Ulcerative colitis associated with vitiligo and IgA deficiency in a young girl

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory disease of non-infectious and plurifactorial etiology, exclusively affecting the colon, with variable expansion. The selective deficiency of immunoglobulin A (IgA) can be frequently associated with UC, as well as with recurrent respiratory tract infections, autoimmune diseases, atopy. The incidence of vitiligo among UC patients is significantly higher compared to the general population. At the same time, recent studies proved a higher incidence of *Clostridium difficile* infections in patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) compared to the general population. We are presenting the case of a 9 year old girl, where UC associated with selective deficiency of IgA and vitiligo hampered the diagnosis and therapeutic approach, particularly in the conditions of a preexisting *Clostridium difficile* infection. The association of these entities is rare in the pediatric population and a multidisciplinary team approach (gastroenterology, dermatology and immunology) can ensure an effective therapeutic management in the case of such patients.

Keywords: *reversal ulcerative colitis, child, IgA deficiency, vitiligo*

Introduction

Inflammatory bowel disease (IBD) includes: ulcerative colitis (UC), Crohn's disease (CD) and atypical/unclassified IBD. Their etiology still remains a controversial subject, some particular trigger factors (infectious agents, environmental factors, drugs) may be involved in patients presenting with a certain genetic susceptibility. Ulcerative colitis (UC) is defined by a chronic, idiopathic inflammation limited to the mucosa, exclusively affecting the colon, with variable expansion and with an evolution alternating periods of remission and relapses [1]. Epidemiologic data in the US reveals an incidence of UC among the pediatric population of 2.1 per 100,000 children/year, while in Europe the incidence of ulcerative colitis among the pediatric population ranges from 0.5 to 3.3 per 100,000 children/year [2]. The incidence of inflammatory disease, particularly in pediatric patients, in Romania, mentioned in literature is insufficient. The clinical manifestations frequently discovered in

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children include semi-consistent stools, abdominal pain, rectal bleeding, and weight loss.

Case report

We are presenting the case of a 9 year old girl living in an urban area, who was admitted to the pediatric gastroenterology department with subfebrility (37.8° C), diffuse abdominal pain, semi-consistent stools, intermittent rectal bleeding, and inappetence. We note that the patient was previously diagnosed with *ostium secundum* atrial septal defect, mitral valve prolapse and IgA deficiency. Three months prior to the admission, the girl had been diagnosed with a *Clostridium difficile* infection (toxin B) at a regional hospital, for which she underwent treatment with metronidazole. The clinical exam upon admission revealed a relatively good general status, no fever, ponderal hypotrophy BMI= 13.4 kg/m2 (< 5 percentile), areas of depigmentation on the upper and lower limbs bilaterally, left parasternal systolic murmur class II/VI, diffuse abdominal pain occurring spontaneously and upon palpation, semi-consistent stools and intermittent rectal bleeding.

The paraclinical investigations revealed the following: microcytic hypochromic anemia (Hb= 9.8 mg/dl, VEM= 70 fL, CHEM=28 g/dL), inflammatory syndrome (VSH=16 mm/1h, CRP>6 mg/dl), hyposideremia (serum Fe=12 µg/dl). The hepatic, renal, phosphorus and calcium blood profile, as well as the anti-transglutaminase antibodies were within normal limits. The immunogram revealed in the dynamics IgA deficiency (73 mg/dl). Stool biochemical analysis indicated a slightly acid pH (pH=6.8) and revealed rare occurrence of extracellular starch. The patient was tested for *Clostridium difficile* toxins A and B, and the results were negative. Calprotectin dosage in fecal matters indicated values over 1000 micrograms/g. The abdominal ultrasound showed a distended gallbladder with moderate sludge and no other pathological modifications. The colonoscopy identified above the anal margin, a congested mucosa, with edema, superficial erosions and ulcerations, with pancolic extension, suggesting active UC (Figure 1).

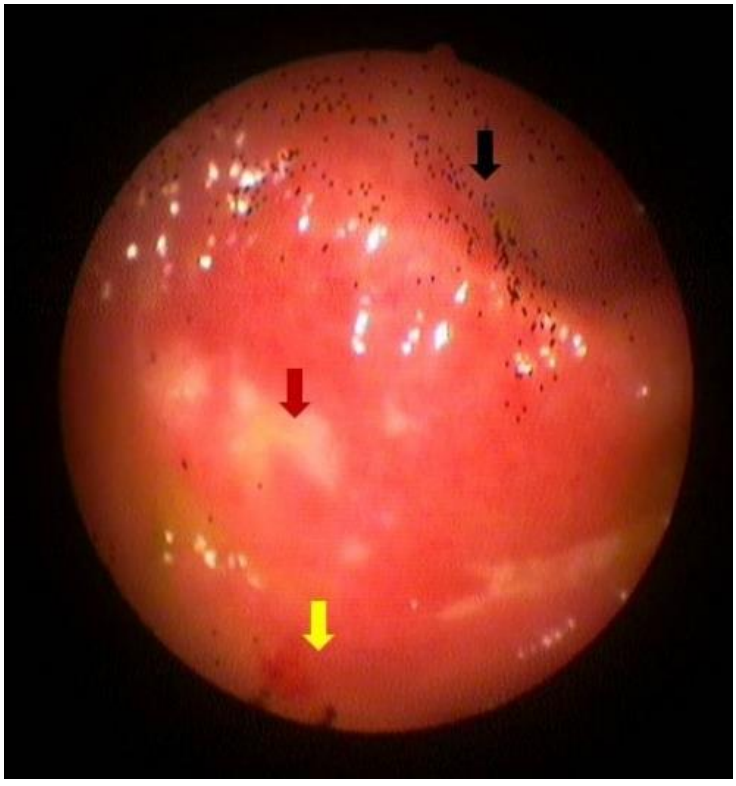

Fig. 1. Colonoscopy: areas of congestion (black arrow) with erosions (red arrow) and ulcerations (yellow arrow).

The histopathological examination of colic biopsies identified mucosa with erosions of the surface epithelium, recent hemorrhage in the chorion, along with abundant and diffuse inflammatory infiltrate, mostly neutrophils and eosinophils; also, foci of intraepithelial granulocytes, congestion, edema and lymphoid follicles in the chorion. Other observations include reactive modifications of isolated crypts; focally, the glandular epithelium presents depletion of mucus secretion and nuclear hyperchromasia with loss of polarity (Figures 2 and 3).

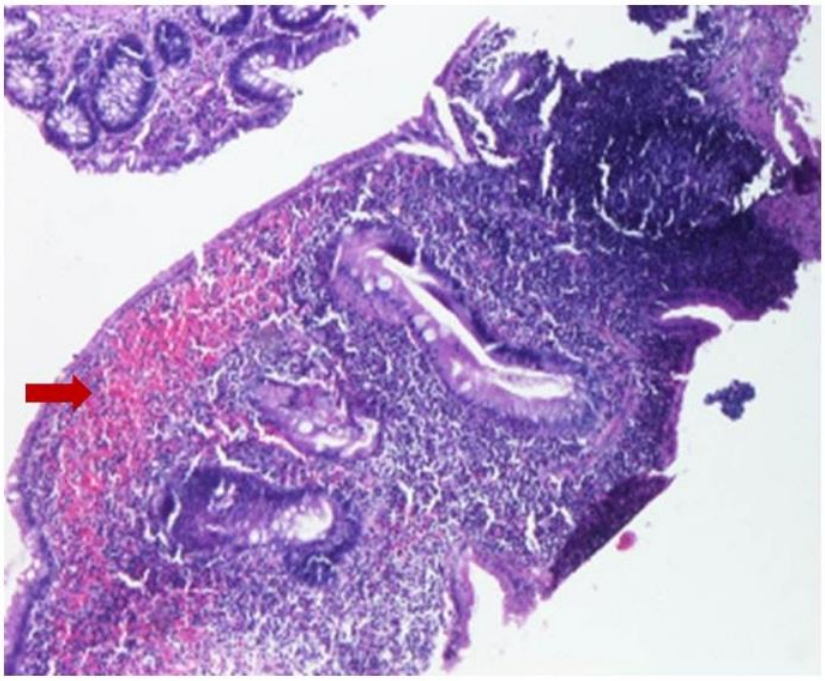

Fig. 2. Colon: hemorrhage in the upper chorion (red arrow) and a lymphoid follicle (HE, x40).

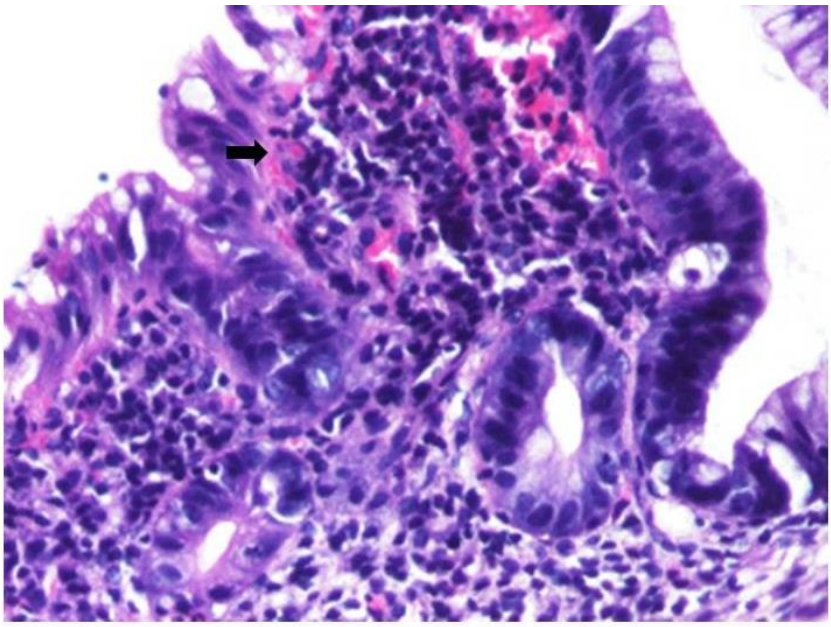

Fig. 3. Colon: mucus secretion depletion, hyperchromatic nuclei losing their position at the base of the cell (black arrow) (HE, x200).

The PUCAI (Pediatric Ulcerative Colitis Activity Index) score was 35 points, indicating a moderate activity of the disease. The dermatological examination established vitiligo diagnosis with topical treatment as recommendation. The treatment included salazopirin - 50 mg/kg. The patient had a clinically favorable outcome while under treatment, noting that abdominal pain and rectal bleeding had disappeared. Clinical remission was achieved after 2 weeks of treatment, however with persistently high levels of calprotectin. The attack dose was maintained for a month, with a gradual decrease of the dosage. Currently, the patient is under treatment with salazopirin on a maintenance dosage. After 3 months clinical and biological exam will be monitored and possibly, after 12 months a subsequent colonoscopy will be performed, depending on patient clinical and biological outcome.

Discussions

It has been demonstrated that IBD patients have a higher incidence of *Clostridium difficile* infection compared to the general population, with a direct impact on the vital prognosis and hospital admission period. The suspicion of *Clostridium difficile* infection should be analyzed both in newly diagnosed patients, as well as in the relapse phases [3]. A possible explanation for the high susceptibility to this infection could be the involvement of the intestinal lympho-epithelial system and the incapacity to present an adequate inflammatory response [4, 5]. In our patient, the positive UC diagnosis was established based on medical history, clinical examination, existing inflammatory syndrome and – first and foremost – the endoscopic and histopathological elements (pancolonoscopy and biopsy) according to the Revised Porto Criteria (ESPGHAN Revised Porto Criteria, 2014). According to these criteria, there are two categories of ulcerative colitis: typical and atypical. Atypical UC comprises 5 distinctive phenotypes (Rectal sparing, Short duration, Cecal patch, Upper gastrointestinal symptoms, and Acute severe colitis) [2]. The clinico-evolutive activity of the disease in children is assessed using the PUCAI score (Table 1) [6].

Table 1. PUCAI score and disease severity estimated for our patient.

Item	Category/Points
Abdominal pain	No pain = 0 Pain can be ignored = 5 **Pain cannot be ignored = 10**
Rectal bleeding	None = 0 **Small amount only, in less than 50% of stools = 10** Small amount with most stools =20 Large amount (50% of the stool content) = 30
Stool consistency of most stools	Formed = 0 **Partially formed = 5** Completely unformed = 10
Number of stools per 24 hours	0- 2 = 0 points **3- 5 = 5 points** 6- 8 = 10 points >8 = 15 points
Nocturnal stools (any episode causing wakening)	**no = 0 points** yes = 10 points
Activity Level	No limitation of activity = 0 **Occasional limitation of activity = 5** Severe restricted activity = 10
Sum of PUCAI	0- 85 points
Disease severity	• severe: 65 points or above • moderate: 35-64 points • mild: 10-34 points • remission (disease not active): below 10 points

In the case we presented, the calculated PUCAI score indicated a moderate activity of the disease, in contrast with the high levels of calprotectin. In addition to recurrent respiratory tract infections, autoimmune diseases, atopy and diseases of the gastrointestinal tract, patients with IgA deficiency can also associate: giardiasis, lactose intolerance, malabsorption, celiac disease and inflammatory bowel disease. IgA secretors play an important role in maintaining the intestinal homeostasis. Of all the inflammatory bowel diseases, UC is the one most frequently associated with selective IgA deficiency [7, 8]. The dermatologic diseases most frequently encountered in IBD patients are pyoderma gangrenosum, hidradenitis suppurativa, lichen planus, rash, secondary amyloidosis [6, 9]. It is also possible to encounter a series of autoimmune diseases, such as bullous epidermolysis, vitiligo and/or psoriasis. Some authors consider that vitiligo pathogenesis associated with IBD is autoimmune or, in other cases, genetic [10, 11]. The incidence of vitiligo in the general population is 0.3%, with a significantly lower rate compared to its 1.1% incidence among UC patients [6, 12].

The current treatment for ulcerative colitis may include the “step-up” or the “top-down” approach, with the former being the most largely used particularly for the pediatric population. The “step-up” approach requires to start treatment with aminosalicylates (salazopirin or mesalazine) and, in case of therapeutic failure, corticotherapy followed by immunosuppressant treatment with azathioprine, cyclosporine, 6-mercaptopurine or methotrexate. The biological agents used for the next treatment phase include TNF-alpha inhibitors, infliximab (only this one is approved by the National Protocol in force for pediatric patients) and adalimumab, which proved an increased efficiency in the treatment of UC [13]. TNF-alpha inhibitors can be used in monotherapy or combination therapy with aminosalicylates, corticotherapy or immunosuppressant agents, noting that the combined therapy brings along more frequent side effects. Probiotics can be beneficial for inducing and maintaining remission in ulcerative colitis, as proved by their effects on the microbiota in the pathogenesis of IBD [14]. There are studies that confirm the role of probiotics containing the *E. Coli* Nissle 1917 strain (Kruis et al, 2004) and VSL#3 (Miele et al, 2009), recommended for therapeutic doses in maintaining the remission for pediatric patients with ulcerative colitis [15, 16]. The inflammation process involved in UC pathogenesis is maintained by colonic dysbiosis. Fecal microbiota transplant (FMT) was recently included in the therapeutic arsenal, acting directly on colonic dysbiosis. In a study published in 2013, Kunde et al certified the benefits of FMT in terms of improving the PUCAI score, as well as in obtaining remission; however, prospective data is needed regarding the effectiveness and especially the safety of FMT for pediatric patients with UC [17]. In our case, we used the step-up therapeutic approach and, for the time being, the patient was not recommended biological therapy (treatment responsive, mild-medium form). Moreover, considering the young age of the patient, the fact that biological therapy becomes ineffective or unsafe after a variable time (development of antibodies, loss of response, risk of allergies) and that, at least for the time being, the therapeutic alternatives in case of loss of response are limited, we believe that it is preferable to delay biological treatment.

The prognosis is that of a chronic disease marked by the risk for severe complications, including colon cancer, which can occur in cases with evolutions that extend over 8-10 years. However, we can note that our case has both positive prognosis factors, such as the inclusion in the mild-medium class of severity and favorable response to the first treatment line, as well as negative prognosis factors, such as the pancolic extension of the disease at the time of diagnosis and the young age of onset. The particularities of the case consist in the association of UC with the constant IgA deficiency, vitiligo and the *Clostridium difficile* infection in the recent case history. As far as this latter aspect is concerned, relapses are frequent especially in patients with ulcerative colitis, which is an additional factor to be taken into consideration for prognosis establishing purposes.

Conclusions

The association of inflammatory bowel pathology with IgA deficiency and vitiligo in children can be considered a rare case in medical practice. Such cases require a multidisciplinary approach based on the collaboration between the pediatric gastroenterologist, allergist and immunologist. Given the chronic evolution of the disease, in the long run the children should benefit from an optimal transfer to the gastroenterology care units for adults.

Conflict of interest

Authors declare no conflicts of interest.

Consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

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