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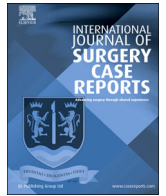
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Nodular lymphoid hyperplasia complicated with ileal Burkitt's lymphoma in an adult patient with selective IgA deficiency

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ABSTRACT

INTRODUCTION: Primary lymphomas of the small intestine are rare. Burkitt's lymphoma (BL) occurs sporadically in adults. Nodular lymphoid hyperplasia (NLH) is a rare disorder characterized by diffuse nodular lesions, which represent hyperplastic lymphoid follicles, and it is often associated with immunodeficiency syndromes.

PRESENTATION OF CASE: We present a 38-year-old male patient in a state of surgical emergency, suspected of Crohn's disease, who had an unusual combination of NLH and BL of the proximal ileum. Furthermore, retrospectively analyzed documentation revealed selective IgA deficiency.

DISCUSSION: Association between NLH and intestinal lymphomas in patients with immunodeficiency syndromes was indicated before. This case report supports the notion on NLH as a transition state between immunodeficiency and intestinal lymphomas.

CONCLUSION: This is one of the first case reports which presents the combination of NHL and BL. The awareness of the existence of this rare combination, especially in young adult males, can improve the diagnostic accuracy and the treatment management.

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1. Introduction

Primary lymphomas of the small intestine are rare and mostly of B-cell and non-Hodgkin types [1]. The problem is that they are hardly recognized unless intestinal complications occur. Their accurate diagnosis is often difficult, because the immune system of the gut can respond on many immunologic stimuli with nonspecific hyperplastic reaction [2]. The most common sites include ileum and terminal ileum, followed by the jejunum and duodenum [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype in the GI tract, in general. Other histological subtypes in the small intestine include mucosa-associated lymphoid tissue (MALT) lymphoma, enteropathy-associated T-cell lymphoma (EATL), mantle cell lymphoma (MCL) and follicular lymphoma (FL). BL occurs sporadically, mostly in boys and adolescent males, representing with symptoms of small bowel obstruction [3,4].

This case report is one of the first presenting a rare combination of BL of the ileum and nodular lymphoid hyperplasia (NLH), probably due to selective IgA deficiency [5]. NLH is a condition char-

acterized with numerous small nodules diffusely distributed along the segments of the GI tract, histologically evaluated as reactive follicular hyperplasia [6]. In children, NLH has a benign course and is often associated with viral infections and food allergies [7]. In adults, associations were found with immunodeficiency disorders, Giardia infection, celiac disease and HP infection [8]. In some cases, lymphomatous transformation has been reported [9].

2. The presentation of the case

A 38-year-old male was admitted to the Department of Surgery for abdominal colic, vomitus, stomach bloating and distention. He had a six-month history of episodes of abdominal colicky pain localized in the periumbilical area. Upon physical examination, the abdomen was distended, with the signs of the wall tenderness and of reduced bowel movements; radiologic assessment indicated the signs of ileus. Laboratory checkup did not indicate significant results, except for mildly increased C-reactive protein (CRP), 33.0 mg/L, and fibrinogen activity level, 3.8 g/L. Gastroscopy indicated multiple tiny polyps in the whole duodenum, histopathologically confirmed as inflammatory infiltrates. Colonoscopy with terminal ileoscopy was also performed to confirm or reject the diagnosis of Crohn's disease (CD). This examination revealed numerous

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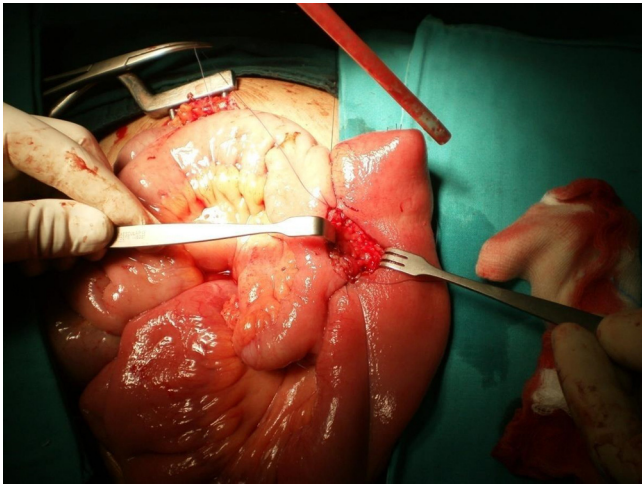


Fig. 1. Numerous tiny polyps diffusely distributed throughout the small intestine mucosa.

polyps, measuring 2–3 mm in diameter, in the cecum. Mucosa in the terminal ileum was hyperemic and edematous, with creases and wrinkles and cobblestone-like appearance. Histopathological examination of the bioptic specimens revealed abundant chronic inflammatory infiltrates, Paneth cell metaplasia and isolated lymphatic follicles with reactive germinal centres, but these findings were not deemed sufficient to confirm the diagnosis of CD. Abdominal ultrasound revealed two small polypoid tumors in the gallbladder, increased small intestine wall thickness, in the segment of 8 cm in length, as well as lumen stenosis, in the parts projected behind the posterior urinary bladder wall. Magnetic resonance (MR) enterography confirmed increased wall thickness of the terminal ileum, visible along the segment of 5 cm in length, and luminal narrowing, in the parts located above the urinary bladder. The evident intraabdominal lymph node or other organs' enlargements were not found. Radiographs of the small intestine indicated delayed contrast discharge at the level of the jejunal loops. The results of other tests performed, including testing for HIV and hepatitis B and C, PPD (purified protein derivative) skin test and parasites in stool, were all negative. Immunoglobulin blood test revealed selective IgA deficiency (IgA values less than 0.05 g/L). Anamnesis indicated a long-term presence of atopic dermatitis of hands and legs as well as chronic rhinosinusitis.

These results, taken together with the clinical findings, were highly indicative of CD. Adequate treatment had already been initiated earlier on. Due to the symptoms and signs of the acute small intestine obstruction at the admittance, the patient underwent the emergency operation. The tumor mass found intraoperative, ranging 3 cm in diameter, caused the complete obstruction of the lumen of the proximal ileum. Surrounding mucosa was densely populated with small polyps, measuring 2–3 mm in diameter. Segmental resection of 11 cm long part of the intestine, with the tumor herein, was performed, and the intestinal continuity was reestablished by latero-lateral anastomosis. There were no further gross pathological findings, except for dilated jejunal loops. Mucosa in the rest of the small intestine also indicated polypoid appearance (Fig. 1).

Histopathological analysis of polypoid intestinal specimens was indicative of reactive follicular lymphoid hyperplasia, showing large lymphoid follicles with prominent germinal centres (Fig. 2). Microscopic examination of the solitary cross-sections of the tumor tissue revealed diffuse cellular infiltrations with medium size to large atypical lymphoid cells and slight nuclear polymorphism. Apoptotic bodies and “tingle body” macrophages were scattered here and there, altogether giving the “starry-sky” appearance (Fig. 3).

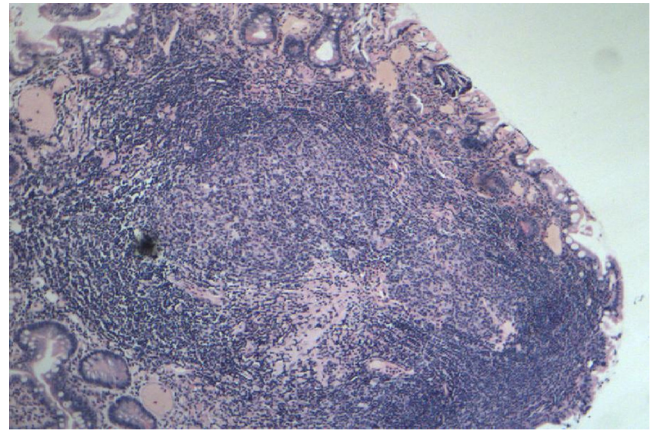


Fig. 2. Microscopic appearance of the lymphoid polyp found in mucosa of the small intestine (H&E, x100).

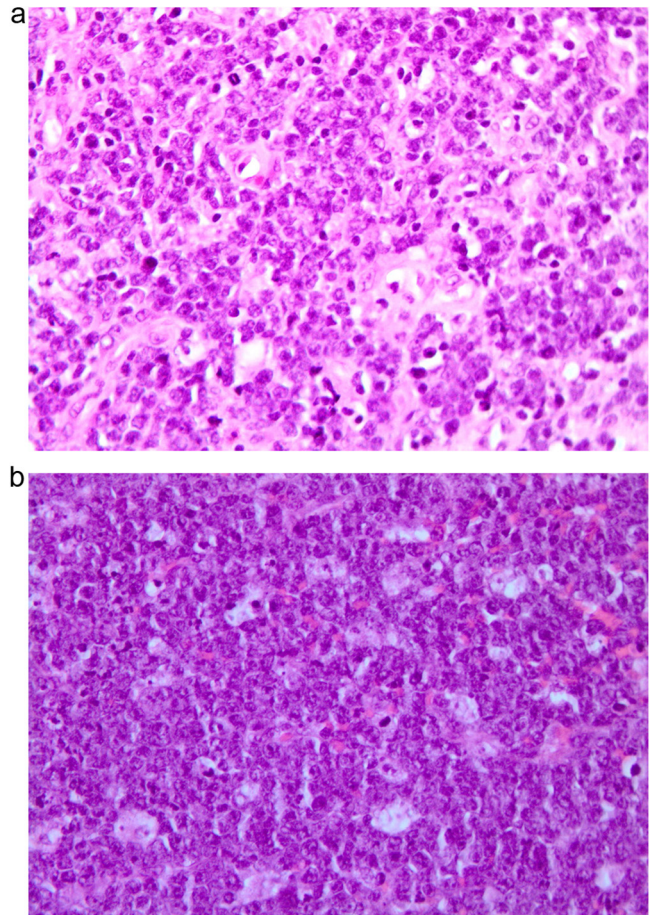


Fig. 3. Primary extranodal B cell non-Hodgkin's lymphoma of the small intestine; the histopathological pattern of the “starry-sky” (H&E, x40).

Immunohistochemical findings revealed the tumor cell phenotype as CD20+, bcl6+ (moderate), bcl2-, CD10+, CD43-, TDT-, CD3-, CK AE1/3-, chromogranin-. CD10 indicated strong positivity (Fig. 4). Proliferative activity, measured by Ki67 expression, was found in almost all cells (Fig. 5). FISH (fluorescence *in situ* hybridization) analysis identified the t(8;14) (C-MYC/IGH) chromosomal translocation. These histopathological and phenotypic analyses pointed to the diagnosis of BL.

Extensive disease staging, including evaluation of the bone marrow aspirate smear and bone biopsy, as well as multi-slice helical

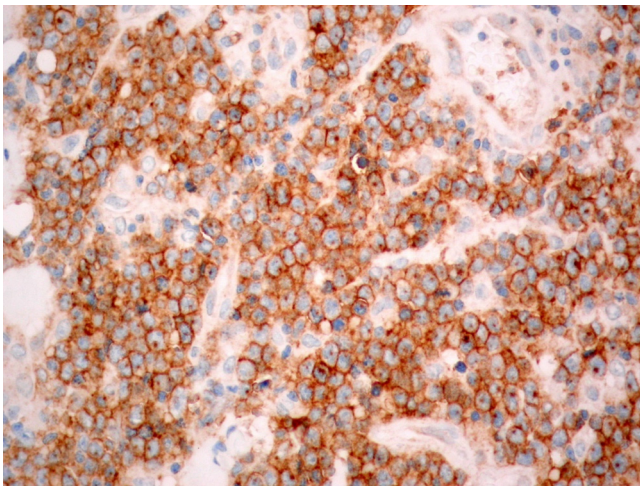


Fig. 4. Immunohistochemistry (anti CD10, x400).

(Immunohistochemical stains were performed on 4- μ m formalin-fixed paraffin-embedded sections for following antibodies: CD20 (clone L26, Dako, Denmark), BCL6 (clone PG-B6p, Dako, Denmark), BCL2 (clone 124, Dako, Denmark), CD3 (clone PC3/118A, Dako, Denmark), TdT (clone EP266, Dako, Denmark) and Ki67 (clone 30-9, Ventana, UK) using an autostainer (Dako, Carpinteria, CA). For epitope retrieval Heat-induced Epitope Retrieval pH6.0 (Dako) method was used to optimize immunoreactivity for all antibodies followed by a peroxidase blocking kit and the Labeled Strep Avidin Biotin 2 kit (Dako) detection kit with diaminobenzidine as a chromogen (Dako) for optimal visualization of a reaction. Appropriate negative and positive controls were included. Staining of normal B and T lymphocytes in lymphoid tissue of an Appendix was used as internal positive control for CD20, BCL6, BCL2, CD10, CD3 and TdT).

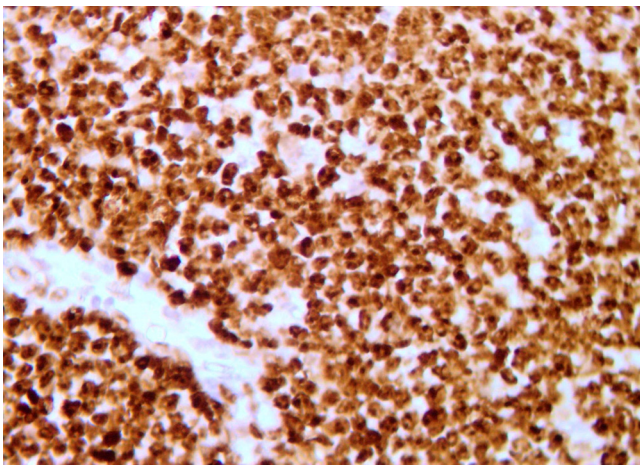


Fig. 5. Immunohistochemistry (anti Ki67, x400).

spiral CT (MSCT) of the neck, thorax, abdomen and pelvis, excluded the systemic disease spread. Multiple lymph nodes, reaching maximal dimension of 2 \times 2 cm, were found along the both sides of the mesentery. The patient was transferred to the Department of Oncology where he was treated according to the DA-EPOCH-R protocols. Six months after the surgery, the patient was in complete remission.

3. Discussion

Our first explanation for the episodes of colicky pain in a younger male patient was CD, not intestinal lymphoma. We have been focused on a disease probability prediction approach. But we were wrong. We missed the well-known fact that patients with IgA selective immunodeficiency have increased risk of getting both gastrointestinal disorders and malignant diseases of the GI tract

[10,11]. Although selective IgA deficiency often remains without significant signs, we could have known that the immune reaction of the presented patient was out of the ordinary, from his medical history, which indicated the upper respiratory tract chronic infection and atopic constitution, both known as manifestations of IgA deficiency [11]. Different, non-specific lymphoproliferative intestinal disorders, including also NLH, often accompany selective IgA deficiency [12]. Those disorders may share some features with autoimmune diseases. Those intermediate states, a combination of NLH and autoimmune-like lympho-proliferative conditions, either developed locally in the GI tract, or as a systemic reaction, are possible, which is supported by several published case reports dedicated to NLH [13,14]. In our case report, the biopsic material taken from the terminal ileum was characterized with chronic inflammatory infiltrates. We considered those changes as incomplete signs of CD. If we had known more of that issue, we would have chosen the other line of thought. Namely, it is known that there is a close association between selective IgA deficiency and celiac disease (an auto-immune mediated intestinal disease), but lack of association between NLH (and associated IgA deficiency) and CD, as visible from genetic NOD2/CARD15 analysis, performed in patients with NLH [15].

The possible divergence between NLH and CD could provide an explanation for the fact that BL, a rare form of the non-Hodgkin's GI lymphoma, was found on the background of NLH, and not, e.g., DLBCL, which is the most common form of GI lymphoma [1]. In addition, DLBCL is known to develop from inflammatory conditions, such as CD. Morphologic changes of the biopsic specimens, taken from the tumor mass of the patient, presented with medium-sized to large lymphoid cells and incompletely cohesive pattern, steered us to dwell between BL and intermediate BL – DLBCL form [16]. However, the morphologic appearance of the “starry-sky” and the results of the immunophenotyping procedures, indicating strong CD10 staining, with the lack of Bcl2, argued towards BL. Apart from the well-known endemic (EBV infection driven and linked to some regions in Africa) and HIV-associated BL forms, there is also a sporadic BL form, elsewhere observed [17]. In the countries of the western part of the world, it is the most common lymphoma type in boys and adolescent males, presented mostly as the tumor of the ileocecal region. In adults, BL is rare, accounting for only 1–2% of all lymphomas. Patients may present with leukemic, solid or combined BL forms. Little is known on the pathophysiology and co-morbid disorders associated with this localized adult BL form. Some older reports on the association between immunodeficiency, NLH and non-Hodgkin's lymphoma of the small intestine proved to be imprecise in terms of determining the exact lymphoma type, due to the lack of modern phenotyping techniques [18]. The tumor localization in the small intestine, patient age and immunologic profile, can impact particular histological patterns.

4. Conclusion

This case report supports the notion expressed by other authors that NLH in adult patients can be considered as a transition state between immunodeficiency and intestinal lymphoma. This is one of the first case reports which presents the combination of NLH and BL and which tends to clarify a wider pathophysiologic context of the adult form of BL.

Conflict of interest

There is no conflict of interest.

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Ethical approval

We involved human data in the study. The Ethics Committee of the Osijek University Clinical Hospital, approved the study.

Consent

Written informed consent was obtained from the patient included in the study for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request. This work has been reported in line with the SCARE criteria [19].

Author contribution

Toni Hannich – study concept and design; Ljiljana Majnarić – design, writing, editing; Dragan Janković – writing, editing; Šefket Šabanović – data collection; Aleksandar Včev – supervision.

Guarantor

Ljiljana Majnarić, MD, PhD.

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