Enzyme replacement therapy in type 1 Gaucher disease and a review of the literature

Tip 1 Gaucher hastalığında enzim replasman tedavisi ve literatürün gözden geçirilmesi

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Abstract

Gaucher disease (GD) is the most common lysosomal storage disorder. Deficiency of the lysosomal enzyme glucocerebrosidase results in the intracellular accumulation of undegraded substrates in the spleen, liver and bone marrow. Enzyme replacement therapy (ERT) is a standard approach for type 1 GD. Here, we present an adult patient with hematological disorders due to type 1 GD, who markedly improved with ERT.
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Özet

Gaucher Hastalığı (GH) en yaygın lizozomal depo hastalığıdır. Lizozomal enzim, glukoserebrosidaz eksikliği dalak, karaciğer ve kemik iliğinde yıkılamayan maddelerin hücre içi birikimi ile sonuçlanır. Enzim replasman tedavisi (ERT) tip 1 GH'de standart bir yaklaşımdır. Burada, ERT ile belirgin olarak düzelen tip bir GH nedeni ile hematolojik bozukluğu olan yetişkin bir hastayı sunmaktayız.
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Introduction

Gaucher disease (GD) is an inherited lysosomal storage disorder (LSD). Lysosomal enzyme activity due to a mutation in the glucosylceramidase (GluCer) gene is decreased or absent, resulting in intracellular accumulation of undegraded substrates. Approximately 300 mutations, mostly autosomal recessive, have been described, and are usually seen in closed communities like in Ashkenazi Jews [1]. Though the consanguinity rate is high in the Turkish population, the disease has been observed to have a low incidence, as 0.23/100,000 live births [2].

Gaucher disease has been divided into three forms according to the clinical manifestations. Type 1 is the most common and mildest form of GD, and is essentially a monocyte/macrophage system disorder, lacking primary central nervous system involvement. It is characterized by varying degrees of splenomegaly and hepatomegaly, anemia, thrombocytopenia, bone pain, and skeletal lesions. Types 2 and 3 are both rare, with acute and fulminating (type 2), or heterogeneous and attenuated (type 3) neurological involvement accompanying visceral manifestations [3].

Quite effective treatment modalities for GD are available today, and they have raised hopes regarding the treatment of other LSDs. In this report, we present a case having severe hematological findings due to GD. The recent developments in the management of GD are also reviewed.

Case Report

A 30-year-old female patient with type 1 GD was referred to our hematology clinic due to an increase in her complaints and clinical findings. She had been diagnosed with GD 10 years ago by pathological examination of the bone marrow biopsy and had been followed with supportive measurements.

She suffered from abdominal fullness, early satiety and severe fatigue. On the physical examination, she was pale in appearance and had a palpable massive hepatosplenomegaly. She did not have any symptoms or signs of abnormalities of the neurological or locomotor systems. Her laboratory results on admission to our clinic are shown in Table 1. Abdominal ultrasound examination revealed hepatomegaly (vertical height was 20 cm) and splenomegaly (100x144x230 mm), including multiple hyperechoic masses with central hypoechogenicity and distinct borders. Bone mineral densitometry monitoring with dual-energy X-ray absorptiometry (DXA) revealed total femur neck T and Z scores of -1.44 each and lumbar vertebrae T and Z scores of -2.20 and -2.19, respectively. Her bone marrow biopsy revealed diffuse Gaucher cell infiltration (Figures 1a, 1b). Glucocerebrosidase enzyme level was measured as 1.6 nmol/s/mpgr (5-13.5 nmol/s/mpgr). She was a heterozygous carrier for N370S and L444P mutations according to genetic mutation screening.

The diagnosis of type 1 GD was confirmed and recombinant human GluCer (Cerezyme®) replacement therapy was initiated once every three weeks intravenously at a dose of 400 IU, in addition to parenteral vitamin B12 supplementation and calcium and vitamin D treatments. After enzyme replacement therapy (ERT), her symptoms and clinical and laboratory findings significantly improved. Gaucher cells were apparently decreased in the bone marrow biopsy within one year (Figures 2a, 2b).

Oral informed consent was obtained from the patient.

Table 1. Laboratory findings on admission to the clinic

Test	Result	Normal Range
Complete blood count		
Hemoglobin (g/dl)	**9.4**	11.7-15.0
Hematocrit (%)	**28.1**	35-45
Leukocyte count (x10e9/L)	**3.9**	4.5-11.0
Absolute neutrophil count (x10e9/L)		
Platelet count (x10e9/L)	**87.0**	150-400
Others		
Direct & indirect antiglobulin test	Negative	
Serum IgG level (g/L)	**19.4**	7.0-16.0
Serum IgM level (g/L)	3.11	0.4-2.3
Serum IgA level (g/L)	3.38	0.7-4.0
Gamma globulin level in serum protein electrophoresis (%)	**23 (polyclonal)**	10.5-19.5
Serum immune-fixation test	Negative	
Serum ferritin level (ng/ml)	263	11.0-306.8
Vitamin B12 level (pg/ml)	**166**	166-970
Folic acid level (ng/ml)	3.7	1.5-16.9

Abnormal values are shown in bold text

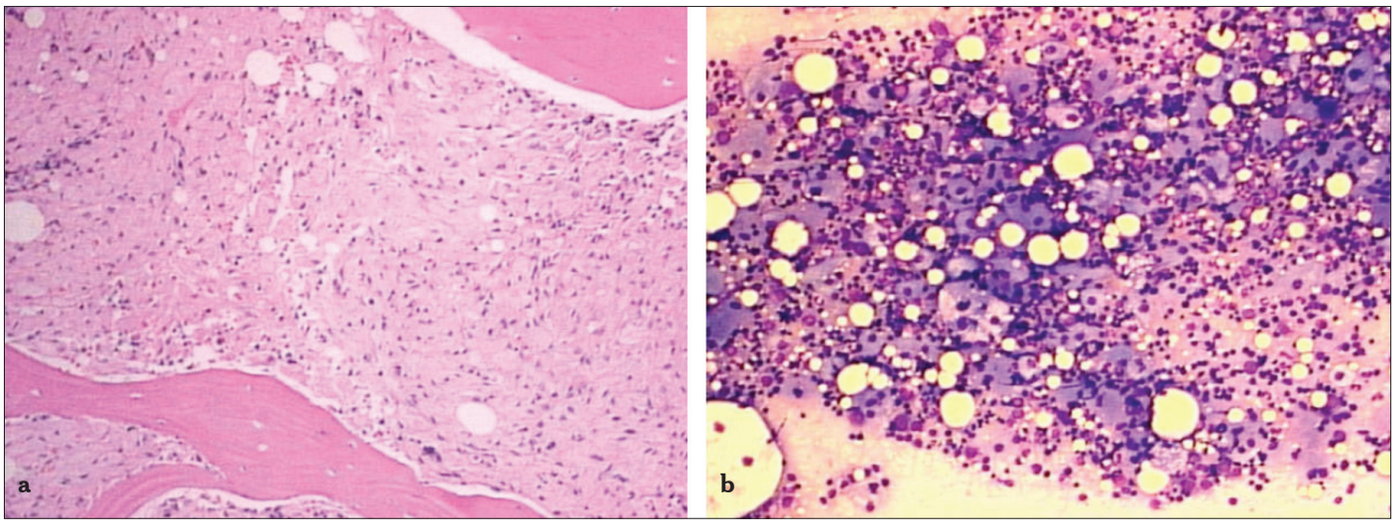

Figure 1. Bone marrow biopsy (a) and smear (b) revealed diffuse infiltration by typical Gaucher cells

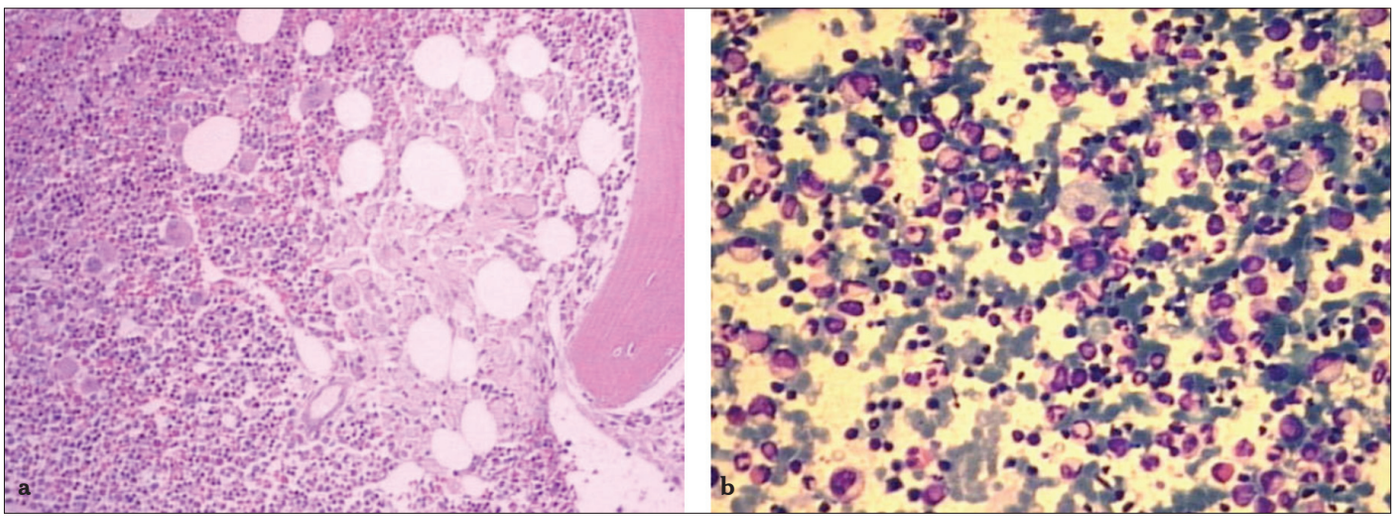

Figure 2. The normal bone marrow cells became the dominant cellular components of the marrow areas after therapy. The decrease in infiltrative cells was examined either on biopsy sections (a) or smear preparations (b)

Discussion

Clinically, GD has been divided into three major subtypes, namely types 1, 2 and 3, although recently there is a trend to consider GD as a continuum of disease states [3]. Despite genotype-phenotype correlations being poor, certain mutations predispose to certain disease forms, for example, homozygosity for L444P mutations results almost invariably in neuronopathic disease [4], whereas the presence of even one mutant allele for N370S normally prevents neurological and pulmonary involvement [4], as in our case. N370S is the most frequent mutation accounting for 70% of mutant alleles in Ashkenazi Jews and 25% of non-Jewish patients [5].

The clinical spectrum may range from the asymptomatic form in type 1 GD to the acute neuronopathic form in type 2 GD, characterized with brainstem and visceral involvement and eventually death in the first 2-3 years of life [6]. Type 1 GD manifests itself with organomegaly, blood cytopenias, and osteopenia, as seen in our patient, and also lytic lesions, pathologic fractures and acute bone crisis episodes, and interstitial lung disease, which are more serious clinical findings [7]. Previous splenectomy history, because of the impact of the overwhelming infections, is an important risk factor for deterioration of lung functions in lung involvement [7].

The most common initial clinical appearance, as seen in our patient, is hematological symptoms and

findings related to anemia and/or thrombocytopenia [8,9]. Cytopenia(s) is related to hypersplenism and/or infiltration of bone marrow with Gaucher cells. Leukopenia is less frequent and is usually due to hypersplenism. Though neutrophil function is defective in many patients, tendency to infection is not common because the neutrophil count is usually in normal range. Splenomegaly is almost invariably more prominent than hepatomegaly; in case of hepatomegaly being the more prominent, other common causes of hepatomegaly must be ruled out.

Other causes of anemia should be sought in a more acute decrease in blood hemoglobin level, especially due to iron and vitamin B12 deficiency, autoimmune hemolytic anemia or associated hematological malignancies. In Gaucher disease, ferritin levels are generally elevated without other biochemical evidence of iron overload, consistent with anemia of chronic disease, whereas typical iron deficiency anemia is characterized by low serum iron, low transferrin saturation and low ferritin levels [9]. In a study among Ashkenazi Jews, it was reported that vitamin B12 levels tended to be lower in the diseased population and decreased in the course of ERT [10]. We gave the patient parenteral vitamin B12 supplementation due to the low level.

Gaucher disease can be associated with hyperactivity of the immune system, which manifests with polyclonal hypergammaglobulinemia or monoclonal gammopathies [11]. We detected polyclonal gammopathy in the sera of our patient as well.

Because of the variability in the clinical manifestations, severity and progression, a comprehensive initial assessment should be done in each patient [12]. In addition, for the diagnosis and prior to treatment, glucocerebrosidase activity should be measured. The main target in the treatment of GD is elimination of or improvement in symptoms, prevention of irreversible damage, and improvement in the overall health and quality of life [13]. There are many therapeutic approaches including ERT, Substrate Reduction Therapy (SRT), Enzyme Enhancement Therapy (EET), and Gene Therapy (GT) (14-17). Currently, the first two modalities, ERT and SRT, are available in the European and United States markets.

The first ERT model among LSDs was recombinant human GluCer (Cerezyme®), 30-120 U/kg/2-4 weeks intravenously, used in GD. Use of ERT has dramatically improved the quality of life for many patients with GD, by decreasing organ volumes, improving hematological parameters and relieving bone symptoms [16].

Enzyme replacement therapy increases the hemoglobin concentration to almost normal levels in 6-12 months. In all patients, peripheral blood platelet count increases to sufficient levels in order to prevent surgical or spontaneous bleeding in the first year of the therapy. Except for life-threatening hemorrhagic events due to severe thrombocytopenia, splenectomy should be avoided since it facilitates lung involvement and decreases pulmonary function capacity [13]. ERT prevents and also reduces enlargement of the liver and spleen within one year after initiating the therapy.

No favorable effect of ERT on neural involvement in types 2 and 3 has been shown, because of poor penetration through the blood-brain barrier [17]. In the case of lung involvement, ERT reverses hepatopulmonary syndrome and improves pulmonary functional status, and thus reduces dependency on oxygen [18].

In the follow-up of patients, monitoring of complete blood count and serum levels of chitotriosidase, angiotensin converting enzyme and tartrate-resistant acid phosphatase, liver and spleen volumetric computerized tomography or magnetic resonance imaging, direct X-ray of long bones, and DXA examination of femur neck and lumbar vertebrae have been suggested in the previous studies [6,19]. The cost of the treatment is one of the most important issues yet to be solved.

For SRT, N-butyl deoxynojirimycin (Zavesca®) is approved as an inhibitor of glucosylceramide syntheses enzyme. It is administered orally and therefore more convenient than ERT, with no intravenous-related complications. Furthermore, it crosses the blood-brain barrier and thus may be useful for relieving symptoms and signs of neuronopathic GD.

Because SRT causes many adverse effects, it is only indicated in patients in whom ERT is unsuitable or not a therapeutic option [16]. Chemical chaperones (EET) are used to stabilize or reactivate improperly formed GluCer. The preclinical studies related to the use of EET in GD are continuing.

Supportive medical treatments for maintaining osteoporosis and pulmonary hypertension and bone marrow transplantation for improving hematological and neurological disturbances are suggested as other approaches with or without ERT [20]. Gene therapy is the major challenge in the future of GD therapy.

Enzyme replacement therapy usually reduces liver and spleen volumes and improves hematological abnormalities within one year. In contrast, decreased bone marrow glycolipid infiltration has been reported to require up to 3-4 years of treatment [21]. However, we observed a significant decrease in Gaucher cells in the bone marrow after the first year of ERT compared to the pretreatment examination of bone marrow (Figures 2a, 2b).

In conclusion, we showed a marked improvement in the clinical and pathological findings in our adult patient severely affected by GD with ERT within one year. However, evaluation and management of patients with GD is continuously and effectively changing. Novel therapeutic approaches have produced exciting results in the clinical a nd pre-clinical studies. In the near future, GD will most probably be an initial success in the LSD therapy era.

Conflict of Interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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