Gaucher Disease and Myelofibrosis: A combined Disease or a Misdiagnosis?

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Abstract

Gaucher disease (GD) and primary myelofibrosis (PMF) share similar clinical and laboratory features such as cytopenia, hepatosplenomegaly and marrow fibrosis, resulting often in a misdiagnosis. We report here the case of a young woman with with hepatosplenomegaly, leukopenia and thrombocytopenia. Based on bone marrow (BM) findings and on liver biopsy showing extramedullary hematopoiesis, an initial diagnosis of PMF was formulated. The patient refused stem cell transplantation from an HLA-identical sibling. Low-dose melphalan was given without any improvement. Two years later, a BM evaluation showed Gaucher cells.

Low glucocerebrosidase and high chitotriosidase levels were indicative for GD. Molecular analysis revealed N370S/complex I mutations. Enzyme replacement therapy (ERT) with imiglucerase was started resulting in clinical and hematological improvements. Due to an unexpected and persistent organomegaly, PMF combined with GD were suspected. $JAK2^{V617F}$, JAK2 exon 12, MPL, calreticulin (CARL) and exon 9 mutations were negative and BM examination showed no marrow fibrosis. PMF combined with GD were excluded. Twenty years after starting ERT, the peripheral cell count and liver size were normal, whereas a mild splenomegaly persisted. In order to avoid future misdiagnosis, a diagnostic algorithm for patients with hepatosplenomegaly combined with cytopenia is suggested.

Introduction

Gaucher disease (GD), a rare autosomal recessive disorder, and primary myelofibrosis (PMF), a rare clonal myeloprolipherative neoplasm (MPN), may present similar features such as thrombocytopenia, anemia, leukopenia, splenomegaly and marrow fibrosis, resulting in a diagnostic challenge.

Case Report

In November 1994, a 32 year-old woman, with a clinical history of non-traumatic bone fractures (femur and tibia) at the age of 15 years with unknown causes, was referred to our center due to hepatosplenomegaly, leukopenia and thrombocytopenia. The patient had been asymptomatic until 1990 when hepatosplenomegaly was found during her fourth pregnancy (she had previously had three spontaneous abortions). At that time, the peripheral blood (PB) cell count, serum proteins and albumin, kidney and liver function were in the normal range, except for mild liver enzyme abnormalities and thrombocytopenia. A liver biopsy, performed during the caesarian section, revealed extramedullary hematopoiesis. Despite this finding, the patient was referred to our Center only in 1994, with a suspect diagnosis of PMF. On admission, clinical examinations revealed

hepatomegaly and palpable splenomegaly; the full blood count showed thrombocytopenia (platelets $78x10^9$/L) and leukopenia (leukocytes $3.2x10^9$/L with a normal differential count) with a hemoglobin (Hb) level of 11.1 g/dL; the serum ferritin level was 566 μg/L. An abdominal ultrasonography confirmed the hepatomegaly (Ø 146 mm) and splenomegaly (Ø 246x112x104 mm). Cytogenetic analysis revealed an inherited translocation t(6,13) without clinical significance. A BM biopsy showed a decreased cellularity, normal megakaryocytic proliferation with atypia (lobulated and nacked nuclei) and a significant increase of reticulin fibers and collagen deposition. A diagnosis of PMF was made. Given the young age and the availability of an HLA-matched sibling, a stem cell transplantation was considered but the patient refused. Low-dose melphalan was then given. Two years after starting treatment, the persisting thrombocytopenia, leukopenia and hepatosplenomegaly led us to perform a BM revaluation. Surprisingly, hystiocyte clusters CD68R+ (PAS/PAS-D+) suggestive of Gaucher cells and an increased marrow cellularity, normal granulopoiesis, erythropoietic and megakaryocytic dysplasia, significant reticulin and collagen fibrosis were found. Low-dose melphalan was stopped. Low glucocerebrosidase activity and high value of chitotriosidase were suggestive for GD. Molecular analysis revealed the N370S/complex I mutations, allowing a diagnosis of non-neuropathic type I GD. A further comprehensive assessment of all potentially affected organ systems was performed. A full blood count was as follows: platelets 71 $x10^9$/L, leukocytes $3.2x10^9$/L, Hb 10.5 g/dL and ultrasonography confirmed increased hepatomegaly and unchanged splenomegaly. Skeletal evaluation (X-rays and dexa mineralometry) excluded bone involvement. In June 1997, enzyme replacement therapy (ERT) with imiglucerase at a monthly dose of 30 U/kg was started. One year later, due to persistent pancytopenia and unchanged hepatosplenomegaly, the ERT dose was increased to 60 U/kg/monthly. Platelets and leukocytes count, as well as the hemoglobin level, reached the normal range 6 years after starting treatment. Subsequently, a persistent hepatosplenomegaly suggested a combined PMF and GD. Human androgen receptor assay (HUMARA) PCR analysis [1] showed a polyclonal hematopoiesis. In February 2008, the $JAK2^{V617F}$, JAK2 exon 12 and MPL mutations were analyzed in PB cells as previously described [2]. No mutations of the investigated genes were found. The patient continued ERT at a dose of 60 U/Kg/monthly. In 2013, calreticulin (CARL) exon 9 analysis was carried out without any evidence of mutations [3, 4]. At this time, the PB values were normal, whereas splenomegaly and mild hepatomegaly persisted. An additional BM biopsy was done. The medullary framework was characterized by a normal hematopoiesis, the presence of scattered Gaucher cells and absence of fibrosis. A diagnosis of PMF was excluded. The patient continued ERT at the same dose obtaining a progressive reduction of the hepatosplenomegaly. At the last follow up in 2017,

twenty years after starting treatment, the PB cell count was normal; ultrasonography and MRI revealed a mild splenomegaly (Ø 140x100x90 mm) and a normal liver size.

Discussion

GD and PMF share many clinical and laboratory features to such an extent that GD can be easily missed as a possible diagnosis. In order to diagnose PMF, a BM biopsy is essential. However, a BM biopsy is also indicated in GD when the differential diagnosis with a hematologic disease is necessary. In the case presented, the first BM biopsy confirmed the suspect of PMF because of a stricking marrow framework of myelofibrosis without Gaucher cells. Instead, the second BM biopsy showing the presence of both fibrosis and lipid-storage macrophages suggested the diagnosis of GD that was confirmed by assessing the glucocerebrosidase activity and by molecular analysis. In both PMF and GD there is an activation of pro-inflammatory cytokine pathways that could have an important role in the modification of the bone marrow microenvironment leading to the development of marrow fibrosis. Genetic and epigenetic abnormalities, that can be found in PMF, play a role in the defective clonal hematopoietic stem cell proliferation, with the release of several cytokines in the marrow microenvironment. While, in GD a malfunction of the lipid-storage macrophages, namely Gaucher cells, induces an increased expression of pro-inflammatory cytokines leading to a marrow fibrosis [5]. The framework from the first biopsy was due to the activation of many pro-inflammatory cytokines by unidentified Gaucher cells, while BM framework of the last biopsy was the result of the ERT activity on the reticulinic and collagen fibers.

Assessment of somatic acquired *JAK2*V617F, JAK2 exon 12, MPL and CALR gene mutations in the PB has recently become a mandatory diagnostic tool in MPN, including PMF, as the presence of one of these mutations is a major criterion for PMF according to the 2016 WHO classification [6]. In conclusion, the diagnosis of GD should be considered in the presence of ~~a~~ long-lasting splenomegaly and hepatomegaly combined with cytopenia. In order to avoid future misdiagnosis, the use of a diagnostic algorithm for patients with combined hepatosplenomegaly and cytopenia is recommended (Figure 1).

Conflict of interests: S. Mariani, G. Palumbo, L. Cardarelli, M. Santopietro, R. Foà, and F. Giona declare that they have no conflict of interests.

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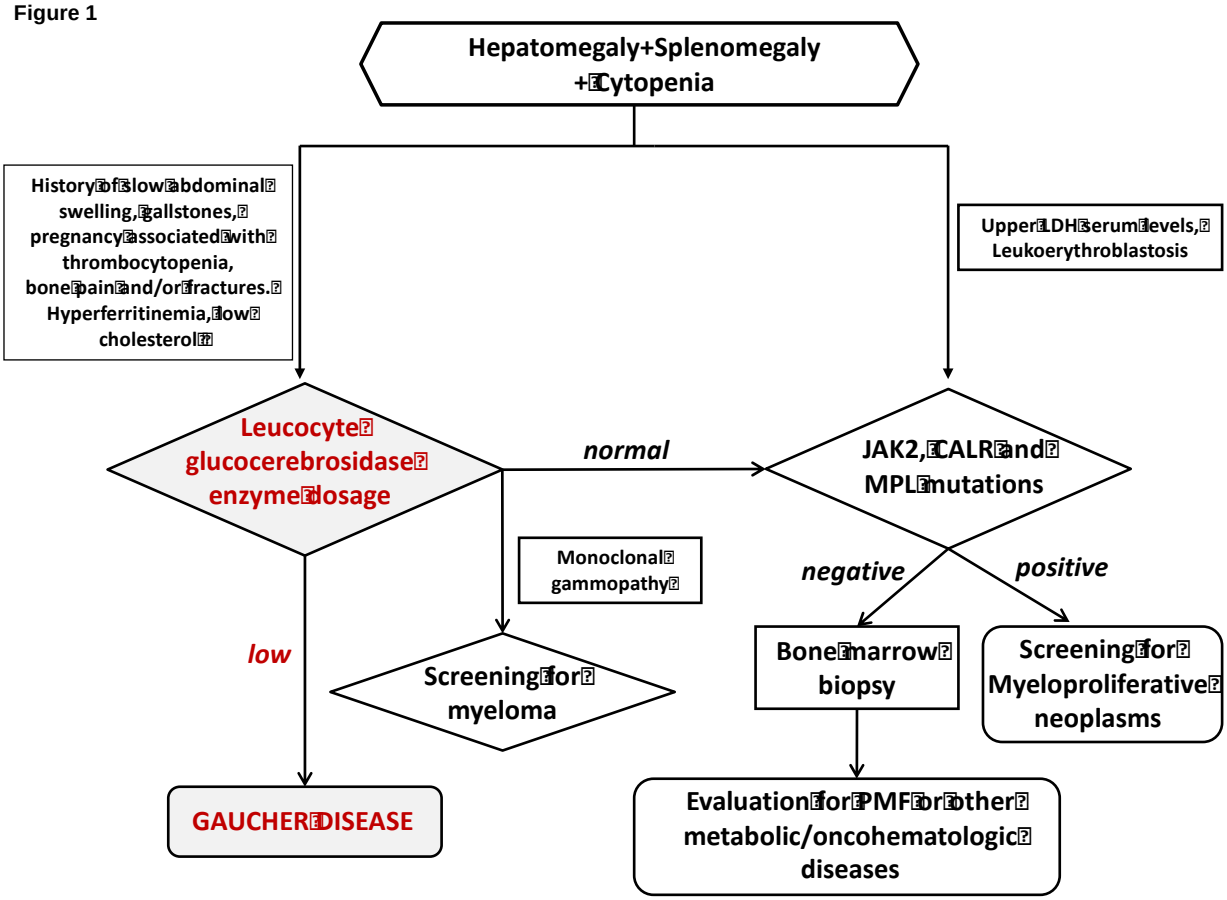
Figure 1. A proposed diagnostic algorithm for patients with long-lasting hepatosplenomegaly and cytopenia.

Figure 1



JAK2: Janus Kinase2; CARL: calreticulin; MPL: myeloproliferative leukemia oncogene; PMF: primary myelofibrosis.

Figure legend