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Review

Very Early Onset-IBD: evidence for the need of a multidisciplinary approach

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Summary

Very early onset inflammatory bowel disease (VEO-IBD) represents approximately 25% of cases of IBD-like colitis occurring during childhood and, by definition, it is characterized by an onset prior to 6 years of age. This subgroup of patients presents significant differences from IBD occurring in older children and in adults, including a more severe clinical course, a reduced responsiveness to conventional IBD therapy, and a greater proportion of cases featuring an underlying monogenic disorder. Histological findings from gastro-intestinal (GI) biopsies are characterized by an IBD-like, apoptotic or enterocolitis-like pattern, complicating the differential diagnosis with other pediatric diseases involving GI tract. Moreover, individuals with monogenic disorders may develop significant comorbidities, such as primary immunodeficiency (PID), impacting treatment options. Without an appropriate diagnosis, the clinical course of VEO-IBD has greater potential for escalated treatment regimens involving extensive surgery, more intensive medical therapies and, even more important, inadequate recognition of underlying monogenic defect that may lead to inappropriate (sometimes fatal) therapy. For these reasons, an adequate context leading to an appropriate diagnosis is imperative, calling for a close collaboration between pediatricians, pathologists, geneticists, and immunologists.

Key words: Crohn's Disease, IBD, monogenic diseases, primary immunodeficiency, pediatric diseases, ulcerative colitis, VEO-IBD

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Introduction

Inflammatory bowel diseases (IBDs) are chronic intestinal inflammatory conditions including Crohn's disease (CrD) and ulcerative colitis (UC), based on clinical characteristics and histological findings[1]. IBDs are the multifactorial result of a dysregulated immune response to environmental exposures in a genetically susceptible host and, in older pediatric patients and adults, are most often polygenic, involving over 200 risk loci spanning over 300 genes [2,3]. Very early-onset inflammatory bowel disease (VEO-IBD) refers to a clinical definition for children with IBD-like symptoms arising before the 6th year of life [4]. In 20-30%

Table I. Definition of IBD based on patient age.

Group	Age range
Pediatric-onset IBD	< 17 years
Early onset IBD	< 10 years
Very early onset IBD	< 6 years
Infantile onset IBD	< 2 years
Neonatal IBD	First 28 days of age

of these patients, causative monogenic or digenic defects have been identified, often involving genes associated with primary immunodeficiencies (PID) [4]. Therefore, VEO-IBD can be a misleading diagnosis, and may represent only a manifestation of a more severe condition. This age group represents the minority of worldwide-reported IBD cases, with an estimated incidence of 4.37 and a prevalence of 14 per 100,000 children [5]. Infantile-onset IBD (IO-IBD) is a subcategory of VEO-IBD, reflecting patients in which the disease presents before 2 years of age. Some authors further describe neonatal-onset IBD as IBD presenting within the first 28 days of life (Tab. I) [4]. Underlying monogenic disorders are more represented in VEO-IBD compared with 'pure' IBD diagnosed at older age; thus, a subset of patients presents with a more severe and heterogeneous phenotype than older onset IBD [6]. The monogenic etiologies of VEO-IBD identified to date can be divided into six main (and sometimes overlapping) categories: (i) general immune dysregulation, (ii) T and B cell defects, (iii) phagocytic defects, (iv) hyper- and auto-inflammatory conditions, (v) epithelial barrier dysfunction, and (vi) other conditions [3]. Unlike older-onset IBD, patients with VEO-IBD have a higher rate of diagnosis of inflammatory bowel disease unclassified (IBD-U) (18-33%), a positive family history (19-41% compared with 5-10% in adults), a more aggressive clinical course, and resistance to conventional therapy for IBD [2,3]. Choosing the optimal therapy for these children can be challenging, especially given the almost inevitable delay in the determination of the underlying causative germinal defect or, more often, misdiagnosis of cases in which the genetic defect is not identified. Therefore, all elements of the diagnostic evaluation must be considered in a clinical suspicion of VEO-IBD, to administer appropriate therapy and follow-up, particularly for patients with PID and aggressive disease [3].

In this review we describe the clinical features, genetic landscape, diagnostic approach, and histological findings of children clinically presenting with VEO-IBD, highlighting the need for a multidisciplinary approach, including a comprehensive immune and genetic evaluation, for directing adequate diagnosis and management of patients with clinical VEO-IBD features.

Clinical features

Critical aspects of the anamnesis that should be investigated include (i) age of onset, (ii) a detailed stooling pattern, (iii) response to dietary interventions, (iv) history of opportunistic and refractory infections/sepsis, (v) severe early onset of perianal disease and (vi) autoimmune or endocrine disorders [3]. Children with clinical suspicion of VEO-IBD might have different clinical presentations, with both gastrointestinal and extra-intestinal symptoms, and a different disease course with respect to older children, adolescents and adults, with a very high morbidity and a high burden of disease [7]. GI symptoms most often include: (i) rectal bleeding and bloody and/or mucus-containing diarrhea, due to the most frequent rectal localization, (ii) emesis, (iii) perianal skin tags or fistulas [8]. Frequently, children may present with an insidious onset of blood- and mucus-stained small-volume diarrhea and failure to thrive [9]. In these cases, the pediatrician's initial set of diagnoses might not take IBD into account and may include more common conditions with similar symptoms, including cow's milk protein intolerance or other food allergies, infections, coeliac disease, and inadequate caloric consumption. Extra-intestinal symptoms may include (i) arthritis, (ii) arthralgias, (iii) folliculitis, (iv) uveitis, (v) sclerosing cholangitis, and (vi) dermatologic manifestations [3]. In particular, the presence of large-volume intractable diarrhoea, severe perianal disease, autoimmunity, severe recurrent infections or unexplained fever, obstruction and atresia of intestine, early-onset tumors, endocrine dysfunction, hepato-splenomegaly, cytopenia, high ferritin (macrophage activation syndrome), and somatic defects in skin, hair, teeth and various other ectodermal elements should raise the suspicion of an underlying immunodeficiency/monogenic disease and prompt the carrying out of specific genetic analyses [4].

Some monogenic forms of VEO-IBD are associated with specific clinical features that can represent a useful tool to distinguish specific monogenic conditions [3]. In particular, recurrent infections or sepsis starting in the first months of life should raise the suspicion of a chronic granulomatous disease (CGD), a deficiency of XIAP, or IL-10 signaling defect. A prompt diagnosis of a CGD is of fundamental importance, given that anti-TNFs are contraindicated in patients with VEO-IBD suffering from CGD [10]. Hemophagocytic lymphohistiocytosis (HLH) or macrophage activating syndromes are suggestive of XIAP deficiency, whereas early onset of neoplasia such as diffuse large B cell lymphoma, severe perianal disease, folliculitis, and arthritis favor an IL-10 signaling defect, respectively [11]. Polyendocrinopathy enteropathy X-linked (IPEX) syndrome is

characterized by immune dysregulation conditions like type 1 diabetes mellitus, eczema, food allergies, and a variety of other autoimmune manifestations [12].

Genetic landscape

In approximately 15-20% of patients with IBD-like symptoms, it is possible to detect an underlying monogenic defect [13]. To date, more than 50 genes have been identified, many of which involve PID genes [14]. The identification of the specific genetic mutation is an integral part of the diagnostic and therapeutic workup. Genetic investigation can be conducted through targeted sequencing of a single candidate gene (if the first level investigations suggest its involvement), gene panels (Targeted Next Generation Sequencing NGS or Panel NGS testing), whole genome sequencing (WGS) or whole exome sequencing (WES) [15]. A summary of the most frequent genetic alterations is reported in Table II.

Table II. Gene-defects based syndrome/disorders in VEO-IBD.

Defects	Syndrome/disorder	Gene	Phenotype
Epithelial barrier function defects	Hereditary multiple intestinal atresia	TTC7A	Intestinal atresia, dermatitis, alopecia
	NEMO	IKBKG	Infections, hypodontia, poor sweat, thin hair, frontal bossing, poor growth and diarrhea
	ADAM17	ADAM17	Staphylococcal infections, psoriasiform dermatitis, pustules, broken hair, abnormal nails, diarrhea
	Familial diarrhea	GUCY2C	Ileal obstruction, esophagitis, electrolyte abnormalities
	Congenital diarrhea	SLC26A3	Secretory diarrhea at birth
	Epidermolysis bullosa	COL7A1	Recurrent blistering or erosions, esophageal stricture, anal fissures and stenosis, enteropathy, hair and nail abnormalities
Immune dysregulation	IPEX – Immunodysregulation Polyendocrinopathy X-linked	FOXP3	IBD onset near birth diarrhea, autoimmunity, psoriasiform dermatitis, alopecia, endocrinopathies, type 1 diabetes
	IL-10 signaling defects	IL10RA, IL10RB, IL10	Folliculitis, perianal disease, arthritis, increased risk of B cell lymphoma
	NOD2 signaling defects	TRIM22	Granulomatous colitis, severe perianal disease
T-cell, B-cell and complex function defects	LRBA deficiency	LRBA	Infections, interstitial pneumonitis, autoimmunity (idiopathic thrombocytopenia, autoimmune haemolytic anemia, type 1 diabetes)
	CTLA4 deficiency	CTLA4	Autoimmunity, autoimmune cytopenias, infections, interstitial pneumonitis
	Wiskott-Aldrich syndrome	WAS	Thrombocytopenia with small platelets, recurrent bacterial and viral infections, eczema, bloody diarrhea, lymphoma, autoimmune disease
	Bruton's agammaglobulinemia	BTK	Recurrent severe bacterial infections, small tonsils, diarrhea
	Hoyeraal-Hreidarsson syndrome (Dyskeratosis congentia)	DKC1, RTEL1	Microcephalic, cerebellar hypoplasia, intrauterine growth restriction (IUGR), nail dystrophy, aplastic anemia and bone marrow failure
	SCID (Severe Combined Immunodeficiency)	ZAP70, IL2RG, ADA, CD3γ	Recurrent severe infections, chronic diarrhea, failure to thrive
	Caspase-8 deficiency	CASP8	Recurrent bacterial and viral infections, hypogammaglobulinemia, Lymphadenopathy, splenomegaly
	Hyper-IgE Syndrome	DOCK8	Cutaneous viral, fungus, staphylococcus infections, eosinophilia, eczema, diarrhea, failure to thrive
	Common variable immunodeficiency	ICOS	Infectious enteritis, small bowel disease prominent and nodular lymphoid hyperplasia of GI tract, splenomegaly

continues

Table II. *follows*.

Phagocyte and NADPH oxidase complex defects	Chronic granulomatous disease	CYBA, CYBB, NCF1-2-4, LACC1	Infections, autoimmunity, maternal discoid lupus
	Congenital neutropenia	G6PC3	Neutropenia, cardiac anomalies, urogenital defects, IUGR
	Glycogen storage disease 1b	SLC37A4	Hypoglycemic episodes, neutropenia, hepatomegaly
Hyperinflammatory and autoinflammatory defects	X-linked lymphoproliferative syndrome 2	XIAP	Infantile onset IBD, Epstein-Barr Virus (EBV) infection, hepatitis, hemaphagocytic lymphohistiocytosis (HLH), splenomegaly
	Familial Mediterranean Fever	MEFV	Periodic fever, oral ulcers, arthritis, serositis, rash, enteropathy
	Mevalonate kinase deficiency (Hyper IgD syndrome)	MVK	Elevated IgD, fever, nausea, abdominal pain, adenopathy, oral ulcers, arthritis, splenomegaly, enteropathy, perianal disease
Others	Trichohepatoenteric syndrome	SKIV2L, TTC37	IUGR, trichorrhexis nodosa, frontal bossing, villous atrophy

Laboratory exams

A critical part of the diagnostic workup is represented by laboratory investigations, comprising a standard panel of blood chemistry tests including complete blood count, metabolic profile, inflammatory indices, serology and fecal cultural examinations. Fecal calprotectin is of little use in this context, given its poor specificity and, under two years of age, also its reduced sensitivity [16].
Regardless of age, chronic diarrhea is most often caused by infectious agents, and infection should be ruled out first with appropriate serology and stool culture. Infective agents include *Shigella, Salmonella, Yersinia, Escherichia coli, Campylobacter, Cryptosporidium, Giardia, Clostridium difficile* and, depending on a patient's geographic location and risk factors, tuberculosis and HIV [17].
In early childhood (children aged < 2 years) IgA class antigliadin antibodies (AGA) are needed to rule out coeliac disease (CD), since they are the first antibodies to appear and they show higher sensitivity in this age group than other tests. Regarding the IgG class of antibodies, their use should be restricted to patients with selective IgA deficiency, because only in this subgroup of patients the response is indicative for CD [18]. In older children, IgA class antitransglutaminase antibodies (tTGA) are the tests with the highest sensitivity for CD (98%); IgA class antiendomysial antibodies (EMA) has a lower sensitivity compared to IgA class tTGA (90% *vs* 98%), but show an almost absolute specificity for CD [18].
The finding of neutropenia, lymphopenia, thrombocytopenia and/or leukocytosis can suggest immunological defects. Markedly elevated inflammatory markers, *e.g.* PCR, can be seen in hyperinflammatory diseases such as XIAP and NLRC4 mutations [14].
The assessment of humoral immunity by assaying the classes (IgG, IgA, IgM, IgE) and subclasses of the immunoglobulins and vaccine antibody titers might allow to rule out diagnoses such as common variable immunodeficiency (CVID), hyper-IgM syndrome, hyper-IgE syndrome, and agammaglobulinemia. Lymphocyte subset analyses can be very informative to detect T cell defects, B cell maturation or their subclasses (severe combined immunodeficiency [SCID], agammaglobulinemia). Additional functional tests such as oxidation tests for dihydrorodamine (DHR) or nitroblue tetrazolium (NBT) can be performed to search for the presence of a chronic granulomatous disease. Other screening tests include evaluation for XIAP deficiency and a flow cytometry-based assay, which should as a general rule always be performed in infantile onset disease, particularly in male patients [14].

Imaging and endoscopic features

Imaging in VEO-IBD is challenging. Despite the predominance of colonic inflammation, imaging of the small intestine is required to determine the extent of intestinal disease. However, this is difficult in very young children. Useful methods are wireless capsule endoscopy (WCE) and magnetic resonance enterography (MRE) [19].
Endoscopy is crucial to explore the pattern of disease, and determine if it is more consistent with an allergic, inflammatory, or infectious process. Diagnostic workup and criteria of VEO-IBD endoscopic findings description are the same applied to other pediatric IBDs, according to the revised Porto criteria and Paris classification [20]. VEO-IBD often presents as unspecific intestinal inflammation with features of both CrD and UC and macroscopic findings of haemorrhagic mucosa, linear ulcerations and cobblestoning, aphthous ulcers, ileitis or ileal ulcers, pseudo-polyps, narrowing or stenosis of the colon or terminal ileum, colitis with rectal sparing, oesophagitis, gastritis and duodenitis or duodenal ulcers [21].

Endoscopic findings of VEO-IBD are more commonly UC-like (35-59%) with a pancolitis involvement, whereas about 30-35% present as CrD-like, with colonic involvement, in contrast with older children and adults in whom a predominant small bowel or ileocecal disease is found [22].

Neonatal IBD shows the features of an intractable ulcerating enterocolitis. Inflammation is transmural and pan-enteric, typically with well-circumscribed, deep flat ulceration of the mucosa, often associated to a severe perianal disease and a poor outcome [23].

Severe ulcerative inflammation in the colon mimicking CrD is decribed in some cases of NEMO and LBRA deficiency, in about 40% of patients with CGD, and in about 20% of patients with XIAP deficiency [20]. A CrD-like cobblestone appearance and inflammatory pseudopolyps, as well UC-like features, are described in Wiskott-Aldrich syndrome (WAS) [24]. IL-10/IL-10R deficiency causes an infantile severe discontinuous UC-like enteritis (colitis or ileocolitis) with pronounced perianal disease and fistulas [25]. CVID can cause aphthous lesions in the colon and enteropathy with villous atrophy, mimicking coeliac disease [26].

The histological examination of endoscopic biopsies is a crucial element in the diagnostic workup of a patient with VEO-IBD and assists in making a final diagnosis, particularly in differentiating between a 'pure' IBD and other forms of non-IBD colitis. All the different segments of the ileo-colic tract should be extensively sampled, regardless of the endoscopic extension of the disease, with at least two biopsies in the terminal ileum and in each segment of the large bowel (caecum, ascending, transverse, descending, sigmoid colon and rectum), even if the mucosa appears endoscopically normal. At the time of the first diagnosis, and for a comprehensive evaluation, esophageal, gastric and duodenal biopsies are recommended [6].

Histological findings

Histological findings in GI biopsies are very heterogenous, being characterized by several patterns of disease, each one associated with gene alterations, rather than clear-cut IBD-associated lesion [27].

The four histological patterns described in gastrointestinal biopsies from VEO-IBD are:

1 **CrD-like pattern**, characterized in the colon by a

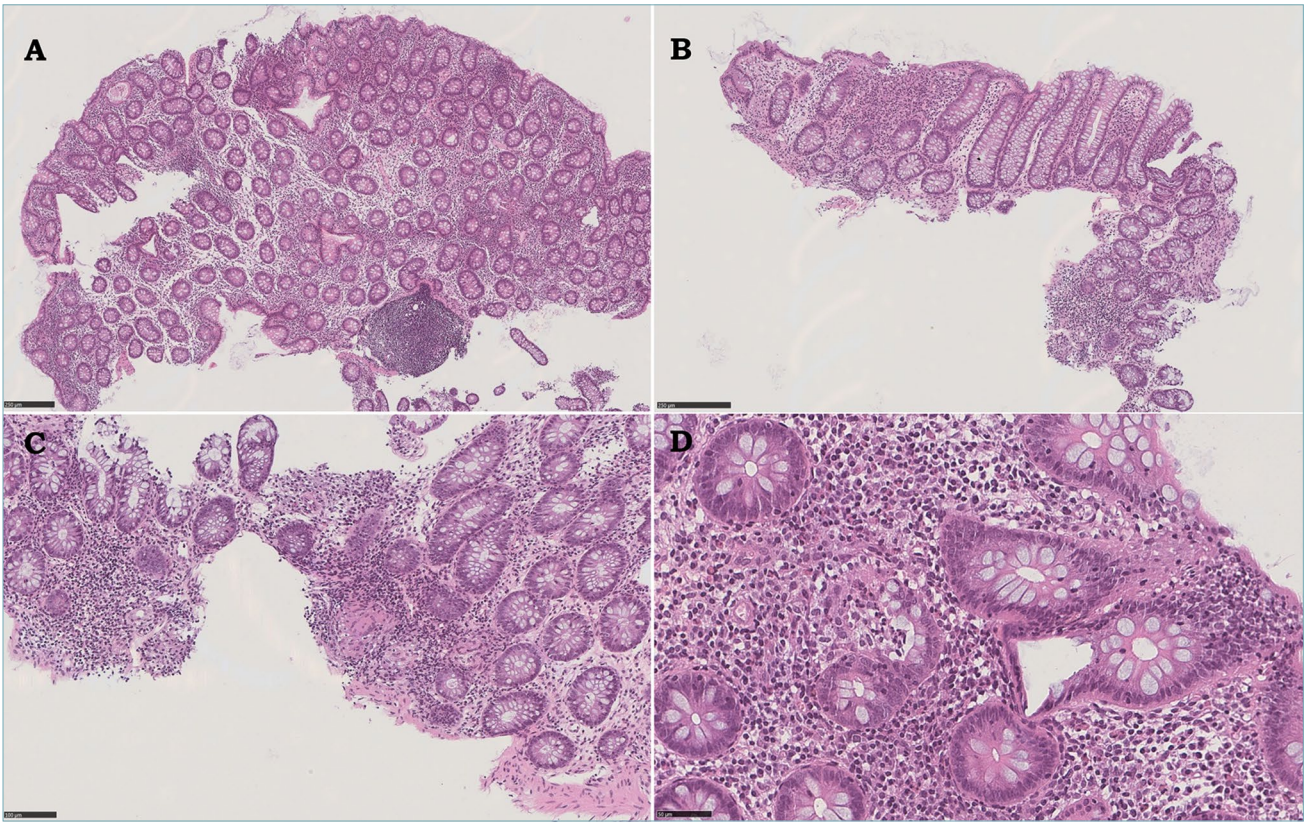

Figure 1. CrD-like pattern VEO-IBD. Discontinuous inflammation in the right colon and in the rectum (A, B respectively; H&E 5x); polymorphous inflammatory infiltrate with epithelioid granuloma (C, H&E 10x) and cryptitis (D, H&E 10x) (3 y.o; male, XIAP syndrome).

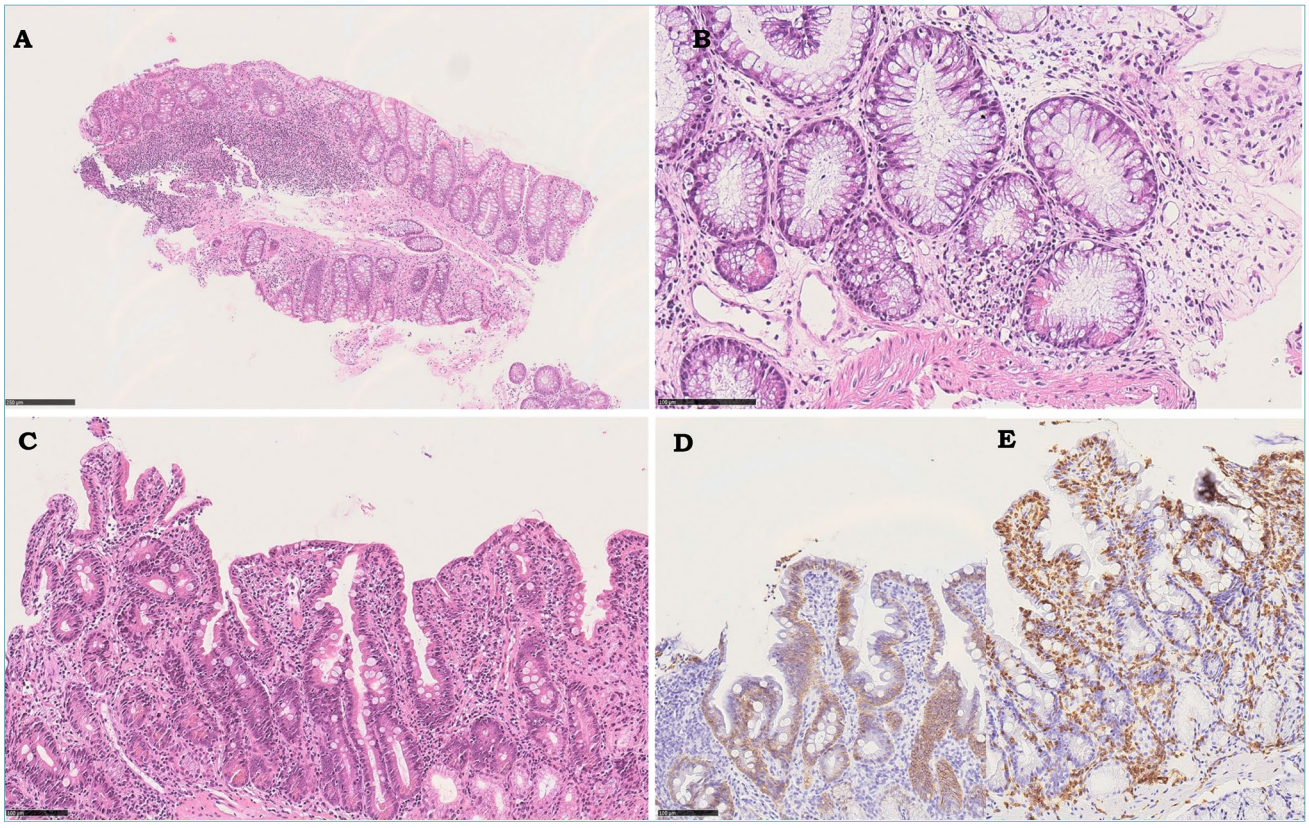

Figure 2. UC-like pattern VEO IBD. Moderate atrophy and glandular distortion in the right colon (A, H&E 5x); polymorphous inflammatory infiltrate with plasma cells and eosinophils with moderate glandular distorsion, apoptotic bodies and Paneth cell metaplasia in the rectum (B, H&E 20x); villous blunting in duodenal biopsy (C, H&E 20x); CD138 immunohistochemistry showing lack of plasma cells (D, 20x); CD3 immunohistochemistry showing intraepithelial T lymphocytes (E, 20x) (6 y.o., male, RAG1 syndrome).

discontinuous inflammatory infiltrate with eosinophils, neutrophils and plasma cells, transmural inflammation and ulceration, deep ulceration of mucosa, crypt abscess formation, granulomas; in the small bowel: villous atrophy; crypt hyperplasia, chronic/active enterocolitis, focal cryptitis, granulomas, pronounced lymphoid hyperplasia, aphthous lesions over lymphoid aggregates (Fig. 1).

2 **UC-like pattern**, characterized by a continuous marked inflammatory infiltrate with eosinophils, monocytes, plasma cells and lymphocytes with or without cryptitis, Paneth cell metaplasia, ulcerations and architectural glands atrophy/distortion, focal detachment of colonic epithelium, ischemic ulcers (Fig. 2).

3 **Enterocolitis-like pattern**, characterized by extensive villous atrophy in the small bowel, widespread leukocytic and eosinophilic infiltrate, ulcerations with architectural distortion, exudate and mucosal friability, and edema. Localized alterations include: karyorrhectic cellular debris, brown-pigment-containing macrophages, susceptibility to CMV colitis with inclusion bodies in the colon, massive T cell lymphocytic infiltrate in the duodenal mucosa (Fig. 3).

4 **Apoptotic pattern**, characterized by severe glandular atrophy, sparse glands, increased mononuclear cells in lamina propria, apoptotic cell death, extensive apoptosis, gland dropout and 'exploding crypts' (Fig. 4).

The differential diagnosis with celiac disease, infective gastroenteritis, eosinophilic gastroenteritis, allergic gastroenteritis, autoimmune colitis, should be taken in consideration. For these entities, we invite the reader to refer to other papers in this Special Issue for a more in-depth discussion of these conditions [18,28-31]. Some peculiar 'minimal histological lesions' have been described in VEO-IBD, and are reported to be more frequent with respect to IBD arising in older pa-

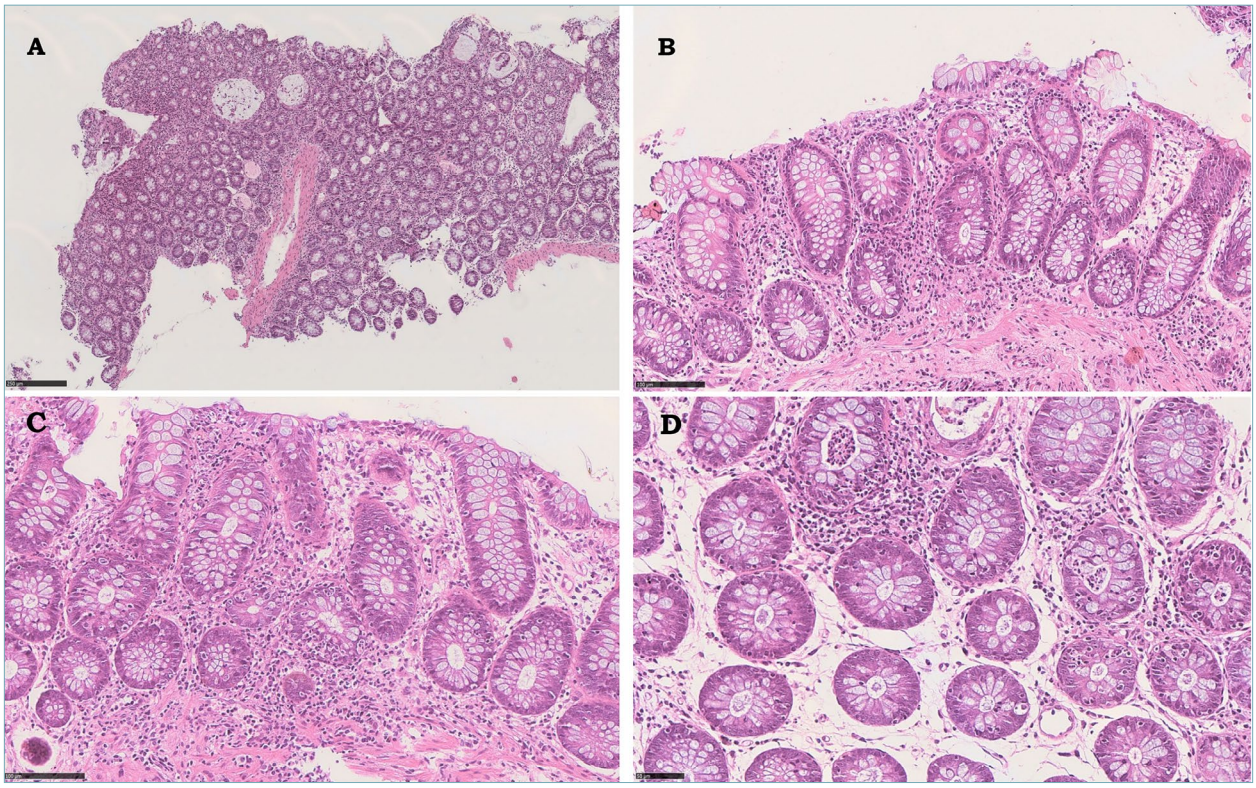

Figure 3. Enterocolitis-like pattern VEO-IBD. Marked homogeneous inflammatory infiltrate with preserved glandular architecture in the transverse colon (A, H&E 10x); mucosal pseudo-detachment (B, H&E 20x); cryptitis (C, H&E 20x); dishomogeneous infiltrate (D, H&E 20x) (infective etiology, 5 y.o. female).

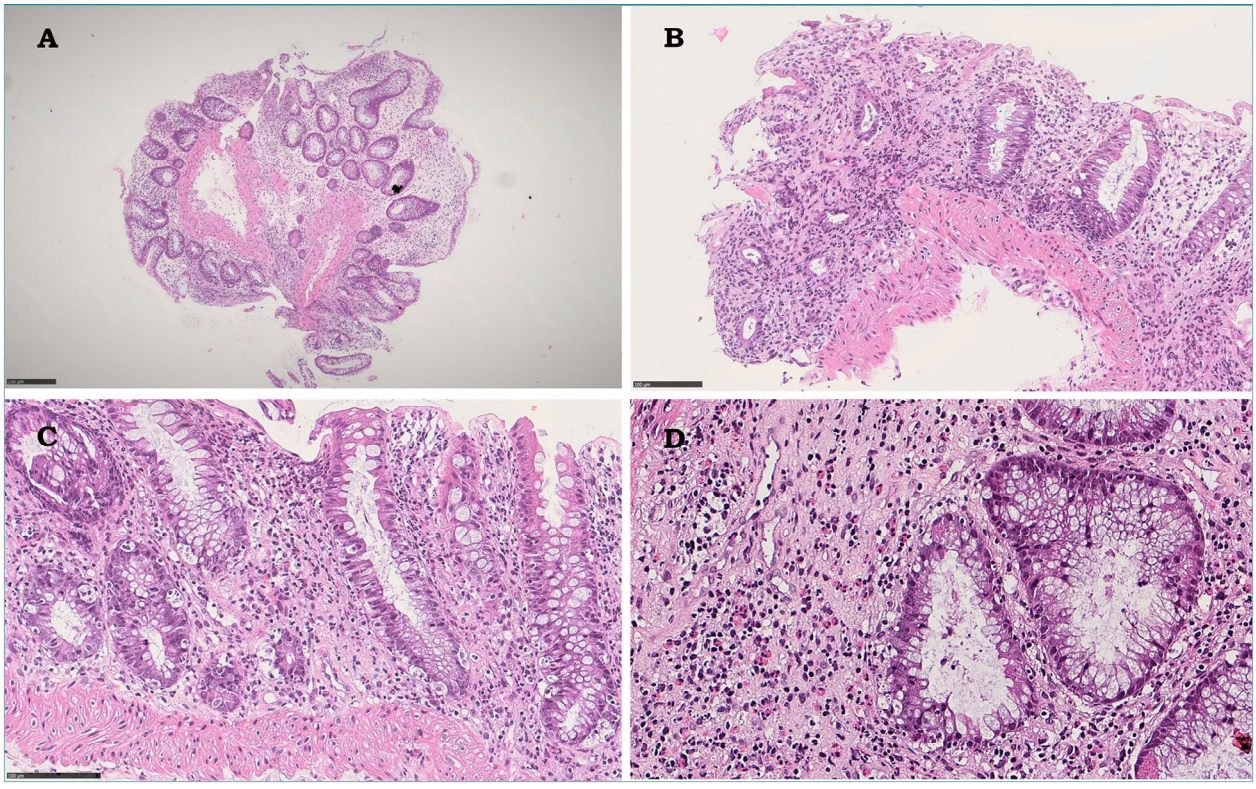

Figure 4. Apoptotic-like pattern VEO-IBD. Severe glandular atrophy in right colon (A, H&E 10x); ischemic-like features, mucosal pseudo-detachment (B, H&E 10x); apoptotic bodies (C H&E 20x); severe glandular atrophy, apoptotic bodies, dense eosinophilic infiltrate in the lamina propria with Paneth cells metaplasia in the rectum (D H&E 30x) (male, 2 y.o., DKC1 monogenic disorder).

tients. These include: increased frequency of apoptosis, moderate to severe chronic architectural changes, small intestinal villous blunting often in the absence of inflammation, and presence of dense eosinophilic infiltrate in the crypts, lamina propria, and surface epithelium[32]. These findings have been previously associated with immunodeficiencies and disorders of immune regulation, such as severe combined immunodeficiency or common variable immunodeficiency.

Pathological report: clues and issues

The issues described above emphasize some considerations. First: in a clinical setting suggesting VEO-IBD, histological lesions in GI biopsies are not as specific as in older-onset paediatric IBD and very unusual findings can be observed. Moreover, histological alterations do not have a homogeneous distribution in the upper and lower GI tract. Extensive mucosal sampling of both upper and lower GI mucosae is imperative to reduce the differential diagnosis landscape. Duodenal biopsies, including the first (duodenal bulb) and second parts of the duodenum, and multiple colonic biopsies from different sites, including the terminal ileum, should be taken and sent for pathologic examination in separately coded vials [6].

Second: even in presence of 'consistent with IBD' histological alterations, an isolate histological diagnosis out of clinical context is dangerous and carries the risk of missing a PID diagnosis, with inappropriate following therapy. Briefly, we stress that immunosuppressive therapy, codified in IBD, can be fatal in children with PID. Labelling 'IBD' early in the disease course as 'CrD' or 'UC' might prevent the physician from considering further investigations. This is particularly dangerous in the case of CrD-like colitis, because typical microscopic and macroscopic features, such as perianal/fistulizing disease, linear or serpentine ulceration, and granulomas have also been reported in a variety of monogenic conditions. On the other hand, in some rare cases, early evolving VEO-IBD without the typical features of IBD may be missed on initial evaluation. Therefore, it is important to not definitively rule out VEO-IBD based on the lack of chronic features alone where clinical suspicion for VEO-IBD is high [32].

Third: it is important to describe all histological alterations in different sites with a final comment suggesting differential diagnosis, and it can direct the pediatricians toward deeper clinical and genetic/immunogenetic investigations. The presence of peculiar histological alterations, such as florid eosinophilic infiltrate, apoptotic pattern, severe atrophy, small intestinal villous blunting in the absence of inflammation should be underlined, because it is associated with monogenic diseases and PID.

Finally: although there is an increased likelihood of monogenic etiologies and PID in patients with VEO-IBD, most children with VEO-IBD do not have an underlying PID. Given the rarity of IBD in this age group and the challenges in making a diagnosis, pediatric gastroenterologists often feel hesitant to diagnose a young infant with an IBD, a disease that comes with the need for medical interventions and a significant risk profile[3]. On the other hand, understandable concerns exist regarding the use of conventional immunosuppressive IBD therapies in underlying (missed) PID. The management of a patient with VEO-IBD should be a coordinated effort of a team of specialists, including gastroenterologists, pediatricians, immunologists, geneticists, bone marrow transplant experts, nutritionists, surgeons, and, of course, pathologists. Referral to centers with expertise in this field is advised.

Conclusions

VEO-IBD represents a subset of intestinal inflammatory disorders, typically occurring in a younger age group, that may be the manifestation of an underlying monogenic disorder. Patients with VEO-IBD typically do not respond to conventional IBD therapy and require specific treatment, ideally targeted against the specific defect, and monitoring of complications. The diagnosis of these unique disorders relies on the use of next-generation sequencing analysis, but their identification can be suggested by a complete clinical investigation and a comprehensive histological evaluation. Moreover, good clinicopathologic collaboration is crucial for the differential diagnosis with childhood enteropathies and a 'pure' IBD with very early onset.

References

1 Langner C, Magro F, Driessen A, et al. The histopathological approach to inflammatory bowel disease: a practice guide. Virchows Arch 2014;464:511-527. https://doi.org/10.1007/s00428-014-1543-4

2 Magro F, Doherty G, Peyrin-Biroulet L, et al. ECCO Position Paper: Harmonisation of the approach to Ulcerative Colitis Histopathology. Crohn's Colitis 2020;7;14:1503-1511. https://doi.org/10.1093/ecco-jcc/jjaa110.

3 Ouahed J, Spencer E, Kotlarz D, et al. Very early onset inflammatory bowel disease: a clinical approach with a focus on the role of genetics and underlying immune deficiencies. Inflamm Bowel Dis 2020;12;26:820-842. https://doi.org/10.1093/ibd/izz259.

4 Uhlig HH, T, Koletzko S, Shah N, et al. The diagnostic approach to monogenic very early onset inflammatory Bowel Disease. Gastroenterology 2014;147:990-1007.e3. https://doi.org/10.1053/j.gastro.2014.07.023.

[5] Benchimol EI, Fortinsky KJ, Gozdyra P, et al. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423-439. https://doi.org/10.1002/ibd.21349

[6] Villanacci V, Reggiani-Bonetti L, Salviato T, et al. Histopathology of IBD Colitis. A practical approach from the pathologists of the Italian Group for the study of the gastrointestinal tract (GIPAD). Pathologica 2021;113:39-53. https://doi.org/10.32074/1591-951X-235

[7] Kelsen JR, Russo P, Sullivan KE. Early-onset inflammatory Bowel Disease. Immunol Allergy Clin North Am 2019;39:63-79. https://doi.org/10.1016/j.iac.2018.08.008

[8] Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr 2015;169:1053-1060. https://doi.org/10.1001/jamapediatrics.2015.1982

[9] Nameirakpam J, Rikhi R, Rawat SS, et al. Genetics on early onset inflammatory bowel disease: An update. Genes Dis 2019;7:93-106. https://doi.org/10.1016/j.gendis.2019.10.003

[10] Uzel G, Orange JS, Poliak N, Marciano BE, Helle T, Hollan SM. Complications of tumor necrosis factor-alpha blockade in chronic granulomatous disease-related colitis. Clin Infect Dis 2010;51:1429-1434. https://doi.org/10.1086/657308

[11] Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med 2009;361:2033-45. https://doi.org/10.1056/NEJMoa0907206

[12] Barzaghi F, Passerini L, Bacchetta R. Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome: a paradigm of immunodeficiency with autoim- munity. Front Immunol 2012;3:211. https://doi.org/10.3389/fimmu.2012.00211

[13] Kelsen JR, Dawany N, Moran CJ, et al. Exome sequencing analysis reveals variants in primary immunodeficiency genes in patients with very early onset inflammatory bowel disease. Gastroenterology 2015;149:1415-24. https://doi.org/10.1053/j.gastro.2015.07.006

[14] Kelsen JR, Sullivan KE, Rabizadeh S, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Evaluation and Management for Patients With Very Early-onset Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2020;70:389-403. https://doi.org/10.1097/MPG.0000000000002567

[15] Birimberg-Schwartz L, Zucker DM, Akriv A, et al. Development and validation of diagnostic criteria for IBD subtypes including IBD-unclassified in children: a multicentre study from the pediatric IBD Porto Group of ESPGHAN. J Crohns Colitis 2017;11:1078-1084. https://doi.org/10.1093/ecco-jcc/jjx053

[16] Spencer EA, Davis SM, Mack DR, et al. Serologic reactivity reflects clinical expression of ulcerative colitis in children. Inflamm Bowel Dis 2018;24:1335-1343. https://doi.org/10.1093/ibd/izy009

[17] Villanacci V, Reggiani Bonetti L, Leoncini G, et al. Non-IBD colitis. The position of the pathologists of the Italian Group for the study of the gastrointestinal tract (GIPAD). Pathologica 2021;113:54-65. https://doi.org/10.32074/1591-951X-234

[18] Villanacci V, Vanoli A, Leoncini G, et al. Celiac disease: histology-differential diagnosis-complications. A practical approach. Pathologica 2020;112:186-196. https://doi.org/10.32074/1591-951X-157

[19] Watson TA, Petit P, Augdal TA, et al. European Society of Paediatric Radiology abdominal imaging task force: statement on imaging in very early onset inflammatory bowel disease. Pediatr Radiol 2019;49:841-848. https://doi.org/10.1007/s00247-019-04375-8

[20] Arrigo S, Signa S, Barabino A. Early Onset IBD: endoscopic features. In: Dall'Oglio L, Romano C, eds. Endoscopy in pediatric inflammatory Bowel Disease. Springer, Cham. https://doi.org/10.1007/978-3-319-61249-2_4

[21] Dahlhamer JM, Zammitti EP, Ward BW, Wheaton AG, Croft JB. Prevalence of inflammatory bowel disease among adults aged ≥ 18 years - United States, 2015. MMWR Morb Mortal Wkly Rep 2016;65:1166-1169. https://doi.org/10.15585/mmwr.mm6542a3.

[22] Bequet E, Sarter H, Fumery M, et al. Incidence and phenotype at diagnosis of very early onset compared with later onset paediatric inflammatory bowel disease: a population-based study [1988-2011]. J Crohns Colitis 2017;11:519-526. https://doi.org/10.1093/ecco-jcc/jjw194

[23] Thapar N, Shah N, Ramsay AD, et al. Long-term outcome of intractable ulcerating enterocolitis of infancy. J Pediatr Gastroenterol Nutr;40:582-588 https://doi.org/10.1097/01.mpg.0000159622.88342.bc

[24] Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel diseases in children and adolescents. JAMA Pediatr 2015;169:1053-1060. https://doi.org/10.1001/jamapediatrics.2015.1982

[25] Kelsen JR, Baldassano RN, Artis D, Sonnenberg GF. Maintaining intestinal health: the genetics and immunology of very early onset inflammatory bowel disease. Cell Mol Gastroenterol Hepatol 2015;1:462-476. https://doi.org/10.1016/j.jcmgh.2015.06.010

[26] Tegtmeyer D, Seidl M, Gerner P, et al. IBD due to PID: inflammatory bowel disease caused by primary immunodeficiencies - clinical presentations, review of literature, and proposal of a rational diagnostic algorithm. Pediatr Allergy Immunol 2017;28:412-429. https://doi.org/10.1111/pai.12734

[27] Ensari A, Kelsen J, Russo P. Newcomers in paediatric GI pathology: childhood enteropathies including very early onset monogenic IBD. Virchows Arch 2018;472:111-123. https://doi.org/10.1007/s00428-017-2197-9

[28] Campora M, Mastracci L, Carlin L, et al. Pathologist's approach to paediatric and neonatal eosinophilic gastrointestinal disorders. Pathologica 2021 In Press.

[29] Rossi C, Simoncelli G, Arpa G, et al. Histopathology of intestinal villi in neonatal and paediatric age: main features with clinical correlation - Part I. Pathologica 2021 Epub December 2. https://doi.org/10.32074/1591-951X-337

[30] Rossi C, Simoncelli G, Arpa G, et al. Histopathology of intestinal villi in neonatal and paediatric age: main features with clinical correlation - Part II. Pathologica 2021 Epub December 2. https://doi.org/10.32074/1591-951X-338

[31] Francalanci P, Cafferata B, Alaggio R, et al Pediatric autoimmune disorders with gastrointestinal expression: from bench to bedside. Pathologica 2021 Epub December 2. https://doi.org/10.32074/1591-951X-339

[32] Conrad MA, Carreon CK, Dawany N, et al. Distinct histopathological features at diagnosis of very early onset inflammatory Bowel Disease. J Crohns Colitis 2019 26;13:615-625. https://doi.org/10.1093/ecco-jcc/jjy212