Primary intestinal lymphangiectasia in adults – diagnostic and therapeutic challenge

Primarne intestinalne limfangiektazije kod odraslih – dijagnostički i terapijski izazov

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Abstract

Introduction. Primary intestinal lymphangiectasia is a rare disorder, characterized by abnormal dilation of intestinal lymphatic vessels and extensive enteric loss of lymph rich in plasma proteins, lymphocytes and chylomicrons. The main characteristics of the disease are hypoalbuminemia, hypogammaglobulinemia, lymphocytopenia, and more rarely, the deficit of liposoluble vitamins and anemia. Except for primary, there are secondary lymphangiectasia, associated with celiac disease, malignant, infective and inflammatory diseases of the small intestine, fibrosis, liver and cardiovascular diseases.

Case report. A male, 33 years of age, presented for his medical examination suffering from diarrhea and edema. The diagnosis was established upon the histological examination of a small intestine biopsy during double balloon enteroscopy, which revealed changes only in one segment of the intestine examined. Such a finding was later confirmed by the video endoscopy capsule.

Conclusion. The diagnosis of intestinal lymphangiectasia is usually established before the age of 3, but it can also be diagnosed in adults. The diagnosis is based on the histological analysis of the intestinal mucosa biopsy, obtained by endoscopic procedures. The diagnosis of primary intestinal lymphangiectasia is also made upon the exclusion of secondary causes.

Key words: diarrhea; lymphangiectasis; hypoalbuminemia; lymphopenia; protein-losing enteropathies.


Ključne reči: dijareja; limfangiektazija; hipoalbuminemija; limfocitopenija; enteropatije sa gubitkom proteina.

Introduction

Primary intestinal lymphangiectasia (PIL) is characterized by abnormally dilated intestinal lymphatic vessels and an extensive enteric loss of lymph rich in plasma proteins, lymphocytes and chylomicrons. The disorder was first described by Waldmann et al. in 1961. The main characteristics of the disease are hypoalbuminemia, hypogammaglobulinemia, lymphocytopenia, and more rarely, the deficiency of liposoluble vitamins and anemia. Except for primary, lymphangiectasia can
be secondary, as a consequence of lymphoma, mesenteric tuberculosis and sarcoidosis, Crohn’s disease, Whipple’s disease, celiac disease, retroperitoneal carcinoma or fibrosis, chronic pancreatitis, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, congestive heart failure, constrictive pericarditis, Budd-Chiari’s syndrome, sclerosing mesenteritis and intestinal endometriosis. The prevalence of the disease is not known, and thus far approximately 300 cases have been described in the literature. In most cases, it is diagnosed between ages 3 and 10 (being rare among adolescents and adults). The precise etiology is unknown, but it is considered to be related to the change in the regulatory molecules involved in the lymphangiogenesis in the intestinal mucosa, with the consequent lymphatic hypoplasia, lymph flow obstruction, which leads to the elevated pressure in the lymphatic vessels, their dilation, rupture and lymph leakage into the intestine lumen. The disease is clinically manifested with edemas in lower extremities, less frequently in the face or scrotum, effusions (pleural, pericardial, ascites), diarrhea or subocclusive intestinal disorders, rarely with anemia, fat and liposoluble vitamin malabsorption. Intestinal lymphangiectasia (IL) is diagnosed on the basis of the histological analysis of intestinal mucosa. The diagnosis of PIL is also made upon the exclusion of secondary causes.

Case report

A 33 years-old patient, was hospitalized under suspicion of nephrotic syndrome, with lower limb swelling, moderate diarrhea, with general weakness and fatigue. He had no history of previous disease or relevant hereditary diseases, occasionally consumed alcohol and was a smoker. The objective examination revealed that the patient’s general condition was good; Body mass index (BMI) was 19.6 kg/m² (normal range (nr): 18.5–25 kg/m²), with prominent edemas in the lower limbs and normal findings in the organ systems. The laboratory findings indicated marked hypoproteinemia [(29 g/L (nr 60–80 g/L)], hypoalbuminemia [(15.4 g/L (nr 35–50 g/L)], with low immunoglobulin levels IgG 2.04 g/L (nr 6.1–16 g/L) and IgM 0.25 g/L (nr 0.4–2.3 g/L), while the values of IgE and IgA are normal. Proteinuria was not within the nephrotic range (24h-proteinuria 239 mg/diuresis). The count of leukocytes was normal, but with the presence of lymphocytopenia [0.36 ×10⁹/L (nr 2–8 × 10⁹/L)]. The parameters of renal and liver functions and the acute phase reactants were within the reference range. Tissue transglutaminase IgA antibody levels were negative and so were the HBsAg, anti HCV and anti HIV. Abdominal ultrasound examination revealed ascites. After the systemic disease of connective tissue was excluded, the suspicion of protein-losing enteropathy was assumed. Upper endoscopy showed the mucous membrane of the descending duodenum which was lightly edematous, whereas the histological finding corresponded to the chronic enteritis without atrophy PAS positive macrophages and polymorphonuclears. Ileocolonoscopy and histological findings are normal and the computed tomography (CT) scan of the abdomen showed a lightly dilated small intestine, with the diffuse edematous wall, without lymphadenomegaly, thrombosis, or changes in the retroperitoneum. Enteroclysis revealed the jejunum with partially thickened folds, and the double balloon (DB) enteroscopy of the proximal jejunum detected several polypoid changes 6–8 mm in diameter (single and clustered) in the bowel segment approximately 15 cm long (Figure 1). The histological examination detected intestinal villi of regular height, some of which were dilated due to enlarged lymph ducts. In the lamina propria there were slightly to significantly enlarged lymph ducts with slight infiltration of lymphocytes, plasmocytes and a lesser count of eosinophils. This finding corresponds to chronic enteritis with lymphangiectasia (Figure 2). In order to evaluate the extent of the changes in the small intestine, video endoscopy capsule examination was performed and it revealed polypoid changes with sporadic white spots, arranged in groups (Figure 3). In view of the histological findings and the patient’s age, further examinations were performed in order to exclude secondary causes of IL. Echocardiography excluded congestive heart failure and constrictive pericarditis, and negative angiotensin-converting enzyme (ACE) and purified protein derivative (PPD) tests, as well as subsequent Mycobacterium tuberculosis.
lose test excluded sarcoidosis and tuberculosis. The bacteriological stool test excluded an infective etiology. The diagnosis of PIL was made on the basis of typical clinical, endoscopic findings and histological confirmation with laboratory findings of lymphocytopenia, hypoalbuminemia, hypogammaglobulinemia and deficiency of proteins (transferrin, ceruloplasmin, fibrinogen), after the exclusion of potential causes of secondary lymphangiectasia. The treatment recommended a diet with a limited intake of fats with the use of medium-chain fatty acids. The hypoalbuminemia was treated with the administration of parenteral albumin preparations. In the subsequent course of the disease the patient did not consistently comply with the dietary recommendations for financial reasons, and as a result was occasionally hospitalized for parenteral albumin administration.

Discussion

IL is characterized by lymph and lymphocyte leakage into the small intestine lumen, due to the dilation of the lymph vessels of the intestinal wall and mesentery. It can be classified into primary and secondary. PIL is a rare disease with approximately 300 cases described in the literature. The prevalence is unknown and is increasing with the introduction of endoscopic video capsule and enteroscopy diagnostic procedures. There is no difference in prevalence between gender, and is most commonly diagnosed between ages 3 and 10, and rarely among adolescents and adults. Secondary lymphangiectasia develops as the consequence of lymph flow obstruction caused by other diseases. Our patient was diagnosed with PIL upon the exclusion of secondary causes of lymphangiectasia (celiac disease, malignant diseases, infective or inflammatory diseases, fibrosis, liver or cardiovascular diseases). The disease is clinically manifested with edemas, effusions (pleural, pericardial, ascites), diarrhea, rarely with obstructive ileus, anemia, malabsorption of fats and liposoluble vitamins.

Alpha-1 antitrypsin is a protein of molecular mass similar to albumin, and alpha-1 antitrypsin clearance is used for the confirmation of protein-losing enteropathy. Unfortunately, this diagnostic procedure was not available to us, so upon the exclusion of other causes of hypoalbuminemia and hypogammaglobulinemia, it was assumed that the disease involved was a protein-losing enteropathy. The loss of certain proteins and their levels in the serum can vary significantly. The lowest concentrations
are found in serum proteins with long half-life and slow synthesis, so the levels of IgG, IgM and IgA will be significantly reduced, while insulin and IgE will be normal due to their short half-life. Lymphophytopenia is a finding that suggests IL and is not found in other protein-losing enteropathies. PIL is not easily diagnosed due to localization of changes in the small intestine, which is the most difficult to access in endoscopic diagnostics. The detection of lesions by upper endoscopy and ileocolonoscopy is limited, while radiologic examination cannot confirm the diagnosis. The diagnosis is made on the basis of the histological examination of the intestine biopsy obtained with DB enteroscopy or the intestine resectate examination. Video endoscopic capsule is more frequently used to detect the disease, and also enabling to determine its extent. In our case the diagnosis was made by small intestine biopsy taken of DB enteroscopy, where the changes were seen in one segment of the intestine examined, and the disease, localized in a single segment, was subsequently confirmed by video endoscopic capsule.

The main method recommended to treat PIL is diet with the reduced intake of fats containing long-chain fatty acids, since they turn into chylomicrons, leading to the obstruction of lymph vessels, elevated lymphatic pressure and lymph leakage. The consumption of medium-chain fatty acids (MCT) is recommended, since they are absorbed directly into the portal blood flow, resulting in the bypass of the lymphatic flow. By analyzing the literature and individual case reports (55 cases extracted), Desai et al. examined the influence of MCT diet in PIL therapy in pediatric population. They examined the outcome of the disease in 27 patients who were on MCT diet, out of which 63% had complete resolution of symptoms, in contrast to the group of 28 patients who were not on the diet and where only 35.7% showed complete resolution. Unfortunately, there is no curative or standard treatment of PIL. In several cases the beneficial effect of octreotide and is described in patients with diarrhea refractory to diet. Although the mechanism of the action is still not clear, it is believed that octreotide significantly reduces splanchic blood flow, thus reducing the intestinal absorption of fats. However, it does not have a significant effect on hypoaluminemia, since thus diarrhea recurs after the discontinuation of the medication. The usage of antipsorins in certain cases led to the increase in the level of T lymphocytes and serum immunoglobulins, and even the withdrawal of endoscopic changes, while corticosteroids were used with varying success. In the localized forms of the disease refractory to diet and medications, as an alternative, surgical procedures were successfully performed. Our patient’s clinical and laboratory improvement occurred after the application of dietary therapy and the parenteral albumin substitution.

PIL patients, in view of the lymphocyte loss, especially CD4+, develop a disposition to virus skin warts and B cell lymphomas, which increases with the duration of the disease. It is still not clear whether the occurrence of B lymphoma is accidental or if it is related to PIL. Five percent of patients in whom the disease persists over 30 years develop lymphoma that can be limited to the gastrointestinal tract, where the disease is localized, or can be extraintestinal. Although they have severe hypogamaglobulinemia and lymphopenia, the risk of the emergence of pyogenic bacterial and opportunistic infections is not significantly increased.

**Conclusion**

Primary intestinal lymphangiectasia is a rare disease which usually requires extensive diagnostics, especially in adult patients, in whom the diagnosis is made upon the exclusion of secondary causes of lymphangiectasia. In protein-losing enteropathy with lymphocytopenia, intestinal lymphangiectases should always be suspected, and regardless of the patient’s age, the possibility of primary intestinal lymphangiectasia should not be discarded. Despite the constant new findings about this disease, no significant advancement in the therapy of primary intestinal lymphangiectasia has been made. In the majority of patients medium-chain fatty acids diet is successfully applied to control the disease, while recurrence and complications are possible if there is no adequate compliance.

**REFERENCES**


Received on February 10, 2016.
Accepted on June 8, 2016.
Online First November, 2016.