the diagnosis of GD. He had had recurrent chest problems consisting of a distressing, nonproductive cough unaccompanied by fever, which had been treated with frequent

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courses of antibiotics with little or no benefit. Developmentally, he had evidence of gross motor delay with delayed walking, was ataxic and falling frequently, and was trying to put a few words together. His parents are unrelated—the father being Egyptian Coptic and the mother Polish.

Initial examination revealed marked horizontal- and vertical-gaze palsy, resulting in ptosis. The other cranial nerves were intact. Tone and power appeared to be normal, and there was cerebellar ataxia. The liver was palpable 5 cm and the spleen 8 cm. There were no abnormal respiratory signs. Coagulation studies were abnormal; a diagnosis of mild von Willebrand disease was made. Molecular analysis of the *GBA* gene revealed compound heterozygosity for the following mutations: L444 P (c.1448 T > C, CTG > CCG, p.Leu483 Pro) and K198 T (c.710 A > C, AAG > ACG, p.Lys237 Thr). This is a previously unreported genotype. Clinical presentation was typical of GD-3. Treatment with imiglucerase (Cerezyme®) was commenced at 3.25 years at 120 U/kg/24 h according to the then existing guidelines for type 3 GD (Vellodi et al 2001). Given the underlying diagnosis, the respiratory symptoms suggested Gaucher lung disease. The chest X-ray revealed a bilateral coarse reticular pattern. He was therefore commenced on prophylactic inhaled steroids (budesonide 100 mcg b.d.) at the same time as enzyme replacement therapy (ERT) and responded well. The inhaled steroids were discontinued after 5 months. Soon after this, his symptoms gradually returned. He was recommenced on inhaled steroids but died soon afterward. Death was sudden and unexpected, occurring 4 days after the last infusion of enzyme. Consent for postmortem was obtained.

The twin brother of the deceased boy had a very similar pattern of respiratory involvement but slightly milder. He was also given inhaled steroids to which he responded well. The inhaled steroids were withdrawn after 5 months and his symptoms slowly returned, upon which the inhaled steroids were recommenced. He responded well and has since remained on inhaled steroids since with no recrudescence of the respiratory symptoms. Both twins had hepatosplenomegaly, which did not compromise their breathing and which responded well to ERT, and both also had mild anemia and thrombocytopenia; these, too, responded well to ERT.

Postmortem findings

Lungs showed interstitial and intra-alveolar edema. There was extensive intra-alveolar hemorrhage (Fig. 1) and mild thickening of the bronchial walls with lymphocytic infiltration with focal lymphoid aggregates. The mucosa showed mild subepithelial fibrosis. There were large collections of macrophages in the alveoli, with fine linear opacities in their cytoplasm—distending contiguous groups of them—in keeping with involvement by GD (Fig. 2). No

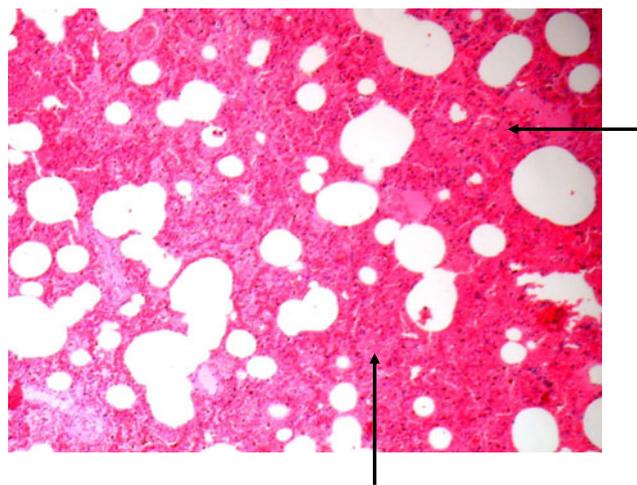


Fig. 1 Lung. Hematoxylin and eosin (H&E) stain showing extensive hemorrhage

Gaucher cells were seen in the interstitium or pulmonary capillaries. There was no hemosiderin deposition. The pulmonary vasculature was normal, and there was no evidence of interstitial lung disease.

Discussion

The lungs are probably more commonly involved in GD than is recognized (Amir and Ron 1999). Careful evaluation of lung function has revealed abnormalities in a significant percentage of patients (Kerem et al. 1996). Children are thought to be more commonly affected (Banjar 1998). Three types of clinical presentation have been described: interstitial pneumonia (Schneider et al. 1977), pulmonary arterial hypertension with or without cor

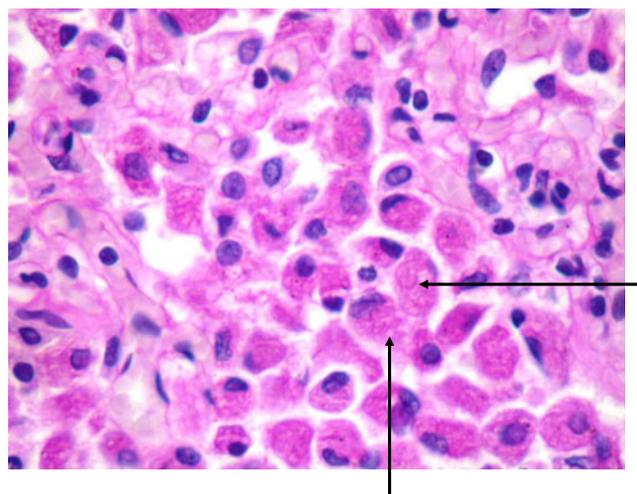


Fig. 2 Lung. Periodic acid-Schiff (PAS) stain showing sheets of PAS-positive vacuolated macrophages with “wrinkled-silk” cytoplasm typical of Gaucher cells

pulmonale (Mistry et al. 2002), and hepatopulmonary syndrome (Kim et al. 1999). Histological findings include intra-alveolar, interstitial, and periarterial collections of Gaucher cells in varying combinations (Lee 2007). However, overt lung disease is uncommon. Treatment with ERT has dramatically reduced morbidity and mortality in GD (Pastores 2010). However, some aspects of the disease remain relatively resistant to ERT, including skeletal (Poll et al. 2002) and lymph-node (Burrow et al. 2007) involvement. Pulmonary disease, too, responds only partially to ERT (Goitein et al. 2001). The reason for this remains unclear. The case presented here is unique for two reasons: first was the overwhelming number of Gaucher cells in the alveoli despite their scarcity elsewhere in a child on ERT, and second was the finding of pulmonary hemorrhage. As mentioned earlier, intra-alveolar Gaucher cells have been previously described but not in isolation. Their finding suggests that the alveoli are a “sanctuary” site. Pulmonary hemorrhage complicating GD has not been described before. It is unlikely that it was related to the mild von Willebrand disease in our patient. Hoffmann et al. (2006) described fatal gastrointestinal bleeding in a patient with neuronopathic GD. Although there was fatal bleeding, the case was different from ours in that there was a clear cause of bleeding (gastrointestinal ulcer). In our patient, the origin and etiology of the hemorrhage were unclear. Apart from its unique pathological features, this case emphasizes the importance of careful monitoring and aggressive management of Gaucher lung disease.

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