Type I Gaucher Disease Following Chemotherapy for Light Chain Multiple Myeloma

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Abstract

Although plasma cell disorders, such as hypergamma globulinemia and monoclonal gammopathy of undetermined significance (MGUS), are reported to occur at higher incidences in patients with Type I Gaucher disease (GD) than in the normal population, pure light chain multiple myeloma (LCMM) has never been described in this context. Our case is the first to highlight a patient with LCMM who developed clinically apparent GD only following chemotherapy and hematopoietic stem cell transplantation. Renal complications are also exceedingly rare in GD, but nephrotic syndrome is one of the presenting features in this patient. The findings from this case will have important screening and diagnostic implications for both clinicians and patients.

Key words: nephrotic, transplantation

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Introduction

Multiple myeloma (MM) is characterized by the proliferation of a single clone of plasma cells capable of producing monoclonal immunoglobulins. Interestingly, MM is reported to occur at higher incidences in patients with Type I Gaucher disease (GD) than in the normal population (1, 2). Type I GD is one of the most prevalent lysosomal storage diseases worldwide, and is especially common among Ashkenazi Jews, affecting 1 in ~800 individuals (3). It follows an autosomal recessive inheritance and is characterized by a deficiency in glucocerebrosidase (lysosomal enzyme) that leads to excessive accumulation of glucocerebroside (glycolipid substrate) in the macrophages of the reticuloendothelial system (4). Typical manifestations of this multi-system storage disease include hepatosplenomegaly, anemia, thrombocytopenia, skeletal complications, pulmonary involvement, and rarely parkinsonism (4).

The relative risk of MM in GD as compared with the general population is estimated to be 5.9% (2). The precise pathophysiology for this association remains unclear. However, chronic stimulation of the immune and inflammatory systems secondary to the body’s storage of glucocerebroside is proposed to play an important role (1, 5). Cases to date have described only heavy chain MM or monoclonal gammopathy of undetermined significance (MGUS) occurring in established GD patients, many of whom are already on enzyme replacement therapy (ERT) for their GD (6, 7).

In contrast to prior reports, the present case is the first to highlight a patient with pure light chain multiple myeloma (LCMM) who developed clinically apparent GD only after receiving high dose chemotherapy and autologous hematopoietic stem cell transplantation. The recurrence of nephrotic range proteinuria after the patient’s remission from LCMM is another distinguishing feature.

Case Report

A 57-year-old previously healthy Ashkenazi Jewish woman presented in early 2003 with progressive fatigue. Physical examination was unremarkable, but investigations...
Figure 1. Wright-Giemsa stain of bone marrow aspirate sample: Gaucher cells (center of view) are surrounded by plasma cells.

Figure 2. H and E (hematoxylin and eosin) stain of bone marrow biopsy sample: The presence of Gaucher cells (center of view) is noted in addition to an increased number of plasma cells.

revealed anemia (hemoglobin 74 g/L) and new onset renal failure (creatinine ~300 μmol/L). White blood cell and platelet counts were within normal range at 4.9 × 10⁹/L and 125 × 10⁹/L, respectively. Twenty-four hour urine study with immunofixation demonstrated 3.85 g/day of pure monoclonal λ light chain proteinuria with no albumin, bone marrow biopsy revealed 40% plasma cells (surface antigen CD20 negative, CD50 partially positive), and skeletal survey showed multiple lytic lesions. There was no monoclonal immunoglobulin on serum protein electrophoresis. A renal biopsy displayed some features of cast nephropathy consistent with light chain disease as well as chronic tubulo-interstitial injury that was unexplained. There was no demonstrable glomerular disease on biopsy. In hospital, her renal function deteriorated from a serum creatinine of ~300 to ~650 μmol/L associated with hypercalcemia (corrected calcium 2.74 mmol/L, albumin 35 g/L). Also, β2-microglobulin was elevated at 15411 μg/L.

With these findings of stage IIIB (Durie-Salmon) or stage III (International Staging System) light chain multiple myeloma, the patient received plasmapheresis for cast nephropathy and full course VAD (vincristine, adriamycin, and dexamethasone) chemotherapy. By late 2003, repeat bone marrow biopsy showed no morphologic evidence of residual myeloma. Renal function slowly improved such that by early 2004, her serum creatinine was ~300 μmol/L. Urinary monoclonal protein by immunofixation was also undetectable. She subsequently proceeded to high dose melphalan (200 mg/m²) and autologous peripheral blood hematopoietic stem cell transplantation (HSCT) in February 2004.

The immediate post-transplant course was complicated by nosocomial pneumonia and thrombocytopenia. Abdominal CT scan revealed new moderate splenomegaly of unknown etiology while her thrombocytopenia persisted. Concurrently, the patient’s renal function began to deteriorate and repeat urine studies revealed denovo proteinuria of 3.6 g/day that was exclusively albumin despite no clinical or laboratory evidence of recurrent myeloma. This finding suggested the presence of glomerular disease that was not present on the original biopsy. By May 2004, platelets had decreased to 15 × 10⁹/L. Another bone marrow examination was performed which showed only an increase in histiocytes and what appeared to be Gaucher cells, enlarged macrophages with undigested glucocerebrosidase (Figs. 1 and 2). A repeat renal biopsy was precluded by the patient’s thrombocytopenia. In June 2004, serum creatinine had reached ~700 μmol/L and hemodialysis was commenced.

Concurrently, in August 2004, the patient’s daughter underwent routine prenatal screening and was found to be a carrier for GD. This prompted genetic testing in the patient. Subsequent DNA analysis detected 1 copy of the N370S mutation and 1 copy of the L444P mutation. Therefore, the patient was a compound heterozygote for 2 mutations in the glucocerebrosidase gene, establishing the diagnosis of Type I GD. Genetic studies revealed that no other family members were affected. Although ERT was started promptly after diagnosis, the patient died shortly thereafter from an intracerebral hemorrhage secondary to coagulopathy and severe thrombocytopenia.

Discussion

Plasma cell disorders such as MM and MGUS may occur in association with GD, where the overall incidence of hematologic malignancies is 6- to 14-fold higher than in the healthy population (1, 2, 6, 7). The mechanisms for this relationship are poorly understood, but a study of 22 patients conducted by Allen et al demonstrated significantly elevated interleukin-6 (IL-6) and interleukin-10 (IL-10) concentrations in the serum of patients with GD when compared with those of age-matched controls (8). Both interleukins are important in the regulation of lymphocyte differentiation and their levels are also shown to be increased in lymphoproliferative disorders (9). Specifically, IL-6 has been implicated in the development of osteolytic lesions characteristically seen in MM (8). The presence of high concentrations of IL-6 and IL-10 in both MM and GD suggests that the two conditions may share a common inciting event or pathogenic pathway.
The timing of plasma cell disorders in the course of GD is largely unknown. Thus far, all reported cases have described patients with symptomatic GD who subsequently developed immunoglobulin abnormalities (1, 2). The current case contrasts previous reports because our patient was first affected with MM prior to developing clinically apparent GD, indicating that the common temporal pattern of GD manifesting before MM is not absolute. Alternatively, given that the severity of Type I GD is highly variable, it is possible that mild splenomegaly may have been overlooked in this patient on early examination. Nonetheless, the phenotypic heterogeneity in adult-onset Type I GD is such that the sequence of events in the present patient may have ramifications for current screening and monitoring strategies used in patients with MM or GD. The factors that determine the sequence of disease presentation have yet to be clearly elucidated.

Although clinically asymptomatic from GD when diagnosed with MM, retrospective review of the patient’s initial bone marrow biopsy does reveal macrophages resembling Gaucher cells. However, morphologic diagnosis of GD by detecting Gaucher cells in the biopsies of affected organs can be challenging and often requires clinical correlation because Gaucher-like or pseudo-Gaucher cells have been occasionally described to appear in various hematologic malignancies, including lymphomas, leukemias, and MM (10). The paucity of suggestive clinical features and the abundance of plasma cells in the bone marrow at the time clearly indicated that the prominent disease process was MM and therefore our index of suspicion for other diagnoses decreased accordingly.

Persistent unexplained thrombocytopenia, new onset splenomegaly, and possible denovo glomerular disease were evidently the first presenting features of GD in this patient. They occurred soon after HSCT. Chemotherapy and other forms of immunosuppression may reactivate immunemediated diseases such as tuberculosis and hepatitis (11, 12). Considering the possible role of interleukins in its pathogenesis, a similar reactivation may occur in GD whereby asymptomatic disease can become clinically apparent when a patient’s “immune reserve” diminishes following chemotherapy.

Another noteworthy feature is that the present patient was affected with pure LCMM, which has never been reported to occur in GD. Most cases of MM are characterized by the accumulation of a single type of monoclonal immunoglobulin (13). The classic immunoglobulin results from the pairing of heavy chains with light chains. Complex gene rearrangements within B lymphocytes are involved in this process and contributes to antibody diversity capable of recognizing different antigens (14-16). However, up to 20% of MM are characterized by the presence of only light chains in the serum or urine, and lacks the immunoglobulin heavy chain (17). To date, the precise mechanisms for LCMM have yet to be defined, although selective proteolysis and genetic mutations in the constant and variable regions encoding for heavy chains have been theorized (18, 19). Similarly, the process by which MM occurs in conjunction with GD remains inconclusive, but it has been postulated that chronic antigenic stimulation plays a central role in the upregulation of lymphoproliferation (5). However, the finding of isolated LCMM in the present case suggests an alternate cause—one that exerts effects exclusively on the light chain gene. Mutations such as chromosomal translocations between the GD locus and the light chain loci, which reside on different chromosomes, is a possible explanation but warrants further study (17, 20, 21).

Finally, the new onset of nephrotic range proteinuria that was exclusively albumin following remission of the patient’s MM raises suspicion for renal dysfunction secondary to another cause. Although storage diseases, such as Fabry disease, frequently affect the kidneys, renal abnormalities such as nephrotic syndrome in GD have been limited to case reports (22, 23). Such patients demonstrated well-defined glomerulopathy often with Gaucher cells in the glomeruli, but this is not a firm requirement for diagnosis (22, 23). In the present patient, there was no other apparent cause to explain her severe albuminuria and progressive renal dysfunction. Neither the morphologic findings nor clinical context supported the recurrence of her LCMM. Notably, in support of renal involvement stemming from GD, the patient’s recurrent proteinuria occurred simultaneously with the findings of splenomegaly and thrombocytopenia. Unfortunately, her severe thrombocytopenia followed by an untimely death shortly after beginning ERT prohibited longer term follow-up. In retrospect, the tubulo-interstitial injury noted on her renal biopsy at the time of initial MM diagnosis may have been the first histologic manifestation of the patient’s GD.

Conclusion

In summary, we report a unique case of GD with nephrotic syndrome presenting after chemotherapy and HSCT for LCMM. Although the occurrence of either LCMM or nephrotic syndrome is rarely described in GD, this case indicates that an index of suspicion for such entities is still warranted, especially after periods of immunosuppression. Until the relationship between MM and GD becomes better defined, we propose that when managing MM or GD, clinical suspicion for the other diagnosis should be maintained so that early disease recognition and effective treatment for either disease can be offered.

References


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