

Gaucher's Disease Presenting with Massive Hepatic Fibrosis and Skeletal Abnormalities: A Case Report with Review of the Literature

Masif Hepatik Fibrozis ve İskelet Anormallikleriyle Gelen Gaucher Hastalığı: Olgu Sunumu ve Literatür Derlemesi

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ABSTRACT The case presented in this manuscript is a 32-year-old female referred to our clinic with massive hepatosplenomegaly, thrombocytopenia, anemia and avascular necrosis at the head of right femur. Gaucher's disease was diagnosed upon observation of specific blood cells in bone marrow and liver. Homozygote N370S mutation was established in the Gaucher's mutation screening. Glycocerebrosidase enzyme level of the patient was quite low (0.66 nmol/hour/mg). Additionally, histological examination of the liver revealed massive hepatic fibrosis without any clinically significant signs of cirrhosis or portal hypertension. Other significant signs of the patient were severe skeletal involvement with stage V/c avascular necrosis of the femoral head and Erlenmeyer flask paralysis. Glycocerebrosidase enzyme replacement therapy was initiated at 60 units/kg after the diagnosis was established. The case presented here is a female patient with signs of hepatic, bone marrow and skeletal system involvement. This rare non-neuropathic type 1 Gaucher's case with massive hepatic fibrosis and pathognomonic skeletal signs has been evaluated in the light of literature.

Key Words: Gaucher disease; liver; fibrosis; musculoskeletal abnormalities

ÖZET Bu yazıda 32 yaşında kliniğimize hepatosplenomegali, trombositopeni, anemi ve sağ femur başı avasküler nekrozu ile gelen bir kadın olguyu sunuyoruz. Gaucher hastalığı tanısı kemik iliği ve karaciğerde spesifik kan hücrelerinin görülmesiyle konuldu. Gaucher mutasyon taramasında homozigot N370S mutasyonu belirlendi. Glikoserebrozidaz enzim seviyesi 0.66 nmol/saat/mg gibi düşük bir düzeydeydi. Ek olarak karaciğer histolojisinde, siroz ve portal hipertansiyonun klinik bulguları olmaksızın, masif hepatic fibroz saptandı. femur başının evre V/c avasküler nekrozu ve Erlenmeyer flask paralizisi hastadaki diğer klinik anlamı olan iskelet tutulumlarıydı. Tanı konduktan sonra glikoserebrozidaz enzim replasman tedavisi 60 ünite/kg düzeyinde başlandı. Burada sunulan olgu hepatic, kemik iliği ve iskelet tutulumu bulguları olan bir kadın hastaydı. Bu nadir görülen, masif hepatic fibroz ve patognomonik iskelet bulguları ile gelen nonnöropatik tip 1 Gaucher olgusu literatürdeki bilgiler ışığında ele alındı.

Anahtar Kelimeler: Gaucher hastalığı; karaciğer; fibrozis; kas iskelet anomalileri

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Gaucher's disease is an autosomal dominant trait and it is the most common lysosomal storage disease.¹⁻³ The disease is caused by lysosomal storage of glycosylceramide which is substrate of the deficient enzyme glycocerebrosidase.⁴ Over 300 mutations have been defined that result in the deficiency of the enzyme glycocerebrosidase.⁵⁻⁸ Glycosylceramide is often stored in the cells of the reticuloendothelial system. Visceral organ involvement results from the storage of glycosylceramide in macrop-

hages. These patients present with hepatosplenomegaly, anemia, thrombocytopenia, pathological bone fractures due to involvement of bone marrow and less commonly, lung involvement.

Visceral organ biopsies obtained in Gaucher's disease have shown Gaucher's cells consisting of fusiform histiocytes of 15-85 microns with one or more small, dark eccentric nucleus, blue staining cytoplasm and wrinkled paper appearance due to the fibrillary structure of the cytoplasm.⁹

Three classical types have been defined in Gaucher's disease according to the clinical features and presence of neurological involvement. The most common type is non-neuropathic type 1 Gaucher's disease with no neurological involvement. These patients are diagnosed at childhood or in an adult age.⁹ Hepatomegaly is a common sign of type 1 Gaucher's disease.¹⁰ Although hepatomegaly is a frequent sign, portal hypertension, cirrhosis and its complications are not common in these patients. However, hepatic failure is an indicator of poor prognosis.¹¹⁻¹³

The case presented here is an adult female patient diagnosed with type 1 Gaucher's disease while searching for the cause of hepatosplenomegaly. She had hepatic, bone marrow and skeletal involvement. Our objective was to evaluate this rare case in the light of the literature data.

CASE REPORT

A 32-year-old female patient was referred to our clinic with the complaints of fatigue and headache. The patient had a history of miscarriage, and her family history revealed a dead sister due to liver cirrhosis. The patient smoked 10 cigarettes/day for 15 years.

Physical examination revealed that patient was in good general condition, conscious, cooperative and oriented. Her vital signs were: Blood pressure 110/70 mmHg, pulse 76/min, body temperature 36;2°C and respiratory rate 13/min. Abdominal examination findings included hepatomegaly which was below the costal line by 10 cm in the middle axis and splenomegaly which was below the costal line by 8 cm.

Initial laboratory signs were, leukocyte: 3500/mm³, neutrophil: 1400/mm³, lymphocyte: 1880/mm³, hemoglobin: 7.6 g/dl, hematocrite: 24%, mean corpuscular volume (MCV): 73 fl, thrombocyte: 98000/mm³, erythrocyte sedimentation rate (ESR): 18 mm/hour and prothrombin time: 12.6 seconds. All other biochemical tests were within the normal ranges including liver function tests. Vitamin B12 and folate levels were normal, whereas ferritin was increased (140 ng/mL).

Serological examination results were: HBsAg (-), anti-HBs (-), anti-HBc (-), anti-HCV (-), anti HAV IgM (-), HIV (-). Thyroid function tests were within the normal ranges. Salmonella and brucella agglutination tests as well as leishmania and malaria tests performed in peripheral blood were negative. Serologic tests performed for Epstein-Barr virus, cytomegalovirus, toxoplasma and rubella were negative. Anti-nuclear antibody (ANA) and rheumatoid factor (RF) were negative. C-reactive protein (CRP) was within the normal ranges.

In the radiological examination of the patient posteroanterior chest X-ray was normal, whereas pathological changes were observed in X-rays of the pelvis, vertebra and extremities. Plane radiological examinations showed osteonecrosis at the right femoral head characterized by avascular necrosis (Figure 1). In addition, knee X-rays showed Erlenmeyer flask deformity (Figure 2). Magnetic



FIGURE 1: X-ray of right femoral head: Sphericity of right femoral head is disrupted, Shenton line is disrupted, more than 70% of femoral head has fragmentation and signs of necrosis (stage V/c according to Steinberg).



FIGURE 2: X-rays of the knee. Erlenmeyer flask paralysis.

resonance imaging of the patient's both hip joints and pelvic bones performed by echo method also showed signs of avascular necrosis at the femoral head (Figure 3a, b). Bone mineral density measurement in osteodensitometric examination indicated 16% loss of bone mineral density (Z-score: -1.5, T-score: -1.5). These results were considered consistent with osteopenia according to the definition of World Health Organization. Abdominal ultrasonography showed that liver was enlarged (205 mm) with homogenous parenchyma and spleen was enlarged (199 mm) with homogenous parenchyma. Upper gastrointestinal system endoscopy was normal.

The patient with hepatosplenomegaly and pancytopenia was initially examined for hematological, infiltrative and infectious diseases. Therefore peripheral blood smear and bone marrow aspirations were performed. Peripheral blood smear showed dacrocytes and hipocromic microcytic anemia. Pseudo-Gaucher cells were observed in bone marrow aspiration. Bone marrow biopsy showed invasion by histiocytes with large cytoplasm (Figure 4) and histiocytes with wrinkled appearance in bone marrow imprints (Figure 5).

Subsequently performed liver biopsy revealed masses of histiocytes with large cytoplasm and zonal distribution (Figure 6). Masson-Trichrom staining demonstrated severe connective tissue formation particularly in the areas dividing the liver into nodules (Figure 7). Immunohistochemical

staining of the liver tissue sample showed HBsAg and HBcAg negativity.

Enzymatic analysis showed reduced beta glucuronidase activity. Glycocerebrosidase enzyme level of the patient was quite low at 0.66 nmol/ hour/ mg (normal values: 9.4 ± 3.2 nmol/hour/mg). Gaucher enzyme analysis method was identical to



a



b

FIGURE 3a, b: Magnetic resonance imaging of femoral head. T1 dominant coronal, T1 dominant transvers cross sections demonstrating destruction, flattening and deformation of right femoral head, avascular areas of necrosis at several different locations. T2 fat tissue printed sequences indicate signal changes in femoral head and intertrochanteric area consistent with edema. Minimally increased fluid in the hip joint as well as atrophic changes in neighboring muscles are evident. There are minimal degenerative changes in the acetabulum; the deformed femoral head is within the acetabulum, however exceeds it slightly.

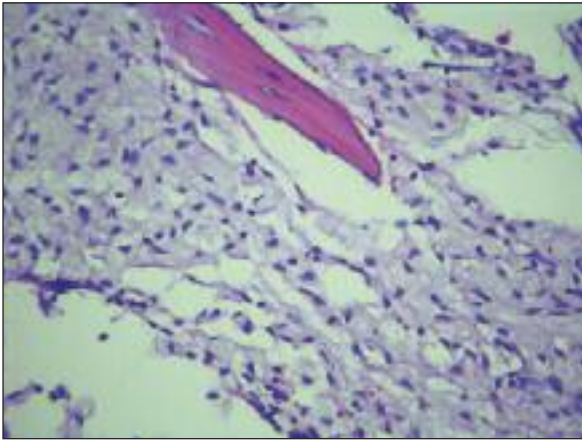


FIGURE 4: Bone marrow biopsy (Hematoxylin-eosine, X40): Gaucher cells with enlarged vacuolated cytoplasm between the bone lamellae.

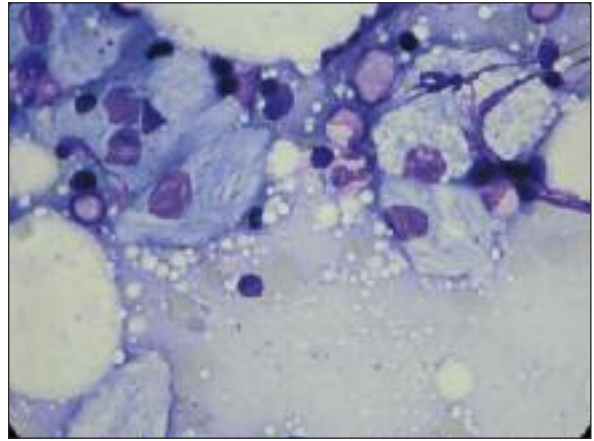


FIGURE 5: Bone marrow imprinting (May-Grunwald, Giemsa, X100): Bone marrow serial cells together with Gaucher cells with nuclei pushed aside and wrinkled cytoplasm.

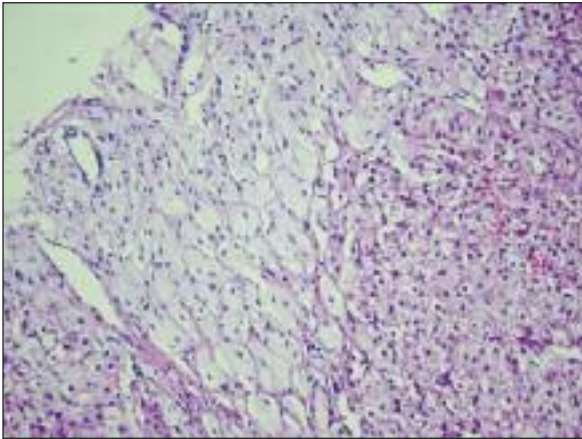


FIGURE 6: Liver biopsy (Hematoxylin-eosin, X20): Gaucher cells in the portal liver spaces extending into the lobule.

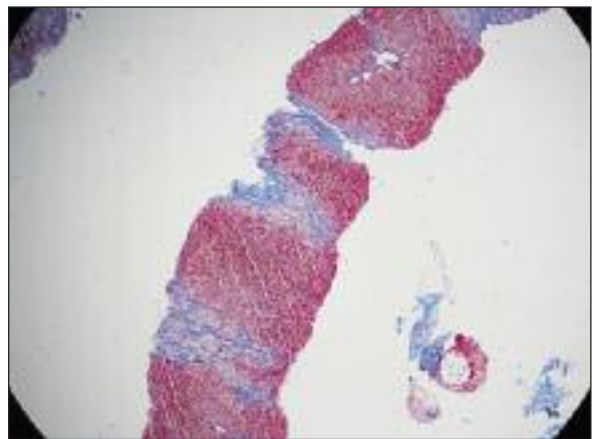


FIGURE 7: Liver biopsy (Masson-Trichrome, X10): Increased porto-portal fibrous connective tissue and Gaucher cells.

the method previously reported by Svennerholm et al.¹⁴

In addition, homozygote N370S mutation was established in the Gaucher's mutation screening. **Mutation analysis of the IDUA gene:** Genomic DNA was extracted from peripheral lymphocytes using Wizard Genomic DNA Purification kit (Promega, Madison, WI). Mutation analysis of the IDUA gene was carried out by amplification and direct sequencing of the whole coding region and splicing site boundaries (at least 30bp of intronic sequences of each splice site). PCR reactions were carried out by the PWO SuperYield DNA polymerase (ROCHE) and the GoTaq DNA polymerase (Promega, Madison, WI). PCR products were purified using

an enzymatic reaction containing 5U of Exonuclease (Celbio) and one U of Alkaline Phosphatase (Promega) according to these conditions: 15 min at 37°C followed by 15 min at 80°C. Fragments purified were sequenced in both forward and reverse directions using BigDye v3.1 terminator technology (Applied Biosystems) and then purified with the enzymatic reaction described above. Sequence reactions were analyzed on an ABI Prism 3100 Avant Automatic Sequencer (Applied Biosystems). Mutations detected from sequencing were further confirmed by a repeated PCR sequencing.

The reduced glucocerebrosidase enzyme levels and demonstration of Gaucher cell infiltration in the bone marrow and liver in addition to the clini-

cal and laboratory findings allowed us to establish the diagnosis of Gaucher type 1. Following the establishment of diagnosis, glucocerebrosidase enzyme (Cerezym® 400U imiglucerase; Genzyme Europe B.V. Gooimeer 10, 1411 DD Naarden-NL) was administered by intravenous infusion at 60 units/kg, every 15 days in order to replace the enzyme levels.

Informed consent was obtained from the patient.

DISCUSSION

Gaucher's disease classically has three clinical types. Type I Gaucher's disease is the most common form and is defined as non-neuropathic or adult-type Gaucher's.¹⁻³ Type 1 Gaucher's disease might present with hepatosplenomegaly due to infiltration of the liver and spleen, anemia, thrombocytopenia due to bone marrow infiltration, bone damage due to involvement of the skeletal system and even pathological bone fractures.¹⁻³ Type 2 Gaucher's disease is defined as the acute neuropathic or infantile type. It presents with neurologic signs in the first six months of life and results in death at about the age of two. Type 3 is the subacute neuropathic Gaucher's disease which presents clinically at about the age of 10 predominantly with neurological symptoms.

Hepatomegaly is the most common finding observed in more than 70% of the patients with type I Gaucher's disease.¹⁰ Although hepatomegaly is a common finding, findings of hepatic failure or portal hypertension are rarely seen. However in the study of Lanchmann et al. performed on four adult cases, complications of portal hypertension developed and three patients died in the follow-up due to sepsis, and one patient received orthotopic liver transplantation due to uncontrollable variceal bleeding.¹⁵ Necroscopic examination of the patients showed diffuse fibrotic bands starting from the sinusoidal spaces with islets of normal hepatocytes in between.

Gaucher's cells are predominant in the borders between fibrous bands and hepatocyte islets. Liver tissue examination demonstrated less Gaucher cells

in patients receiving enzyme replacement therapy compared to patients not receiving this treatment. One third of these patients were able to receive enzyme replacement therapy and clinically significant improvement was observed in bone lesions and hematological parameters. One of these three patients receiving replacement therapy underwent orthotopic liver transplantation due to frequently recurring variceal bleedings, and the remaining two patients died due to sepsis.

Another case presentation discussed a patient with type 1 Gaucher's disease without cirrhosis in liver biopsy but with the signs of portal hypertension. It was suggested that Gaucher cells pressurized the sinusoids and thus impaired hepatic flow resulting in portal hypertension.¹⁶

In this present case, there was abundant Gaucher cell infiltration with zonal distribution and fibrous bands separating the hepatocytes in the form of small islands in the histological examination of the liver. The exact mechanism of liver fibrosis is not known in Type 1 Gaucher's disease.^{2,15} Although Fellows et al. suggested that enlarged fibrous bands with no alive cells in the central location resulted in serial areas of necrosis with fibrotic tissue formation, James et al. examined the liver biopsies of 23 patients and concluded that they did not encounter any signs of necrosis.^{17,18} James et al. suggested that pericellular fibrosis initially occurred which was followed by cellular ischemia due to intense fibrosis and consequent cell death. This mechanism is thought to explain the acellular hyaline necrosis and calcification in the middle of the wide area of fibrosis. Another component of Gaucher's disease is the lack of hepatic inflammation despite the presence of hepatic fibrosis, which was the case in our patient.¹⁹ In addition, Gaucher's disease might involve multiple focal hepatic lesions resembling liver malignancy. These lesions develop secondary to infiltration of Gaucher's cells.²⁰

Other important findings of type 1 Gaucher's disease are anemia and thrombocytopenia due to both bone marrow infiltration and hypersplenism. As a result of bone and bone marrow infiltration, normal bone marrow tissue is replaced with Gauc-

her's cells. All three clones of the bone marrow were suppressed in our case resulting in anemia, leucopenia and thrombocytopenia.

Several complications resulting from bone and joint involvement may be seen in the course of Gaucher's disease. Patients may thus present with bone pain, Erlenmeyer flask deformity, osteopenia, osteonecrosis, osteosclerosis and pathological bone fractures. These complications might be asymptomatic or lead to serious and severe clinical pictures.²¹⁻²³ Osteonecrosis, also called avascular necrosis, is the most important and most disabling of the skeletal deformities observed in Gaucher's disease.^{24,25} Osteonecrosis is believed to be the bone death resulting from secondary ischemia due to chronic infarction. Necrotic process is irreversible after it has started. Femoral head, proximal humerus and vertebrae are involved and lead to fractures and joint collapse.²² Our patient had osteonecrosis of stage V/c according to the Steinberg classification characterized with avascular necrosis (Figure 1).²⁶ The patient was thus limping. Fractures due to osteonecrosis of the femoral head may be diagnosed in plane radiological examinations. Therefore plane X-rays should be used in diagnosing the complications.²⁷

Glycocerebrosidase enzyme replacement therapy was initiated at 60 units/kg after the establishment of diagnosis. This rare disease is

potentially curable and enzyme replacement therapy has been shown to be effective.²⁸ Early diagnosis and treatment of Gaucher's disease is utterly important, however in most cases the diagnosis is established in the late period. Although the case presented in this manuscript was diagnosed in the late period, enzyme replacement therapy was initiated in order to halt the disease progression and prevent harmful complications.

Enzyme mutation analysis of the patient showed N370S type mutation which is common in our country.²⁹ This mutation is one of the most common forms of mutation and is characterized by milder clinical forms.

Various hepatic complications including hepatic fibrosis, portal hypertension, cirrhosis, chronic active hepatitis, cholelithiasis and hepatocellular carcinoma might be observed in the liver due to Gaucher's disease.^{9,15-17,19,30-33} Our case presented with hepatosplenomegaly and pancytopenia with underlying Gaucher cell infiltrations in the bone marrow and liver with accompanying hepatic fibrosis, and no complications of cirrhosis or portal hypertension were present. Liver's synthesis functions were maintained and severe skeletal abnormalities were predominant in this non-neuropathic type 1 Gaucher's disease. This rare case has been discussed in the light of the literature.

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