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Lymphocytic colitis: an unexpected cause of chronic diarrhoea in a paediatric patient

Limfocytarne zapalenie jelita grubego: zaskakująca przyczyna przewlekłej biegunki u pacjenta pediatrycznego

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Abstract

This case report presents a paediatric patient diagnosed with lymphocytic colitis – a histological subtype of microscopic colitis. The disease is characterised by chronic, watery, non-bloody diarrhoea, a normal endoscopic image, but abnormal histopathological findings. While this condition predominantly affects adults, there are few published cases of lymphocytic colitis in the paediatric population. A five-year-old male patient with vitiligo and nephrotic syndrome was admitted for further diagnostic evaluation of chronic diarrhoea. Remission of the diarrhoea had previously been observed during steroid therapy for nephrotic syndrome, but the symptom recurred after discontinuation of treatment. A thorough differential diagnosis was conducted. Endoscopic examination revealed no macroscopic abnormalities. Only the histopathological examination confirmed the diagnosis of lymphocytic colitis. Although the association between microscopic colitis and certain autoimmune diseases is well-established, there are no reports of coexisting vitiligo or nephrotic syndrome in a child with lymphocytic colitis.

Keywords: lymphocytic colitis, vitiligo, nephrotic syndrome, child

Streszczenie

W pracy przedstawiono opis przypadku pacjenta pediatrycznego z rozpoznanym limfocytowym zapaleniem jelita grubego – histologiczną postacią mikroskopowego zapalenia jelita grubego. Choroba objawia się przewlekłą wodnistą biegunką, prawidłowym obrazem w badaniach endoskopowych i nieprawidłowym wynikiem badania histopatologicznego. Dotyczy głównie dorosłych, chociaż w literaturze opisano pojedyncze przypadki zachorowań dzieci. Pięcioletni chłopiec z bielactwem i zespołem nerczycowym został przyjęty do szpitala w celu dalszej diagnostyki przewlekłej biegunki. W przeszłości obserwowano jej ustępowanie podczas steroidoterapii prowadzonej z powodu zespołu nerczycowego. Biegunka nawracała po każdorazowym przerwaniu farmakoterapii. Podczas hospitalizacji przeprowadzono dokładną diagnostykę różnicową. Obraz makroskopowy w badaniach endoskopowych nie wykazał odchyleń od normy i dopiero wynik badania histopatologicznego ostatecznie potwierdził rozpoznanie. Związek pomiędzy mikroskopowym zapaleniem jelita grubego i niektórymi chorobami autoimmunologicznymi jest znany, ale nie ma doniesień o współwystępowaniu bielactwa lub zespołu nerczycowego u dziecka z limfocytowym zapaleniem jelita grubego.

Słowa kluczowe: limfocytarne zapalenie jelita grubego, bielactwo, zespół nerczycowy, dziecko

INTRODUCTION

Lymphocytic colitis (LC) – a histological subtype of microscopic colitis (MC) – was first recognised and described four decades ago[1]. LC is a rare intestinal disorder that typically manifests with chronic diarrhoea and abnormal inflammatory histopathological findings, but normal radiological and endoscopic results[2]. The diagnosis of LC is based on microscopic assessment of colonic mucosal biopsies, where characteristic abnormalities are found in macroscopically normal or near normal colonic mucosa[3]. As the condition affects primarily adults, paediatric data is limited. Very few cases of LC have been reported in the paediatric population and documented in the medical literature[4,5].

CASE DESCRIPTION

A five-year-old male patient with a history of psychomotor development disorder, vitiligo, and nephrotic syndrome (NS) diagnosed in October 2021 was admitted to the Department of Paediatric Gastroenterology and Hepatology in May 2022 for further diagnostic evaluation of chronic diarrhoea. The boy was born at term (38 Hbd) with a birth weight of 2,720 g by caesarean section due to oligohydramnios and threatening birth asphyxia (nuchal cord). The child scored 9/9 on the Apgar scale. During pregnancy, a cytomegalovirus infection, oligohydramnios, and nuchal cord were diagnosed. Echoencephalography and abdominal ultrasound were performed, with both showing no abnormalities. At 11 months, a neurological examination revealed a head circumference below the 3rd percentile, a closed anterior fontanelle, a flattened occiput, alternating convergent strabismus, decreased tension in the head-trunk axis, increased tension in the limbs, and abnormal electroencephalography (EEG), but without seizure activity and with normal magnetic resonance imaging (MRI) findings. Psychological examination based on the Child Development Assessment Scale showed a delay in psychomotor development below the 1st percentile. At 16 and 17 months, the boy was hospitalised in the neurology department following two generalised seizures preceded by an upper respiratory tract infection. At that time, the EEG was abnormal. Since birth, the boy has been under the care of a psychologist, speech therapist, and neurologist due to a history of seizures, muscle tension, and speech disorders. In addition, the patient has been under the care of a dermatologist due to the presence of vitiligo which first appeared when the boy was two years old. His mother noticed the first depigmented patch in the perianal area, and the disorder has since progressed, now affecting 70% of the skin surface (the face, trunk, back, and all extremities). The patient's father is also suffering from vitiligo, so there is a positive family history of the disease. In June 2021, the first episode of diarrhoea occurred (4–5 watery stools per day). Due to dehydration, the boy was admitted to a general paediatric ward, where an infectious cause was suspected. However, the hospitalisation did not confirm any infectious aetiology, and when the symptoms subsided, the boy was discharged. At that time, results of biochemical tests were within the normal range. Due to recurrent symptoms, consultation with an allergologist was recommended, but subsequent testing excluded any food allergies. At the end of September, the boy developed significant weakness, drowsiness, intense vomiting, swelling in the lower extremities, and oliguria during bronchitis. As a result, he was admitted to the general paediatric ward, where NS was suspected (based on laboratory findings of proteinuria, hypoalbuminaemia, and hypercholesterolaemia). The diagnosis of NS was eventually confirmed during his stay in the nephrology department. Due to the persistent watery stools, the boy was consulted in the gastroenterology unit, where an ultrasound examination revealed thickening of the terminal ileum wall up to 0.37 cm and surrounding lymphadenopathy. From October 2021, following the diagnosis of NS, the patient began receiving Encorton. During the period when the drug was administered, the diarrhoea resolved. However, after the discontinuation of corticosteroids in March 2022, the symptom recurred. Despite steroid therapy, no weight gain had been observed for about a year. On admission to the Department of Paediatric Gastroenterology and Hepatology, the child's general condition was assessed as good. Physical examination revealed severe vitiligo macules covering most of the skin, isolated atopic lesions (in the antecubital fossa), hypertonia of the limbs, alternating strabismus, ogival palate, and intellectual disability (with only non-verbal communication possible) (Fig. 1). Laboratory findings were normal, as were the results of the faecal calprotectin test. Ultrasound examination revealed small intestine loops fragmentarily filled with liquid content, with normal peristalsis, and widened loops of the large intestine with liquid content and very vigorous peristalsis. In the first place, the image ruled out an organic disease of the gastrointestinal tract. The macroscopic findings in both gastroscopy and colonoscopy were normal. Microscopic examination of H&E-stained sections showed prominent intraepithelial lymphocytes (IELs) in both the surface and crypt epithelium, along with increased cellularity of the lamina propria, composed mostly of plasma cells and a smaller number of lymphocytes. The crypt architecture was intact and undistorted (Fig. 2). On Masson-stained sections, there was no thickening of the subepithelial collagen (collagen band <10 μm) (Fig. 3). Although easily seen in H&E sections, CD3 staining highlighted IELs at >20/100 per surface epithelial cells (EC) (Fig. 4). With >20 IELs/100 EC, normal collagen thickness, and the clinical and endoscopic history, the patient was diagnosed with LC.

The patient was prescribed budesonide at a daily dose of 9 mg, which led to complete resolution of symptoms, with no diarrhoea observed. After three months, it was possible to reduce the dose to 9 mg every other day, with good results and no recurrence of diarrhoea. Previous attempts

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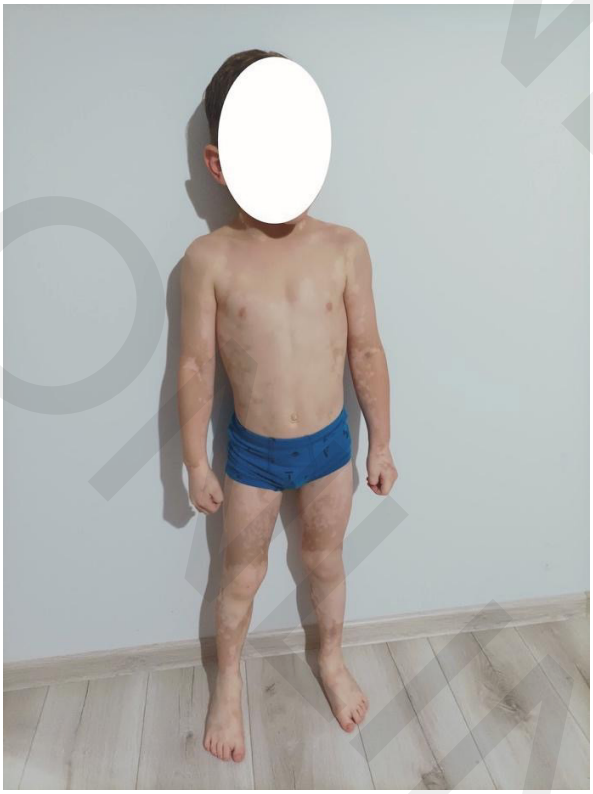

Fig. 1. The boy with visible vitiligo macules and limb hypertonia

to lower the dose had been unsuccessful, resulting in symptom relapse. In January, a follow-up endoscopic examination was performed. During that time, both the macroscopic image and histopathological findings were normal. Considering this, the discontinuation of glucocorticosteroids will be pursued. Due to slowed height velocity and an increase of below the 3rd percentile, a wrist X-ray was performed, revealing delayed bone age. Consequently, the date of hospitalisation at the Department of Paediatric Endocrinology was scheduled with the aim of furthering the diagnostic process.

DISCUSSION

LC and CC are histological subtypes of microscopic colitis. LC is a chronic inflammatory disease rarely diagnosed in children. The condition generally affects adults, especially older women, and it is characterised by non-bloody, watery diarrhoea, normal endoscopic findings, and a distinctive histological pattern of injury[2].

According to the literature[2,4], the most common presenting symptom in children is watery diarrhoea accompanied by abdominal pain, which was also observed in this case. The boy exhibited diarrhoea and recurring abdominal pain several times a day. Less frequent symptoms reported in the literature included nausea, vomiting, flatulence, and weight loss. In this case, a lack of weight gain over the course of a year was noted. The boy's mother also reported episodes of uncontrolled bowel incontinence, occurring 7 to 8 times

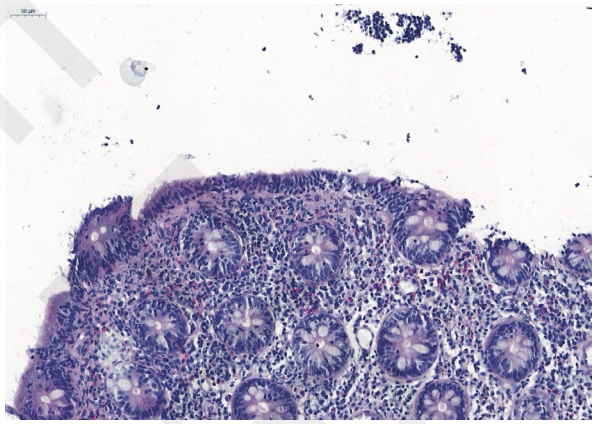

Fig. 2. Haematoxylin and eosin staining

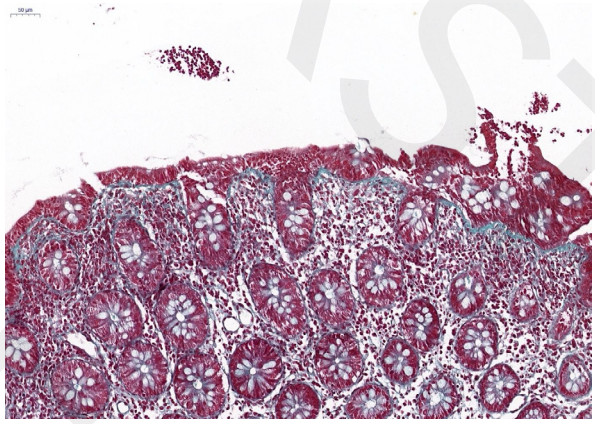

Fig. 3. Masson's trichrome staining – normal subepithelial collagen band (colour blue)

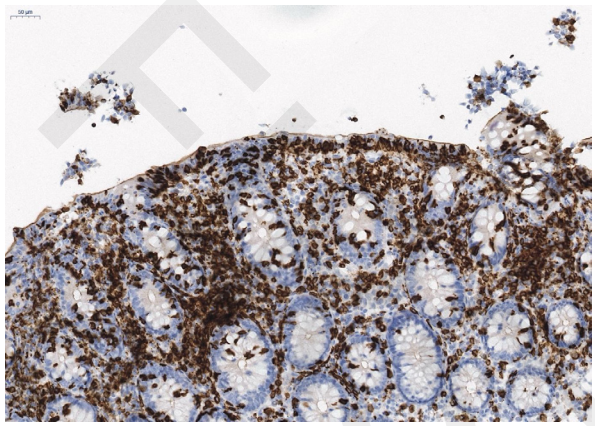

Fig. 4. CD3 staining – enhanced visualisation of lymphocytes

a day. Such incidents are characteristic of inflammatory bowel diseases and are also found in the literature on LC (from faecal urgency to faecal incontinence)[1,3,6,7].

The estimated incidence of CC is between 2.0 and 10.8 per 100,000 per year, while LC is reported between 2.3 and 16 per 100,000 per year, with a higher incidence observed in northern Europe and northern parts of North America[5,8]. The median age at diagnosis for MC is between 55 and 68.7 years[3,5,6,8]. Available data indicate that although MC

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is reported in children, it is rare, and the incidence of the condition in the paediatric population is difficult to determine. The case described here represents the first documented occurrence of LC in a Polish child. Although several retrospective cohort studies have been conducted to investigate cases of LC among children[1,4,5], only one case study specifically concerning a child has been published[9]. Some sources also describe incomplete MC or MC not otherwise specified. The terms have been used to characterise a subgroup of patients who cannot be unambiguously assigned to either LC or CC. It is uncertain whether this represents a separate subtype of MC, as such findings may be seen in a variety of conditions (e.g. secondary to an adenoma, ischemic colitis, irritable bowel syndrome, and chronic trauma)[10].

This report describes the case of a five-year-old male patient diagnosed with LC, with concomitant autoimmune diseases including vitiligo and NS. Although the patient presented the classical features of LC, the young age at diagnosis and the co-occurrence of other autoimmune disorders make the case exceptional.

Several retrospective studies have reported an association between MC and certain autoimmune diseases, such as coeliac disease, thyroid disorders, rheumatoid arthritis, fibromyalgia, type 1 diabetes mellitus, and Raynaud's/CREST syndrome, as well as immune deficiency disorders (common variable immunodeficiency and IgA deficiency). This association can be also found in children[2,5,6,10]. One study also indicated the coexistence of LC with vitiligo, however it was conducted in adults (out of 199 patients diagnosed with LC, three were found to have vitiligo)[3]. Therefore, LC with vitiligo in a child is an exceptional and uncommon manifestation.

None of the cohort studies on LC report its coexistence with NS, although NS has been recognised as a rare extra-intestinal manifestation of other inflammatory bowel diseases both adults and in paediatric patients[11].

Childhood NS is most commonly caused by one of two idiopathic diseases: minimal-change nephrotic syndrome and focal segmental glomerulosclerosis. A third type, membranous nephropathy, is rare in children. Other causes of isolated NS can be subdivided into two major categories: rare genetic disorders and secondary diseases associated with drugs, infections, or neoplasia. The cause of idiopathic NS remains unknown, but evidence suggests it may be a primary T-cell disorder that leads to glomerular podocyte dysfunction[12]. In the reported case, NS was in early remission after steroid therapy, so additional diagnostic workup with kidney biopsies or searching for secondary causes was not necessary. During treatment with oral budesonide, the boy has not experienced a recurrence of NS so far. Due to the clinical course, a kidney biopsy would be considered in the event of relapses[13].

Several groups of drugs have been implicated as potential causes of MC. Most frequently listed are nonsteroidal anti-inflammatory drugs (NSAIDs), but also proton pump inhibitors (PPIs), statins, selective serotonin reuptake inhibitors, and others (e.g. pembrolizumab)[2,3,6,14]. In this case, the boy had not taken any of these medications prior to the onset of symptoms of LC.

A retrospective clinicopathologic analysis from Johns Hopkins Hospital[2] identified 27 patients with MC (23 LC and 4 CC) ≤18 years of age. Of these, 56%[15] had a family history significant for autoimmunity and immunodeficiency, and 30%[8] had a family member with either Crohn's disease or ulcerative colitis. In the case reported here, the family history was positive for autoimmunity, as the child's father was also suffering from vitiligo.

Usually, endoscopic examination reveals a normal colon appearance, although subtle, non-specific macroscopic abnormalities such as slight oedema, erythema, friability, exudative lesions, and scars may sometimes be seen. These abnormal endoscopic findings can also be found in children[2,3]. In the case reported here, there were no visible abnormalities during the examination.

Collagenous colitis is characterised by a colonic subepithelial collagen band ≥10 micrometres in diameter (absent in the case presented here). LC is defined by ≥20 IELs per 100 surface EC[3,5]. This characteristic was observed in both in H&E sections and CD3 staining. While crypt architecture is usually not distorted, focal cryptitis may be present. In the present case, crypt architecture was intact and undistorted. Even though the inflammatory cell response is similar in both LC and CC, consisting mainly of mononuclear infiltrates, with few neutrophils and eosinophils in the lamina propria, there are certain key histological features that are used to differentiate between LC and CC. It is uncertain whether they are related colitides[14] These criteria apply to both children and adults. In an analysis of children from Johns Hopkins Hospital, a significant subset of subjects had active crypt inflammation (26%) or increased crypt apoptosis (33%) on initial biopsy. These findings have been also described in some of the original MC studies in adults[2].

The main goals of treatment are to achieve clinical remission (<3 stools per day, no watery stools during a one-week period) and improve the patients' quality of life. For managing the symptom, anti-diarrhoeal agents are used. In patients with active disease (≥3 stools daily or ≥1 watery stool daily) or persistent symptoms unresponsive to anti-diarrhoeals, it is recommended to add oral budesonide at a dose of 9 mg every day for 6–8 weeks. Although budesonide is, for now, the best-studied treatment with overall favourable results in inducing and maintaining clinical remission in adults with both CC and LC, knowledge of treatment responses in children is limited. The response to budesonide treatment in paediatric patients can vary, ranging from complete clinical remission to no change in symptomatology[4,9]. In this case, the patient responded well to budesonide treatment – the symptoms resolved and a subsequent histopathological evaluation showed a normal picture without lymphocytic infiltrate. However, slowed height velocity could be caused by the administration of budesonide,

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so further diagnostic investigations are needed. If symptoms are persistent, other glucocorticosteroids, such as prednisone or prednisolone, and subsequently cholestyramine, bismuth subsalicylate, anti-tumour necrosis factor therapy (e.g. infliximab, adalimumab) or immunomodulators (e.g. 6-mercaptopurine, azathioprine), are used[15].

CONCLUSIONS

LC should be considered in the differential diagnosis of chronic watery diarrhoea in paediatric patients with no macroscopic abnormalities on endoscopic examination.

Conflict of interests

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study; critical review of manuscript; final approval of manuscript: KBD. Collection, recording and/or compilation of data: MS, AO, AK, AJ, PZ. Analysis and interpretation of data: MS, AO, AJ. Writing of manuscript: MS, AO, AJ, PZ.

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