Letter to the Editor
Diagnostic Hematology

Ann Lab Med 2016;36:177-179
http://dx.doi.org/10.3343/alm.2016.36.2.177
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Clinical Utility of Bone Marrow Study in Gaucher Disease: A Case Report of Gaucher Disease Type 3 With Intractable Myoclonic Seizures

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Dear Editor,

Gaucher disease (GD) is the most common lysosomal storage disease, characterized by glucosylceramide accumulation in macrophages owing to inherited glucocerebrosidase deficiency caused by *GBA1* mutation [1]. Clinical manifestations include thrombocytopenia, hepatosplenomegaly, bone pain, osteopenia, dyspnea, and seizure, depending on the organ involved [2]. Among these, neurologic involvement plays a crucial role in the classification of the following three subtypes: GD types 1, 2, and 3, called non-neuronopathic, acute neuronopathic, and chronic neuronopathic types, respectively [1, 2]. β-glucocerebrosidase activity in peripheral leukocyte is considered the confirmatory diagnostic indicator of GD [2]. Bone marrow (BM) study to detect Gaucher cells (GCs) with the classical "wrinkled tissue paper" appearance has not been routinely recommended because of procedural risks and false-positive results [3]. We present a patient with recurrent seizures as a sole symptom who was correctly diagnosed as having GD type 3 through a BM study.

A 31-yr-old woman with recurrent seizures was referred to our hospital. She experienced the first seizure attack at the age of 23 yr. Despite constant antiepileptic medications at the outpatient clinic, she had drug-resistant myoclonic seizures, intermittently evolving to generalized tonic-clonic seizures, which required 11 hospital admissions during the last three years. The initial complete blood count showed no specific findings other than mild leukopenia, with the following values: hemoglobin, 11.9 g/dL; platelets, 162×10^9/L; and leukocytes, 3.32×10^9/L, with normal differential counts (Fig. 1A). Physical examination and abdominal ultrasonography revealed no evidence of splenomegaly or hepatomegaly. Drug-induced leukopenia related with long-term use of antiepileptic medications was initially suspected, but the patient showed mild leukopenia during the recent eight weeks, with leukocyte levels ranging from 3.00×10^9/L to 3.59×10^9/L. Accordingly, the attending physician performed a BM study.

In hypocellular marrow with normal distribution, GCs accounted for 17.5% of all nucleated cells on the aspiration smear (Fig. 1B). Of the GCs, 10.5% showed atypical vacuolations, while the others showed typical fibrillary cytoplasm with an eccentrically placed nucleus (Fig. 1C). Despite the consistent BM biopsy findings of GCs (Fig. 1D), reticulin staining showed no evidence of abnormal reticulin fibrosis (i.e., grade 0). In addition, β-glucocerebrosidase activity test revealed 0.6 nmol/hr/mg protein, which is much lower than the reference limit of 6.0 nmol/hr/mg protein. *GBA1* sequencing to confirm the diagnosis revealed two point mutations (i.e., N188S and R257Q), both

Received: July 15, 2015
Revision received: September 17, 2015
Accepted: November 10, 2015

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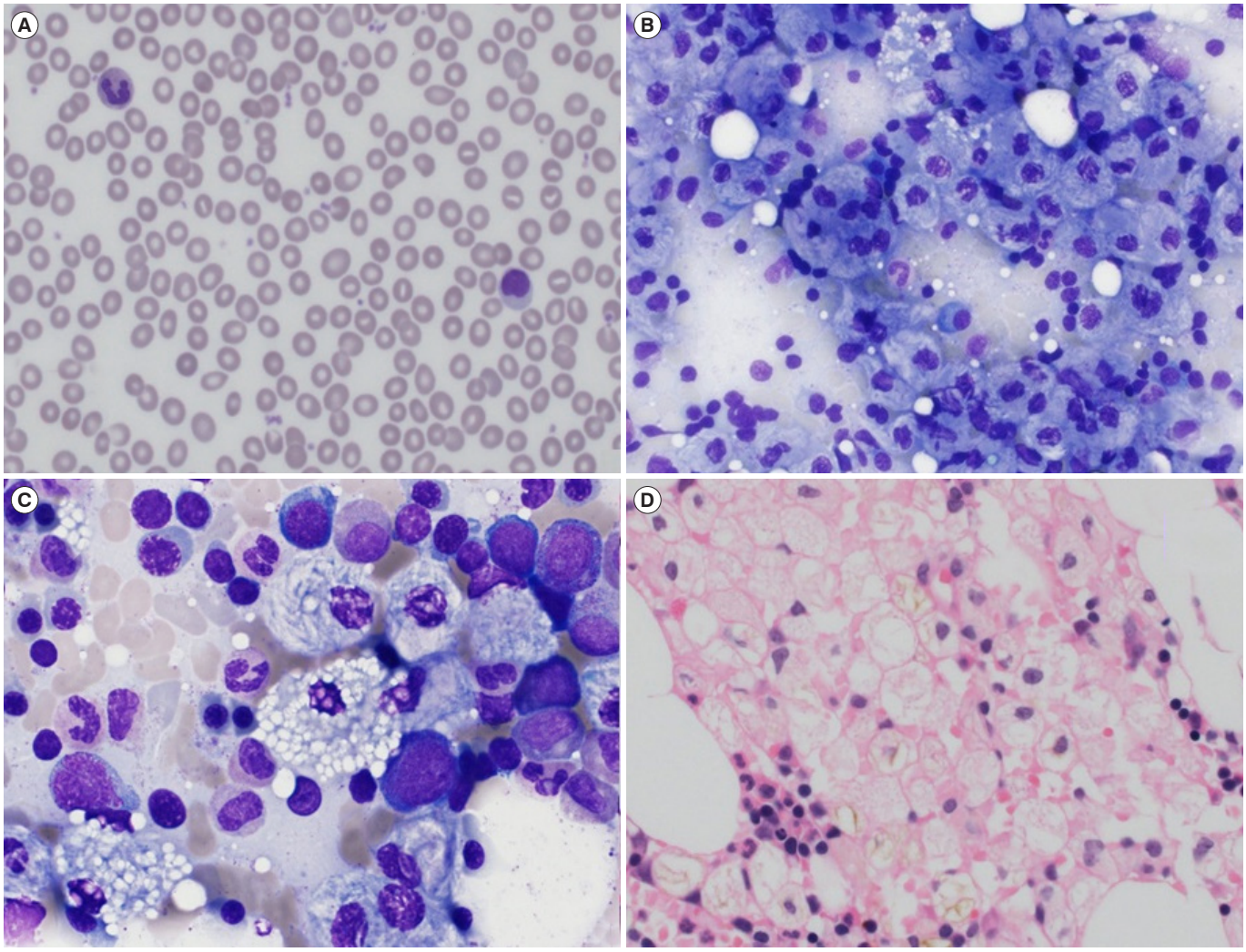

Fig. 1. Microscopic examination of the patient's (A) peripheral blood (×400, Wright-Giemsa stain) and (B) bone marrow aspiration (×400, Wright-Giemsa stain). (C) Atypical Gaucher cell with vacuolations and typical Gaucher cell with a "wrinkled tissue pattern" on bone marrow aspirate smear (×1,000, Wright-Giemsa stain). (D) Bone marrow biopsy specimen presenting with several Gaucher cells (×400, Hematoxylin & Eosin stain).

previously reported as the cause of GD. Under the diagnosis of GD type 3, the patient was given enzyme replacement therapy with imiglucerase (Cerezyme, Genzyme Corporation, Cambridge, MA, USA), and her leukocyte count returned to normal. However, the neurological symptoms did not alleviate, coinciding with the fact that imiglucerase is well known to be unable to penetrate the blood-brain barrier.

Owing to the phenotypic variability of GD, which might hinder prompt diagnosis or timely clinical impression, several guidelines for optimal diagnostic algorithm and evaluation steps have been suggested [4, 5]. Regardless of GD subtypes, hepatosplenomegaly and thrombocytopenia were considered as the most common clinical features. Therefore, hematologic aspects of GD have been emphasized for the early diagnosis of preventable complications [2, 6]. Even though the clinical utility of BM study in GD is controversial, GCs detected in BM have been the most important diagnostic indicator in our patient. The long seizure history was explained on the basis of the BM finding, which suggests the reappraisal of the clinical utility of BM study in GD despite professionally appropriate evaluation.

Atypical GCs in BM of type 1 GD were evaluated by using the cytomorphological approach in a recent study, in which seven types, including foamy cytoplasm, multinuclearity, erythrophagocytosis, and cytoplasmic projections, were described [7]. The authors suggested that foamy transformation of GCs might be associated with an abnormal storage pattern triggered by an ex-

http://dx.doi.org/10.3343/alm.2016.36.2.177

ternal factor, possibly seizure attacks in this case. Another recent study focused on the differential clinical utilities of BM biopsy and aspiration to detect the presence of GCs [8]. Although biopsy seemed more sensitive to GCs, our patient showed a comparable percentage of GCs in aspiration and biopsy, which might be related to the absence of abnormal reticulin fibrosis in this case.

In conclusion, we report a GD patient with recurrent seizures as the single classical symptom, in whom GC detected in BM indicated the correct diagnosis of GD. Our case might emphasize the clinical utility of BM study for GD, especially in cases of unexplained seizures without prominent hematologic abnormalities. Further studies to investigate the roles of BM study for GD for monitoring enzyme replacement therapy response are expected.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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