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GAUCHER DISEASE TYPE 1 AND GASTRIC CANCER: A CASE REPORT

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Gaucher disease (GD is a liposomal storage disease that is inherited in an autosomal recessive manner. The basis of the disease is a mutation of the gene that codes for the enzyme glucocerebrosidase. The clinical division of GB into type 1, 2 and 3 is based on the absence (type 1) or presence (type 2 and 3) of manifestations by the central nervous system. In order to establish a definitive diagnosis, the level of β-glucose cerebrosidase in leukocytes and the value of chitotriosidase in the serum are determined. Genotype analysis is helpful in assessing the type and severity of the disease. Since 1991, Gaucher disease has been treated with enzyme replacement therapy (EST). We present the clinical characteristics of a patient with type 1 Gaucher disease diagnosed in November 2004 in the Hematology Clinic, UKC of Serbia. The patient was a heterozygous carrier of the N307S mutation. In February 2006, treatment was started with imiglucerase (Cerezyme^{R}) IV at a dose of 30 U/kg body weight every two weeks. After 24 months of imiglucerase therapy, a significant improvement in the patient's condition was registered, but she complained of nausea, an urge to vomit and pain in the epigastrium. MSCT of the upper abdomen was performed, and esophagogastroduodenoscopy with a biopsy of changes in the stomach. Pathohistological findings of biopsied changes in the stomach indicated the existence of gastric adenocarcinoma. A total gastrectomy with splenectomy and cholecystectomy was performed. PH finding was adenocarcinoma ventriculi intramucosum (early cancer). After the surgical intervention, the patient continued enzyme replacement therapy with imiglucerase. Patients with GD have an increased risk of developing malignant diseases, most often lymphoproliferative, although solid tumors (hepatocellular carcinoma) have also been described. In our case, to the best of our knowledge, the association of Gaucher disease with gastric cancer has been rarely reported in the literature.

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Key words: *Gaucher disease, enzyme replacement therapy, imiglucerase, gastric cancer*

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Introduction

Gaucher disease (GD) is the most frequent lysosomal storage disease caused by an autosomal recessive mutation in the beta glucocerebrosidase gene. The basis of the disease is a mutation of the gene that codes the enzyme glucocerebrosidase (1–5).

As a result of reduced enzyme synthesis, lack or disruption of enzyme function or saposin C (enzyme activator) deficiency, glucocerebroside accumulates in the macrophages of the liver, spleen, bone marrow, less often in the lungs and other organs, which causes numerous multiorgan complications (hepatomegaly, splenomegaly, anaemia, thrombocytopenia, skeletal and neurological changes) (1, 6–10).

The clinical division of GB into type 1, 2 and 3 is based on the absence (type 1) or presence (type 2 and 3) of manifestations by the central nervous system (1, 10).

Type 1 is the most frequent form and it can vary from asymptomatic forms to the forms with severe complications in childhood and adult period. It is characterized by visceral and skeletal involvement. Clinical manifestations include hepato- and splenomegaly, anaemia, leukopenia, thrombocytopenia, bone changes, and pulmonary disease (1).

Type 2 is the acute and lethal neuronopathic form and type 3 Gaucher disease is the chronic neuronopathic form with visceral, skeletal and cardiac involvement.

The variegated pathology observed in Gaucher disease is not only a consequence of the deposition and mechanical effect of glucocerebroside but also the activation of macrophages and the secretion of cytokines. In the serum of these patients, the level of interleukin 1b, interleukin 6, TNF alpha, soluble interleukin 2 receptor, as well as CD14 was elevated (11−14).

In order to establish a definitive diagnosis, the level of β-glucose cerebrosidase in leukocytes is determined (6, 10). The presence of Gaucher cells in the bone marrow and other tissues is not pathognomonic for Gaucher disease because it can be found in a number of other diseases (acute and chronic lymphoproliferative diseases, chronic granulocytic leukemia, thalassemia). Genotype analysis is helpful in assessing the type and severity of the disease.

In biochemical analyses of patients with Gaucher disease, there are elevated levels of acid phosphatase, ferritin and angiotensin-converting enzyme (ACE) in the serum, which is a consequence of their intense secretion from Gaucher cells and monocyte precursors. In patients with Gaucher disease, a markedly elevated value of the enzyme chitotriosidase, which originates from Gaucher cells, is registered and an indication of macrophage activation and immune response induction (1, 15−18).

Since 1991, Gaucher disease has been treated with enzyme replacement therapy (EST), i.e., replacement of β-glucocerebrosidase with an enzyme obtained by recombinant technology (aglucerase, imiglucerase, velaglucerase, taliglucerase alfa). The therapy is effective, corrects anaemia, thrombocytopenia, and organomegaly, improves bone status and side effects are rare (10, 18−25).

In the serum of patients with Gaucher's disease, the activity of chitotriosidase, a human chitinase produced by tissue macrophages, is typically increased. The level of chitotriosidase is used as a surrogate marker of the total amount of deposited glucocerebroside in the body to assess the effect of EST.

Case presentation

We present the clinical characteristics of a patient with type 1 Gaucher disease, in whom the diagnosis of the disease was established by determining glucocerebrosidase in leukocytes and genotype based on PCR and direct gene sequencing. In this patient, the level of chitotriosidase was monitored as a reliable indicator of the amount of accumulated substrate.

We present the results of monitoring and treatment of a patient who was on enzyme replacement therapy.

In October 2004, a 52-year-old female patient, deaf-mute since birth, was admitted to the Infectious Department of the Health Centre in Prokuplje because of fever (38.5 ^{0}C), weakness and pain in the right hip. On admission, she had accelerated sedimentation (SE 100 mm/h), and mild anaemia (Hgb 117 g/L). In addition, multiple osteolytic lesions were observed on the X-ray image of the right femur, which were interpreted as secondary deposits. The patient was referred to the Clinic of Hematology, University Clinical Centre Niš for further examination. A magnetic resonance imaging (MRI) of the thoracolumbar spine and both femurs was performed. It indicated an Erlenmeyer flask deformity of both femurs, the presence of infarct lesions in the distal third of the diaphysis of the left femur, and altered signal intensity of the vertebral bodies Th9, L1, and L3-changes suggested fat infiltration (Figure 1).

Suspecting the existence of a lipid thesaurus, the patient was referred to the Institute of Haematology, University of Belgrade. Based on the decreased activity of β-glucocerebrosidase in peripheral blood leukocytes (1.2 nmol/h/mg protein), elevated levels of the chitotriosidase enzyme (8788 nmol/ml/h), acid phosphatase (12.6 U/L), ferritin (2359.4 ng/ml), hepatosplenomegaly (confirmed by ultrasound examination of the abdomen, computerized tomography of organs, CT volume of organs—liver 2614 ccm, spleen 539 ccm), with the finding of Gaucher cells in the bone marrow punctate, the patient was diagnosed with Gaucher disease type 1 in November 2004. The type of genetic mutation pAsn409ser (N3075)/p.Ser146Leu(S107) was determined. The patient was a heterozygous carrier of the N307S mutation.

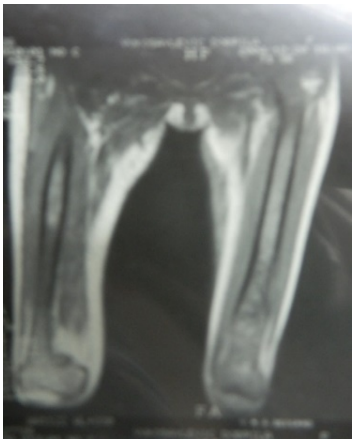
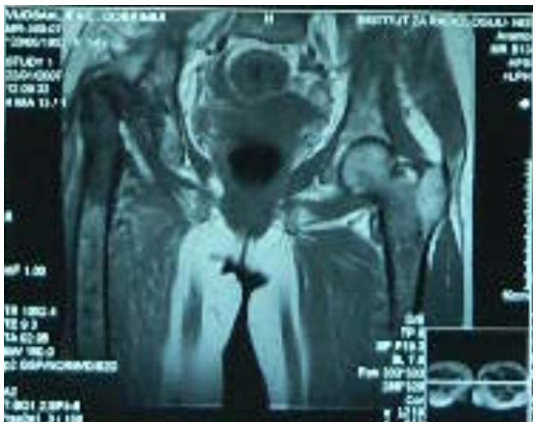
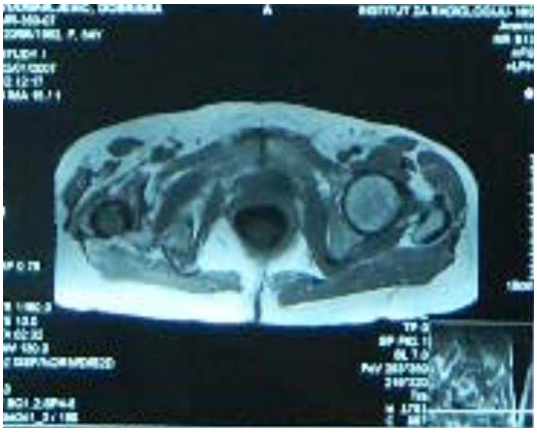


Figure 1. MRI of the femur: Erlenmeyer flask deformity of both femurs





Figures 2 and 3. MRI of the femur and right hip

As a part of the humanitarian program in February 2006, the treatment with imiglucerase (Cerezyme R) was started at a dose of 30 U/kg IV every two weeks. At the time of starting the therapy, the patient was immobile and bedridden, with intense pain in her right hip. She had a mild anaemia (Hgb 106 g/L). The magnetic resonance imaging (MRI) of the femur and right hip showed a fracture of the head of the right femur, and signs of infarction of the upper third of the right femur (Figures 2 and 3). The bone densitometry showed osteopenia, a T-score on the lumbar spine of -2.04, T-score on the hip joint of -0.3 (Figure 4).

In January 2007, after 11 months of imiglucerase therapy, a significant improvement in the patient's condition was registered. The patient moved with the help of a cane, and the pain in the right hip was less intense. Anaemia was corrected (Hgb 135 g/L), and chitotriosidase values decreased (5638 nmol/ml/h), as did acid phosphatase (8.25 U/L). The organ volumetry showed changes in the liver and spleen (liver 1283 ccm, spleen 238 ccm) (Figure 5). The bone densitometry (DEXA) showed osteopenia, a T-score on the lumbar spine of -1.7, T-score on the hip joint of -0.3 (Figure 6).

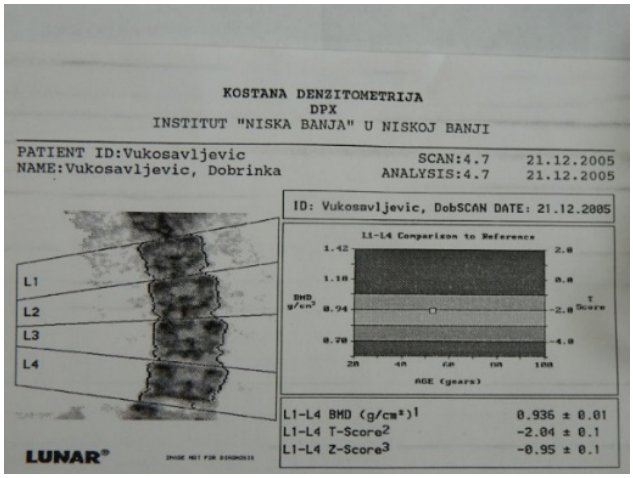


Figure 4. DEXA of the lumbar spine: osteopenia

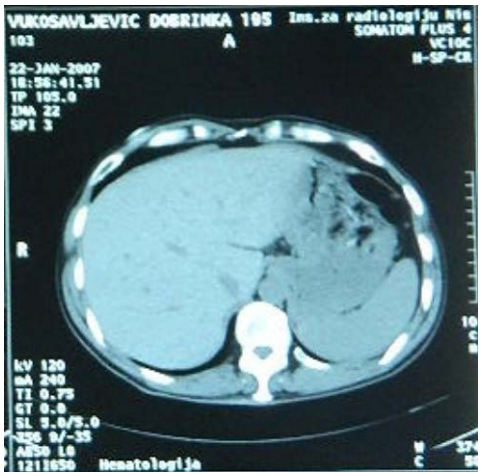


Figure 5. The organ volumetry of the liver and spleen

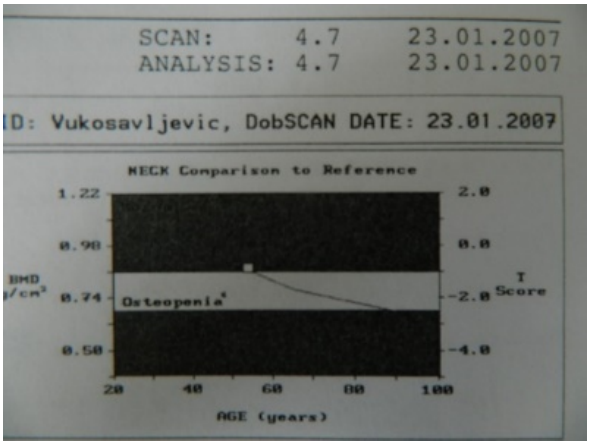


Figure 6. DEXA of the lumbar spine and hip joint—osteopenia

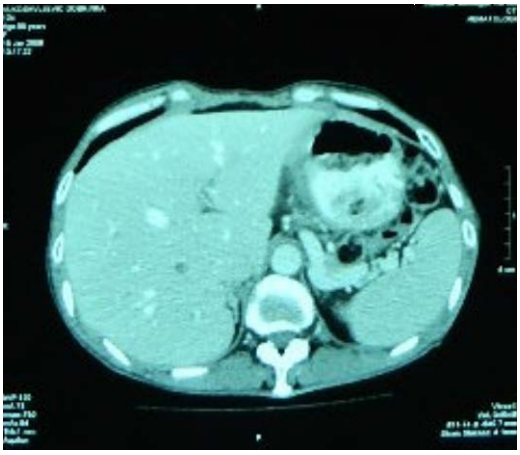


Figure 7. MSCT of the upper abdomen—an expansive change in the stomach

In February 2008, 24 months after the therapy, the patient was mobile and walked without the help of a cane, but she complained of pain, nausea and pain in the epigastrium. Because of the new complaints, an examination of the underlying disease was performed (blood count, biohumoral examination, chitotriosidase value of 3956 nmol/ml/h, echotomography and CT volumetry of the liver and spleen, MRI of the hips and lumbar spine) which indicated the stability of the underlying disease.

Because of the present complaints, in January 2008, an MSCT of the upper abdomen was performed, which indicated an expansive change in the stomach with a secondary spread in the liver (3 focal changes in the VII segment of the liver, the posterior wall of the stomach with irregular contours, greatly thickened in the antropyloric segment (Figure 7). An esophago-gastroduodenoscopy in January 2008 indicated a bizarre ulcer-vegetative change from the antrum to the corpus of the stomach which partially deformed the lumen of the stomach and this change was biopsied. In order to make a precise diagnosis, an MRI of the abdomen was performed in January 2008 which showed a suspect mass intraluminally in the stomach, and the presence of a cyst in the liver. The pathohistological findings of the biopsied changes in the stomach were obtained in January 2008 and indicated gastric adenocarcinoma, PH Gastric microglandular adenocarcinoma, Chronic gastritis with intestinal metaplasia.

In February 2008, the patient underwent total gastrectomy with splenectomy and cholecystectomy at the Clinic of Surgery of the Clinical Center Niš. The pathohistological findings of the operative material were obtained in March 2008. Microscopic findings of the stomach revealed superficial type of early gastric carcinoma

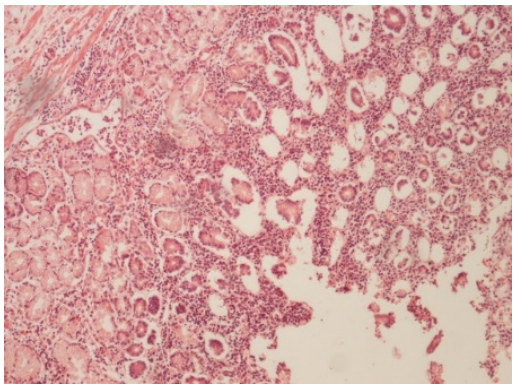
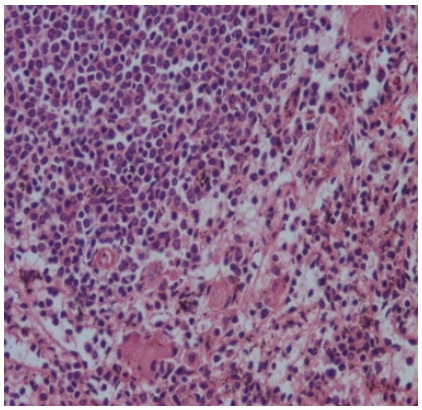
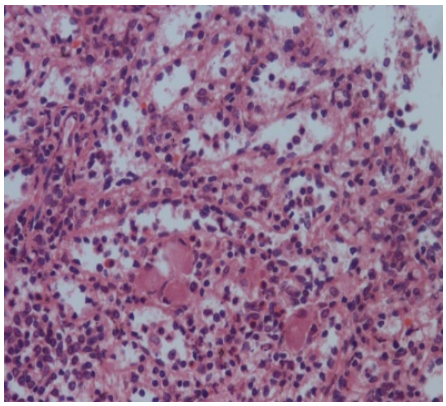


Figure 8. Adenocarcinoma ventriculi intramucosum (early cancer): HE x 150 (Hematoxylin and eosin stained)





Figures 9 and 10. Spleen with Gaucher cells. HE 100, HE X 200

Type 0-IIc surrounded by atrophic gastritis with intestinal metaplasia, chronic atrophic gastritis grade II with atypical foveolar hyperplasia grade I-II, gastric intramucosal adenocarcinoma (early cancer), surrounding lymph nodes without metastatic process (Figure 8), chronic cholecystitis with fibrosis calcification and atrophy, spleen with Gaucher cells (Figure 9, 10).

After the surgical intervention, the patient continued enzyme replacement therapy with imiglucerase in agreement with the responsible member of the Gauche registry.

In December 2010, the patient was in good general condition during the check-up, and she was actively mobile. The pain in the right hip was still present and the patient described it as a pain of low intensity. There were no significant complaints related to the digestive tract. Blood count and hemostasis tests were normal. Chitotriosidase activity was 3956 nmol/ml/h. X-ray and MRI of the hips and lumbar spine showed no significant changes compared to previous findings. Bone densitometry showed worse findings of osteoporosis in the lumbar spine (T-score was -2.7) and the left hip joint (T-score was -2.4). Echocardiography showed preserved global contractile function of the left ventricle, EF was 65%, and mean pressure in the right ventricle was 33 mmHg. The liver was without significant changes compared to the previous finding, determined by CT volumetry (liver volume was 1300 ccm). Electrophoresis and immunofixation of serum proteins were performed on several occasions, always without signs of monoclonal gammopathy.

The patient was on enzyme replacement therapy until 2011, when the therapy was stopped because of the unavailability of the drug due to the termination of the donation. Since 2015, a gradual worsening of the condition has been registered, a decrease in independent mobility, hip pains were more pronounced, there were deformities and swelling of both knees and the patient became bedridden again. Anaemia was registered (Hgb was 10.9g/dl), while leukocytes, platelets and hemostasis tests were normal. X-ray of the pelvis revealed a deformed pelvis. Changes predominated on the right, with deformity of the ipsilateral iliac and pubic bones and ischial axis. Bone structures of the first order were damaged. Changes dominated along the proximal metaphysis and epiphysis of the right femur, as well as in the acetabulum itself. The right hip joint was deformed, joint edges were destroyed, with

irregular bone structure and irregular linear marginal osteosclerosis (Figure 11).

X-ray of the knee showed that the distal half of the femur was deformed, club-like, thinned compact. The bone was inhomogeneous, with traces of darkness, in the distal third it looked like a cluster, which most likely corresponded to bone infarcts. The proximal ends of the tibia were deformed, with signs of fragmentation. The joint crack of both knees was narrowed and deformed, and the contours of the picture were disturbed (Figure 12).

X-ray of the lumbosacral spine showed degenerative changes in the lumbosacral vertebrae, narrowing of the intervertebral space L5-S1 and atrophy of bone tissue with signs of osteoporosis.

Bone densitometry shows severe osteoporosis in the lumbar spine, T-score was -5.2 (Figure 13).

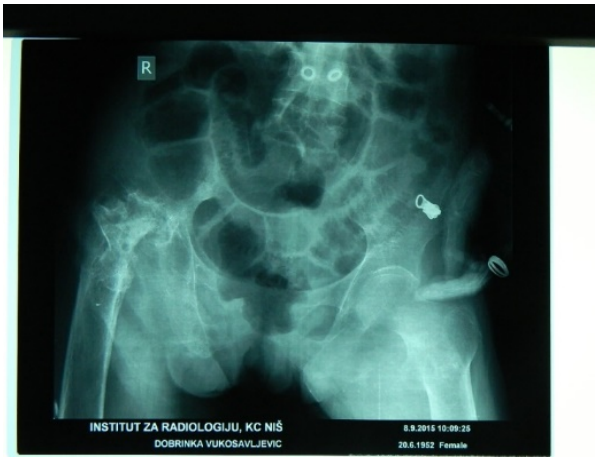


Figure 11. X-ray of the pelvis

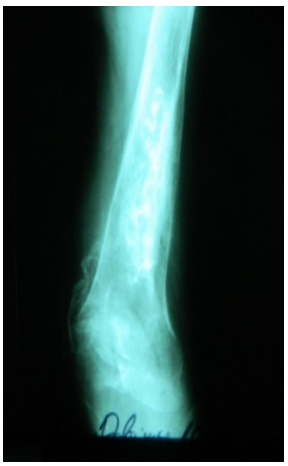


Figure 12. X-ray of the knee

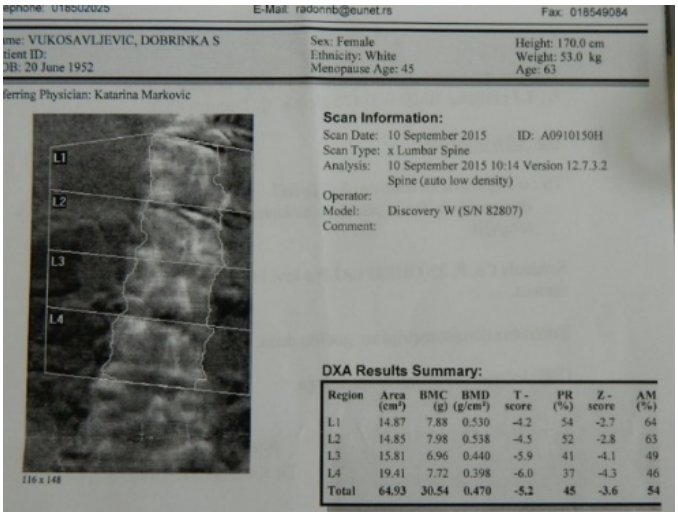


Figure 13. DEXA of the lumbar spine: severe osteoporosis

Discussion and conclusion

This is a case report of a rare association of GD and gastric cancer (26). Patients with GD have an increased risk of developing malignant diseases, most often lymphoproliferative, although solid tumours (hepatocellular carcinoma) have also been described (27–30). The association of GD with multiple myeloma, monoclonal gammopathy of undetermined significance (MGUS), chronic lymphocytic leukemia, marginal zone lymphoma and amyloidosis is found in the literature. A statistically increased risk of the

disease has been proven only for multiple myeloma (31–34).

As possible mechanisms of carcinogenesis in patients with Gaucher disease, the constant stimulation of the immune system by accumulated glucocerebroside as well as the carcinogenic action of glucocerebroside and its metabolites are mentioned. Zimran mentions the onset of malignancy as a complication of long-term enzyme therapy and suggests that in mild forms of the disease, treatment is not indicated, especially not with high doses, because the potential harm is greater than the benefit (19, 30, 35).

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GOŠEOVA BOLEST TIP 1 I KARCINOM ŽELUCA: PRIKAZ SLUČAJA

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Gošeova (Gaucher) bolest (GB) jeste lipozomalna bolest nakupljanja koja se nasleđuje autozomno-recesivno. U osnovi bolesti nalazi se mutacija gena koji kodira enzim glukocerebrozidazu. Klinička podela GB-a na tip 1, 2 i 3 zasniva se na odsustvu (tip 1) ili prisustvu (tip 2 i tip 3) manifestacija od strane centralnog nervnog sistema. Sa ciljem postavljanja definitivne dijagnoze određuju se nivo β-glukozocerebrozidaze u leukocitima i vrednost hitotriozidaze u serumu. Analiza genotipa od pomoći je u proceni tipa i težine bolesti. Od 1991. godine Gošeova bolest leči se enzimskom supstitucionom terapijom (EST). U ovom radu prikazuju se kliničke karakteristike bolesnice sa tipom 1 Gošeove bolesti kojoj je bolest dijagnostikovana novembra 2004. godine na Insititutu za hematologiju Univerzitetskog kliničkog centra Srbije. Bolesnica je bila heterozigotni nosilac mutacije N307S. Februara 2006. godine započeto je lečenje imiglucerazom (*Cerezyme*^{R}), sa dozom od 30 U po kilogramu telesne težine i. v. na svake dve nedelje. Iako je posle 24 meseca terapije zabeleženo značajno poboljšanje stanja bolesnice, ona se žalila na mučninu, nagon na povraćanje i bolove u epigastrijumu. Urađeni su multidetektorska kompjuterizovana tomografija (engl. *multislice computed tomography* – MSCT) gornjeg abdomena i ezofagogastroduodenoskopija sa biopsijom promene u želucu. Patohistološki (PH) nalaz promene u želucu ukazao je na postojanje adenokarcinoma želuca. Urađena je totalna gastrektomija sa splenektomijom i holecistektomijom. PH nalaz je pokazao da je posredi *adenocarcinoma ventriculi intramucosum* (*early cancer)*. Bolesnica je posle hirurške intervencije nastavila enzimsku supstitucionu terapiju imiglucerazom. Kod obolelih od GB-a povećan je rizik od nastanka malignih bolesti, najčešće limfoproliferativnih, mada je opisana i pojava solidnih tumora (npr. hepatocelularni karcinom). Prema našim saznanjima, Gošeova bolest udružena sa karcinomom želuca retko se pominje u literaturi.

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***Ključne reči**: Gošeova bolest, enzimska supstituciona terapija, imigluceraza, karcinom želuca*