Case Report

A simultaneous diagnosis of multiple myeloma and Gaucher disease

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Abstract

Gaucher disease (GD) is a rare autosomal recessive metabolic disorder caused by the deficiency of the enzyme glucocerebrosidase, required for the degradation of glycosphingolipids. This leads to the accumulation of glucosylceramide and glucosylsphingosine in lysosomal macrophages (Gaucher cells). The diagnosis of GD should be made on the deficiency of the glucocerebrosidase activity (GBA) in leukocytes, fibroblasts, and/or dried blood spots, but also be confirmed through molecular analysis of the GBA gene. GD is linked to an increased risk of cancer in general, and hematological malignancies in particular. Due to an excessive accumulation of glucocerebroside in bone marrow, both cytopenia and bone lesions can be seen in GD, which are clinical presentations that may overlap with multiple myeloma (MM). We report here the case of a patient with synchronous GD and MM, with the description of the evolution.

Keywords: Gaucher disease; Multiple myeloma; Metabolic disorder; Monoclonal gammopathy.

Introduction

Gaucher disease (GD) is a rare autosomal recessive metabolic disorder that affects 0.4 and 5.8/100,000 worldwide inhabitants. It is caused by the genetic deficiency of the lysosomal enzyme glucocerebrosidase that leads to the accumulation of its natural substrate (glucosylceramide) and its deacylated product (glucosylsphingosine) in lysosomal macrophages (Gaucher cells). The absence of neurological involvement defines GD type I, whereas neuronopathic features define GD type II and III [1,2]. The diagnosis is based on demonstrating a deficiency of glucocerebrosidase activity (GBA) in leucocytes, and the low GBA activities are typically confirmed through molecular analysis of the GBA gene [3]. GD is a heterogeneous disease with a wide range of clinical presentations that may overlap with multiple myeloma (MM) such as anemia and skeletal manifestations (diffuse bone pain, osteonecrosis, osteolytic lesions, and pathologic fractures) [4]. Patients with GD have also a 5.9 to 51.1 times higher risk of developing MM compared to normal population [5,6]. We report here the case of a patient with synchronous GD and MM, with the description of the evolution.

Case report

A 63-year-old woman with no medical history was admitted to the hospital for a pathological fracture of her left femur in 2012. She reported diffuse bone pain for a few months. Lytic lesions were found in her right femur and skull. No hepatosplenomegaly was found in physical examination. The diagnosis of multiple myeloma was suspected. On review of her laboratory results, she had anemia (9.7 g/dL; normal range, 11.7–15.3 g/dL) with normal red cell indices and normal white blood cell and platelet counts. She had normal serum calcium, renal, and liver function tests. Serum protein electrophoresis showed a monoclonal protein of 0.03 g/L, characterized as IgG-kappa by immunofixation. Albumin and Kappa free light chains were also detected in the urine. Her Ig profile showed an elevated IgG with a decreased IgA and IgM. Free light chain assay showed an ele-
vated kappa light chain (2397.27 mg/L; normal range, 3.3–19.4 mg/L), a normal lambda light chain (21.1 mg/L; normal range, 5.71–26.3 mg/L), and an abnormal free light chain ratio (113.56; normal range, 0.26–1.65). Bone marrow aspiration showed a hypercellular marrow with an excess of dystrophic plasmocytes (24%) and the presence of Gaucher disease (GD) cells. The diagnosis of GD (associated to multiple myeloma) was confirmed by a low dosage of β Glucosidase (1.9 nmol/h/mg; norm: 31.2 nmol/h/mg) and high dosage of serum acid phosphatase (256 nmol/h/ml; norm: 176 nmol/h/ml) and serum chitotriosidase (6950 nmol/h/ml; norm: 333 nmol/h/ml). The screening for the mutation in the GBA1 gene couldn’t be made. We considered that diffuse bone pain and pathologic fracture were related to multiple myeloma and chemotherapy was started since she had a stage III IgG multiple myeloma with ISS score of 1 and R-ISS score of 1. She received 3 cycles of Dexamethasone-Thalidomide (and zoledronic acid) with a very good partial response of 97% and had an autologous stem cell transplant with a complete response. We noted a second pathological fracture during the first cycle of treatment, and two episodes of lung infections. The patient reported the disappearance of bone pain after the MM treatment.

In March 2016, she experienced a relapse and had a decompressive radiotherapy over a spinal cord compression. She was treated for her MM by 4 cycles of Dexamethasone-Lenalidomide leading to a complete response. We did not perform a second autologous stem cell transplantation because of an insufficient number of stem cells. She also had an osteonecrosis of the jaw in september 2016 and the zoledronic acid was stopped. In 2017, she began the maintenance treatment with Thalidomide with a complete disappearance of her bone pain but had a third pathological fracture of her left humerus this time. The patient died in 2018 of an unknown cause.

Discussion

Our patient presented GD type 1 and MM. The diagnosis of GD was made coincidentally while performing bone marrow aspiration for a plasmocyte assessment. It is well known that cell dyscrasias and lymphoproliferative disorders can be associated with the accumulation of monoclonal immunoglobulin crystals in the lysosomes of histiocytes in the bone marrow or lymphoid and extra-lymphoid tissues. These cells can mimic the Gaucher cells and are therefore called Pseudo-Gaucher cells [7,8]. We confirmed the diagnosis of GD by a low dosage of β Glucosidase and a high dosage of serum acid phosphatase and chitotriosidase, but we couldn’t do a molecular screening. The diagnosis of GD should be made on the deficiency of the glucocerebrosidase activity (GBA) in leukocytes, fibroblasts, and/ or dried blood spots, but also be confirmed through molecular analysis of the GBA gene [3]. GD is linked in particular to an increased risk of hematological malignancies, specifically multiple myeloma (MM) with an estimated risk between 25-0 and 51-1, which is the consequence of a high prevalence of monoclonal gammapathy of undetermined significance (MGUS) [9]. In fact, the prevalence of MGUS was seen in up to 25% of the cases reported by Pratt et al. and, similarly to the general population, is more frequent in older patients [10]. Nguyen et al. found that only age was a significant risk factor of monoclonal gammopathy development, in a series of 278 patients treated for GD [11]. The physiopathology of cancer genesis in GD is complex. In fact, a systematic review of the literature on the prevalence of monoclonal gammopathies and malignancies in GD made by L. van Dussen showed that many risk factors are included such as immune dysregulation, splenectomy, genetic modifiers, endoplasmic reticulum stress, altered iron metabolism and insulin resistance [12].

Due to excessive accumulation of glucocerebrosidase in bone marrow, both cytopenia and bone lesions can be seen in GD. Most patients have mild-moderate thrombocytopenia and anemia is a common feature in GD [13], it’s therefore hard to determine its origin in situations of synchronous GD and MM. Hypercalcemia and renal impairment are not seen in GD, while hepato-splenomegaly are common at presentation. The skeletal manifestations are similar in GD and MM, characterized by diffuse bone pain, osteonecrosis, low bone density, osteolytic lesions, and pathological fracture [13,14]. In fact, bioactive lipids originating from Gaucher cells engage other bone marrow cell types, such as osteoblasts and possibly endothelial cells, setting the stage for avascular osteonecrosis and osteopenia. The decreased mineral density could lead to fractures and more dramatically to acute bone crisis [15].

The GD treatment, enzyme replacement therapy, has been available since the nineties and has proven its efficiency in the treatment and prevention of visceral complications [12,16]. It can have a significant impact on skeletal manifestations except avascular necrosis which is irreversible [17]. In our reported case, no enzyme replacement therapy was prescribed but bone manifestations disappeared after MM chemotherapy, which leads us to think that her bone manifestations were due to MM.

Initiation of treatment with ERT in patients with GD is tailored to the individual patient and is aimed at improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life [18].

Conclusions

In summary, GD is a rare disease and its association with MM is even more rare, but has been well documented in the literature. However, the physiopathology of this association still has not been clearly defined. It is then the duty of hematologists to be more familiar with the clinical presentation and diagnosis of GD and its association with monoclonal gammopathies, which will lead to a better understanding of the disease and why not to the establishment of codified treatment protocols.

Declarations

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References


