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DIFFICULT CASE

Glycogen Storage Disease Ib and Crohn Colitis in a Young Woman

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The occurrence of inflammatory bowel disease in patients with glycogen storage disease Ib is rare (GSD-Ib). We present the case of a young woman with the diagnosis of GSD-Ib Crohn-like colitis developed at age 22. Clinical evaluation revealed severe malnutrition, secondary amenorrhea, leukopenia, neutropenia, dysfunctions of phagocytosis, and subtotal stenosis of the ascending colon. Right hemicolectomy was performed and pathohistologic analysis of the resected bowel showed chronic bowel inflammation consistent with Crohn disease. Clinical status of the patient markedly improved after surgery.

Key Words: Glycogen storage disease Ib; inflammatory bowel disease; Crohn's colitis.

Introduction

Glycogen storage disease (GSD) types Ia and Ib are rare metabolic disorders of carbohydrate metabolism *(1)*. They are characterized by hypoglycemia, growth retardation, and hepatomegaly *(2)*. In GSD-Ia, hepatic glucose-6-phosphatase activity is absent, while in GSD-Ib there is deficient hepatocyte microsomal transport of glucose-6-phosphate *(3,4)*. GSD-Ib can be distinguished from GSD-Ia by neutropenia and a severe neutrophil chemotactic defect *(5,6)*, resulting from defective translocase, which is essential for neutrophil function *(6)*. Frequent infections and anal and oral mucosal lesions are well documented in GSD-Ib but are not characteristic of GSD-Ia, in which abnormalities of either neutrophil number or function have not been described *(1,2, 7)*. Crohn-like colitis is very rarely encountered in patients with GSD-Ib, and its occurrence is associated with long-lasting low-grade bowel infection *(2)*. We present a rare case of a young Caucasian female with GSD-Ib who developed Crohn-like regional colitis and moderate neutropenia refractory to conservative corticosteroid treatment.

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Results and Discussion

The occurrence of Crohn-like colitis in patients with GSD-Ib is rare *(2,7)*. Our case patient was a 22-yr-old woman with the diagnosis of GSD-Ib, confirmed by physical and biochemical examinations. Immunologic assessment revealed markedly reduced ingestion and microbicidal functions of granulocytes and monocytes, with leukopenia and neutropenia. These changes are reported to be predisposing factors for the development of acute and chronic inflammation of digestive tract mucosa *(7)*. Crohn-like IBD is associated with primary neutrophil deficits, and, conversely, various disorders of the oxidative metabolism of neutrophils are linked to Crohn disease *(8,9)*. These observations suggest that neutropenia and neutrophil dysfunction in patients with GSD-Ib predispose to the development of IBD *(7)*. Our patient developed Crohn-like colitis at the age of 22, confirming the hypothesis that long-lasting low-grade bowel infection, resulting from neutrophil deficiency, may predispose such patients to chronic inflammation *(2)*. The severity of bowel inflammation and the degree of bowel stenosis resulted in marked catabolic state, manifested as a severe reduction in BMI, central hypothalamic hypofunction, and secondary amenorrhea. After successful surgical treatment, these dysfunctions subsided.

The activity of G-6-Ptase in the frozen liver biopsy specimen was within the normal range, confirming the diagnosis of GSD-Ib. This enzyme is deficient in GSD-Ia, and normal values are found in GSD-Ib after hepatic microsomes are disrupted with freezing or by exposure to deoxycholate *(7)*.

Although successful treatment with granulocyte colony-stimulating factor (G-CSF) has been described in GSD-Ib patients with neutropenia *(2)*, we did not utilize this therapy in our patient. G-CSF in neutropenic patients normalizes the absolute leukocyte and neutrophil counts and oxidative metabolism, but with no improvement in chemotactic function *(2)*. Since the bone marrow biopsy in our patient showed mature myelopoiesis, we did not treat her with G-CSF.

Most of the symptoms and dysfunctions related to Crohn colitis subsided after surgery, the patient was gaining weight, and normal menstrual cycles were restored. Large bowel enema 1 yr after surgery showed normal morphology of both the small and large intestines. The patient is currently receiving oral mesalazin therapy, with no clinical signs of active Crohn disease.

Materials and Methods

A 22-yr-old female with the diagnosis of GSD-Ib was hospitalized at the Clinical Hospital "Sestre Milosrdnice." The patient was born as the seventh child of a 39-yr-old mother. There was no family history of either GSD or inflammatory bowel disease (IBD). Vomiting and diarrhea started immediately after birth, and growth failure was apparent at early months. The diagnosis of GSD-Ib was established at 10 mo. The patient began to talk at 12 mo and to walk at 14 mo. Menarche occurred at the age of 11, and was immediately followed by secondary amenorrhea.

In March 1999, at the age of 22, the patient was hospitalized in the Department of Internal Medicine because of abdominal pain and constipation. Physical examination revealed short stature and malnourishment (height = 145 cm, weight = 30 kg, body mass index [BMI] = 14.2 kg/m^2), round face, and scanty hair. The liver was enlarged 5 to 6 cm below the right costal margin. Blood analysis showed marked leukopenia (2100/μL, normal: 4000–10,000/μL) and neutropenia with 19.9% neutrophils (normal: 42.2–75.2%).

Although there were no typical symptoms of Crohn disease, appart from abdominal pain, the presence of leukopenia and neutropenia in this patient with GSD-Ib suggested further examination of the gastrointestinal tract. Double contrast barium enema showed narrowing and a polyp of the ascending colon (Fig. 1), and stenosis was confirmed by colonoscopy. Histologic examination revealed a transmural chronic inflammation consistent with the diagnosis of Crohn disease.

Serum levels of triglycerides, cholesterol, lactate, and uric acid were elevated (Table 1). For the glucagon test, there was no increase in the level of blood glucose, and the level of insulin remained normal.

Low levels of gonadotropins, estrogen, and progesterone were noted, but gonadotropin response was normal in the luteinizing hormone–releasing hormone test, possibly indicating a central (hypothalamic) disorder as a result of severe catabolic condition, leading to secondary amenorrhea.

Leukocyte function tests revealed marked deficiency in phagocytosis (Table 2). No circulating antigranulocyte or antileukocyte antibodies were found. The count of T-lymphocytes (CD3$^+$, CD4$^+$, CD8$^+$) was low, while the count of B-lymphocytes (CD19$^+$) was within the normal range (Table 3). Bone marrow aspirate was normal with mature granulopoiesis. Total leukocyte and neutrophil count remained below the normal range on repeated assessments.

Fig. 1. Double contrast barium enema of colon showing stenosis of ascending colon.

Table 1
Serum Biochemical Values

Test	Result (mmol/L)	Normal values
Triglycerides	6.34	0.85–2.0 mmol/L
Cholesterol	7.13	3.8–5.7 mmol/L
Lactate	7.1	0.67–2.47 mmol/L
Uric acid	493	120–420 μmol/L

Table 2
Leukocyte Function Tests

Test	Result	Referral values
Granulocyte ingestion	0.98	2.70–3.90
Granulocyte microbicidal activity (%)	2	6–12
Monocyte ingestion	0.16	0.90–2.00
Monocyte digestion (%)	18	40–65

Since bowel movements were still maintained, without threatening obstruction, it was decided to treat the patient with high doses of corticosteroids (8 mg of methylprednisolone daily, given orally). In September 1999, the patient was again hospitalized because of abdominal pain and constipation. Repeated endoscopic examination of the colon

Table 3
Concentrations of T- and B-Lymphocyte Subpopulations

Test[a]	Result	Control
$CD3^+$	0.345×10^9/L	$1.210–2.180 \times 10^9$/L
$CD4^+$	0.208×10^9/L	$0.830–1.550 \times 10^9$/L
$CD8^+$	0.244×10^9/L	$0.450–0.900 \times 10^9$/L
$CD19^+$	0.048×10^9/L	$0.100–0.330 \times 10^9$/L

[a] $CD3^+$, $CD4^+$, $CD8^+$ = T-lymphocytes; $CD19^+$ = B-lymphocytes.

Fig. 2. Control double contrast barium enema of colon 1 yr after surgery showing normal morphology of ileal-transversal anastomosis.

showed progression of the stenosis. Steroids were gradually withdrawn; a combined oral and parenteral hyperalimentation was started; and at surgery, chronic obstructive inflammatory process of the right colon was found. Right hemicolectomy and primary termino-terminal anastomosis was performed. Intraoperative liver biopsy was done for assessment of G-6-Ptase activity.

Histologic examination of the resected bowel revealed a chronic transmural inflammatory reaction with prominent lymphocyte infiltration in the muscularis mucosa and subserosa, and with five chronic reactive lymph nodes. No granulomas were seen. Findings were consistent with the diagnosis of Crohn disease. Postoperative course was uneventful, and the patient was discharged after 22 d of treatment with 250 mg of oral mesalazin three times daily. G-6-Ptase activity in the liver specimen was 4.45 μmol/(min·g) (normal: >2 μmol/[min·g]), thus confirming the diagnosis of GSD-Ib.

As of September 2000, there were no signs of active Crohn disease, the patient was gaining weight (43 kg at that time), and normal menstrual cycles were established. Control double contrast barium enema of the colon revealed regular ileotransversal anastomosis (Fig. 2). Leukocyte count and the percentage of neutrophils were still low (white blood cell count = 2500/μL, neutrophils = 18.6%).

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