

Clinicopathologic Features of Primary Immunodeficiency Monogenic Disease-related Very Early Onset Inflammatory Bowel Disease: Focus on Gastrointestinal Histologic Features in *IFIH1* Mutations

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Abstract: Very early onset inflammatory bowel disease (VEO-IBD) is a clinical term referring to IBD-like symptomatology arising in children younger than 6 years. VEO-IBD may be due to polygenic etiology in “pure” IBD (Crohn disease-CD and ulcerative colitis-UC), or it may be caused by primary immunodeficiency underlined by monogenic disease. Primary immunodeficiency monogenic diseases have a Mendelian inheritance and affect the immune system with multiorgan morbidity and possible effects on the gastrointestinal system. Primary Immunodeficiency monogenic diseases differ from “pure” IBD as the latter primarily affect the gastrointestinal tract with mitigated extraintestinal symptomatology. Since their first description, primary immunodeficiency monogenic diseases, although rare, have been the subject of increasing interest due to their dramatic phenotype, difficulty in reaching a timely

diagnosis, and specific therapeutic approach. In this paper, we present a brief review of primary immunodeficiency monogenic diseases, focusing on to their clinicopathologic features as well as delving, in greater detail, into monogenic diseases caused by *IFIH1* mutations. The clinicopathologic features of 4 patients with *IFIH1*, a gene involved in interferon pathway deficiency, will be described using a histologic pattern of damage approach confirming the need to avoid the histologic diagnosis of VEO-IBD in children younger than 6 years.

Key Words: apoptotic enteritis, Crohn disease, *IFIH1*, MDA5, monogenic disease, PID, ulcerative colitis, VEO-IBD

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Very early-onset (VEO) inflammatory bowel disease (IBD) is a clinical umbrella term referring to IBD-like gastrointestinal (GI) symptoms, such as chronic diarrhea, vomiting, perianal lesions, haematochezia, abdominal pain, and rectal bleeding, arising in children before the sixth year of life.¹ The VEO-IBD term includes both “true” IBD, such as Crohn disease (CD) and ulcerative colitis (UC), and monogenic diseases.² Monogenic diseases-related VEO-IBDs are typically rare, severe, refractory to conventional therapies and are caused by monogenic variants of genes involved in primary immunodeficiencies and in intestinal epithelial disorders.³ Monogenic diseases are characterized by Mendelian inheritance in contrast to “true” IBDs, which derive from multigene alterations and environmental factors.³ Age of onset, family history, atypical endoscopic findings, severity, atypical infection history, and extra-intestinal comorbidity point to a monogenic disease-etiology with IBD-like symptoms rather than a “true” polygenic IBD.³ To date, between 80 to 90 causative genes of monogenic diseases associated with IBD-like symptoms have been reported and, in recent years, the number of novel genes has increased. In this setting, the identification of a primary immunodeficiency monogenic disease cause is critical, as it has major implications in clinical management, treatment, and prognosis. The overriding need to identify primary immunodeficiency monogenic diseases-related VEO-IBD is, however, rendered difficult by often poorly understood clinical and histologic aspects which require a better understanding by the clinicians and pathologists.⁴

The present review will summarize what is known about primary immunodeficiency monogenic diseases, from their identification to recent classifications, describing the clinicopathologic features of the most frequent types. In particular, from a pathologic point of view, we aim to alert the general and GI specialist pathologists to monogenic disease etiology and provide pointers for their pathologic recognition in daily diagnostic practice. Moreover, the review will focus on clinical features and histologic patterns of GI damage in children with VEO-IBD associated with Interferon-induced helicase C domain 1—*IFIH1*- loss of function (LoF) variants, as these have only more recently come to clinical attention with the aim of enabling a prompt diagnosis, thus improving prognosis, predicting clinical course, and establishing new treatment strategies.

PRIMARY IMMUNODEFICIENCY-RELATED MONOGENIC DISEASE: A BRIEF HISTORICAL REVIEW

The first systematic approach to monogenic diseases was proposed more than 10 years ago by Uhlig, who published an in-depth review focusing on monogenic diseases associated with intestinal inflammation,⁵ underlining an earlier age of onset in primary immunodeficiency monogenic diseases-related VEO-IBD and a more severe clinical phenotype. Moreover, despite the markedly lower prevalence of monogenic diseases with respect to common intestinal infections, celiac disease, or IBD, these monogenic defects are associated with higher morbidity and even mortality. In particular, Uhlig focused on only 3 genes out of the 40 related to monogenic diseases (known at the time), common with key IBD genes, highlighting that monogenic diseases-related genes are “key functional nodes within inflammatory networks” in VEO-IBD. According to this hypothesis, Uhlig categorized the 40 known monogenic diseases based on 6 main immune pathway disorders as: (1) general immune dysregulation, (2) T and B cell defects, (3) phagocytic defects, (4) hyperinflammatory and autoinflammatory conditions, (5) epithelial barrier dysfunction, and (6) other conditions, with a detailed pathogenetic description. Most importantly, Uhlig strongly emphasized that intestinal inflammation in monogenic diseases, characterized by Mendelian inheritance, is indistinguishable, both endoscopically and histologically, from a “true” IBD, suggesting the “IBD-like pattern” as a better clinical definition. Primary immunodeficiency monogenic diseases-related VEO-IBDs, therefore, require a different therapeutic approach, which may change according to specific primary immunodeficiency-related etiology, and may range from hematopoietic stem cell transplantation to gene therapy. In fact, conventional “true” IBD therapy, such as nutritional support, anti-inflammatory and immunosuppressive treatments, show only partial effectiveness in monogenic diseases-related IBD.⁵

The background, clinical findings, and treatment strategy in VEO-IBD were extensively described by Ouahed et al,⁴ and further classification of VEO-IBD in infantile-onset IBD (IO-IBD; reflecting patients in which the disease presents before 2 years of age) and neonatal-onset IBD (IBD presenting within the first 28 days of life) was proposed. An updated description of syndromes, according to the 6 immune pathway disorders, featured clinical features, key laboratory findings, extraintestinal comorbidities, and, for the first time, the histologic features in each monogenic

disease (63 monogenic diseases had been described at the time) was reported. Most importantly, an algorithm for clinical workup (including in-depth medical history and physical examination, extensive laboratory assays, and extraintestinal comorbidities investigations) was suggested in VEO-IBD, with the function of recognizing primary immunodeficiency monogenic diseases-related VEO-IBD as early as possible with expedient genomic testing and appropriate therapeutic approaches, referring the patient to specialist centers as quickly as possible.⁴

Recently, Babcock et al⁶ proposed that monogenic diseases due to epithelial barrier dysfunction (the fifth immune pathway disorder) should be considered a distinct group of genetic intestinal disorders. Epithelial barrier dysfunctions target intestinal mucosa leading to congenital diarrhea and enteropathy syndrome, and are characterized by little to no chronic mucosal inflammation and, only in rare variants, by lymphoplasmic cellular infiltrate increased in the lamina propria. This is different from other primary immunodeficiency monogenic diseases that primarily affect immune cell function with only secondary involvement of the intestinal tract. Moreover, congenital diarrhea and enteropathy syndrome affect mainly the small intestine with variable involvement of the colon, resulting in a generalized enteropathy with consequent nutrient malabsorption and loss of normal fluid and electrolyte homeostasis, leading to malnutrition in infancy with effects on physical and cognitive development. Finally, hematopoietic stem cell transplantation is often curative in primary immunodeficiency monogenic diseases-related VEO-IBD, whereas congenital diarrhea and enteropathy syndrome lack effective treatments.⁶

Due to the need for timely diagnosis for appropriate treatment and genetic counseling, genetic screening was recently recommended in the clinical workup from the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) for all patients with IO VEO-IBD in the presence of relevant comorbidity, extra-intestinal manifestations, or positive family history, using a genetic sequencing panel of 75 genes.⁷

PRIMARY IMMUNODEFICIENCY MONOGENIC DISEASES ASSOCIATED VEO-IBD: PATHOLOGIC FEATURES

Histopathologic findings in GI samples from primary immunodeficiency monogenic diseases have a very broad-spectrum of phenotypes due to different genes involved in different inflammatory pathways, variable gene penetrance, timing of diagnosis, treatment-related modifications, and environmental factors. In this setting, 4 main pathologic patterns have been described.

The presence of chronic mucosal damage (architectural gland atrophy/distortion) identifies the Crohn disease-like/CD-like pattern and ulcerative colitis-like/UC-like pattern. In particular, the presence of a discontinuous lymphoplasmic cellular and eosinophilic infiltrate, transmural inflammation with deep ulceration, and aphthous lesions differentiate a CD-like pattern from a UC-like pattern, the latter characterized by ulcerations, crypt distortion, Paneth cell metaplasia and a homogenous lymphoplasmic cellular and eosinophilic inflammatory infiltrate.^{8,9} The gastroduodenal mucosa is often involved with focally enhanced gastritis, extensive duodenal villous blunting, and atrophy with

increased CD3-positive lymphocytes and variable inflammation as well as apoptotic bodies.

Acute inflammation with possible ischemic-like features but no evidence of chronic damage is diagnostic of the enterocolitis-like pattern, while severe glandular atrophy with extensive apoptoses, gland dropout, and “exploding crypts” without inflammation is typical of the apoptotic-like pattern. Finally, a dense eosinophilic inflammatory infiltrate in the lamina propria and mucosal surface is found in the eosinophilic pattern with possible “minimal histologic changes” such as increased frequency of apoptosis and minimal architectural changes.^{8,9} Of note, the described patterns seen in primary immunodeficiency monogenic diseases—related disorders are undistinguishable from “true” IBD and other GI disorders, such as infective disease, food intolerance, drug reactivity, autoimmunity, and celiac disease. For these reasons, a description of the mucosal damage pattern (ie, UC-like pattern) rather than a definitive diagnosis (ie, UC) is desirable in the pathologic report.¹⁰

EPIDEMIOLOGY OF PRIMARY IMMUNODEFICIENCY MONOGENIC DISEASES—RELATED VEO-IBDS AND MOST FREQUENT VARIANTS

Monogenic Diseases have been reported in about 15% to 20% of VEO-IBDs,¹ although the exact prevalence of primary immunodeficiency monogenic diseases—associated VEO-IBD is not well established, due to several factors such as bias in the geographic representation/selection of the investigated cohorts, differences in severity at clinical onset, reduced opportunities for health service access in the developing world (who may be the ones at greater risk due to the greater likelihood of inbreeding relationships). Finally, different molecular approaches (Next Generation Sequencing versus Whole Exome Sequencing versus whole genome sequencing) can affect the detection of peculiar gene alterations.⁷ Notwithstanding this, a recent systematic review has identified the most frequently reported Monogenic Diseases,¹¹ and large case studies have contributed to better describe the most frequent primary immunodeficiency monogenic diseases.^{12,13} Here, we describe the three most common primary immunodeficiency monogenic diseases genes related to VEO-IBD and summarize the main clinical and pathologic features in Table 1.

Interleukin 10-associated Disease

Interleukin 10 (IL-10) acts with anti-inflammatory effects and is involved in both innate and acquired immunity. In particular, IL-10 affects the production of proinflammatory cytokines such as interferon- γ , IL-2, IL-3, and TNF- α with an inhibitor effect. Mutations in *IL-10* and its *IL-10R* receptor (*IL-10RA* and *IL-10RB*) lead to disorders in the inflammatory pathway, with excessive immune response to infectious agents.¹⁴

IL-10 gene alteration is the most frequent primary immunodeficiency monogenic disease described in VEO-IBD with 37.4% of cases¹¹ and is significantly more common in East Asia.¹² Due to wide and ubiquitous action, IL-10 alterations lead to multiorgan involvement with GI symptoms and extraintestinal comorbidities, mainly represented by recurrent infections. The loss of IL-10 signaling promotes intestinal damage, probably due to an excessive immune response to gut microbiota.¹⁴

Chronic Granulomatous Disease (CGD)

CGD is due to mutations in genes (*CYBA*, *CYBB*, *NCF1*, *NCF2*, *NCF4*) encoding the subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex, leading to impaired phagocytic function with granuloma formation, without micro-organism deletion. Clinical phenotype and prognosis are severe in the X-linked type and moderate in the autosomal recessive type. This primary immunodeficiency monogenic disease is characterized by an increased susceptibility to recurrent and severe opportunistic bacterial and fungal infections, hyperinflammation, and autoimmunity.¹⁵

CGD is the second most frequent primary immunodeficiency monogenic disease in VEO-IBD, with 11.1% of cases described.¹¹ GI symptoms and extraintestinal comorbidities stem from recurrent infections with multiple and persistent granulomas. The CD-like pattern is, therefore, the most frequently reported in GI samples.

X-linked Inhibitor of Apoptosis (XIAP) Deficiency

X-linked inhibitor of apoptosis (XIAP) protein is involved in both the innate and acquired immune response through antiapoptotic functions, mainly on invariant natural killer T cells (iNKT) and mucosal-associated invariant T cells (MAIT). XIAP also modulates proinflammatory cytokines and chemokines in the autophagic elimination of intracellular bacteria.¹⁶

Interestingly, XIAP affects intestinal homeostasis and Paneth cell function. Impaired signaling leads to a reduction of chemoattraction of granulocytes to the gut with loss of clearance of pathogens and chronic granulomatous inflammation development. Gut immunity is also affected by increased susceptibility to apoptosis of MAIT and iNKT cells.¹⁶

XIAP-syndrome is the third most frequent primary immunodeficiency monogenic disease in VEO-IBD, with 6.5% of cases.¹¹

PRIMARY IMMUNODEFICIENCY MONOGENIC DISEASE-ASSOCIATED VEO-IBD WITH *IFIH1* LOF VARIANTS: CLINICO-HISTOPATHOLOGIC DESCRIPTION OF 4 CASES

As new types of monogenic diseases are being identified and more information is being collected on previously described primary immunodeficiency monogenic diseases causes of VEO-IBD, even rare variants are coming to clinical attention. In particular, primary immunodeficiency monogenic diseases—associated VEO-IBD with *IFIH1* defects, have been better described from a clinical and pathologic perspective, and the description of 4 such cases, 3 from a series of 93 VEO-IBD patients, will, hopefully, prove useful when faced with biopsies from a young VEO-IBD patient.

Interferon-induced with helicase C domain 1 (*IFIH1*; also known as melanoma differentiation-associated protein 5, MDA5) is a cytosolic sensor of dsRNA that induces an anti-viral type I interferon (IFN) state. IFNs are an important group of cytokines that control inflammasome signaling; type I IFNs have been shown to suppress inflammasome activity and reduce the production of proinflammatory cytokines. Moreover, type I IFNs can also trigger inflammasome activity during microbial infections.¹⁷ Monoallelic gain-of-function (GoF) variants in *IFIH1*, underlined by different point mutations, cause

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TABLE 1. Clinical and Pathologic Features in IL-10, CGD, XIAP, and IFIH1 Syndromes

PID-MD	Genes	Inheritance	Endoscopic findings	GI symphoms	EIC	Laboratories data	Histopathological pattern	Therapy
IL-10	<i>IL10, IL10RA, IL10RB</i>	AR	CD-like > > > UC-like	Bloody diarrhea, perianal disease and fistula, oral ulcers	Atypical infections and recurrent pneumonia; AHA; skin, nail, and hair abnormalities and infections; thrombotic complications; arthropathy; developmental delay; DM; bone malformations; B-Lymphoma	Hypogammaglobulinemia; selective IgG2 deficiency; defective STAT3 phoshorylation in response to IL-10; decreased functional IL-10	IBD-U-like pattern	HSCT
CGD	<i>CYBA, CYBB, NCF1, NCF2, NCF4</i>	AR, X-linked, AR, AR, AR	CD-like > > > UC-like	Bloody diarrhea, perianal disease, and fistula	Recurrent multiorgan abscesses; fungal pulmonary nodules; osteomyelitis; attention deficit disorders; gastric outlet obstruction; eczema; chorioretinitis; HLH; failure to thrive	Decreased neutrophil oxidative burst study; elevated IgG	CD-like pattern	HSCT
XIAP	<i>XIAP</i>	X-linked	IBD-like	Bloody diarrhea, recurrent strictures, and abscesses; GI hemorrhage; parasitic infections	Atypical and recurrent infections; skin, nail, and hair abnormalities and infections; lympho-organ abnormalities; HLH/MAS; cholangitis; renal failure; vasculitis; coagulopathy	Neutropenia; hypogammaglobulinemia; elevated IL-18, IL-6, IL-2, IFN-γ, TNF-α and neopterin	CD-like pattern; eosinophilic gastroenteritis-like pattern; Celiac disease-like pattern	HSCT
IFIH1	<i>IFIH1</i> Case 1 Case 2 Case 3 Case 4	LoF, MAIP, AR, LoF	CD-like	Bloody, protein-losing inflammatory diarrhea, recurrent vomiting	Recurrent respiratory infections; failure to thrive; neonatal sepsis; postnatal CMV infection; urinary infections; interstitial pneumonia	Mild elevation of systemic inflammatory indexes; hypoalbuminemia; leucocytosis	UC-like; CD-like; IBD-U-like	Systemic steroids and Azathioprine; 5-ASA

5-ASA indicates 5-aminosalicylic acid; AHA, autoimmune hemolytic anemia; AR, autosomic recessive; CD, Crohn disease; CGD, chronic granulomatous disease; DM, Diabetes Mellitus; EIC, extraintestinal comorbidity; GI, gastrointestinal symptoms; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; IBD-U, inflammatory bowel disease unclassified; LoF, loss of function; MA, monoallelic; MAIP, monoallelic incomplete penetrance; MAS, macrophage activation syndrome; MD, monogenic disease; PID, primary immunodeficiency; UC, ulcerative colitis; XIAP, X-linked inhibitor of apoptosis.

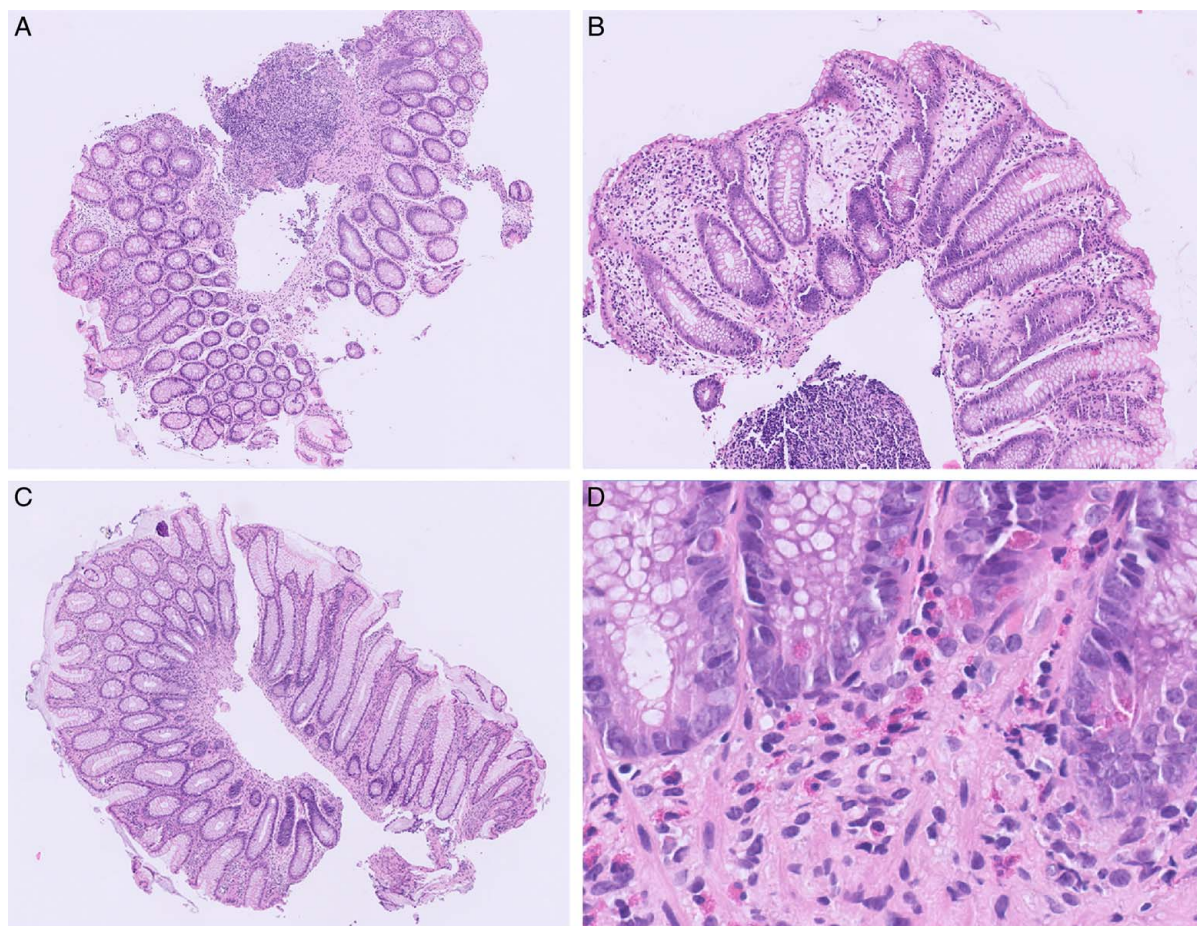


FIGURE 1. Case 1: Mild atrophy and glandular distortion with discontinuous plasma cells and eosinophilic infiltrate in the lamina propria in the biopsies from right (A, hematoxylin and eosin, $\times 5$), transverse (B, H&E, $\times 10$) and homogeneous in descending colon (C, H&E, $\times 5$) was observed, with Paneth cells in the rectum (D, H&E, $\times 40$) (IBD-U like pattern).

increased Type I IFN activity and are clinically associated with Aicardi-Goutières syndrome (AGS),¹⁸ Singleton-Merten Syndrome 1 (SGMRT1) and early-onset systemic lupus erythematosus with IgA deficiency.¹⁹ Monoallelic and biallelic LoF variants cause susceptibility to viral infections and have been associated with recurrent life-threatening respiratory infections during infancy.^{20–22} GI manifestations, including IBD, are extremely rare in patients with germline GoF *IFIH1* variants,²³ whereas complete and partial *IFIH1* deficiency has very recently been associated with VEO-IBD.¹⁹ When present, GI manifestations may predominate over extraintestinal comorbidities, potentially delaying the recognition of *IFIH1* deficiency.

As previously mentioned, 3 out of 4 *IFIH1* cases belong to a series of 93 VEO-IBD patients, which have been previously included in a recent, morphologic pattern validation study.²⁴ As previously published, the main morphologic patterns identified on histology slides were classified as follows: (1) UC-like pattern, (2) CD-like pattern, (3) enterocolitis-like pattern, (4) apoptotic pattern, (5) eosinophilic pattern, and (6) IBD-like pattern not otherwise specified/unclassified (IBD-U).^{8,24}

Out of a series of 93 VEO-IBD children, 13 were found to have monogenic diseases-related VEO-IBD, and, more specifically, 3 of these children were found to be carriers of

either mono- or biallelic *IFIH1* LoF variants; a fourth child was subsequently identified and included in this morphologic re-evaluation. The endoscopic biopsy sets of these 4 children were specifically re-evaluated for morphology and described in detail. The clinical history of all cases was also reviewed.

All samples were handled in compliance with the Declaration of Helsinki (<https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/>).

Case 1

A 1-year-old boy was admitted to the Gastroenterology Department with GI symptoms consisting of bloody, protein-losing inflammatory diarrhea, recurrent vomiting, and growth failure since the age of 6 months. Shortly afterward, the patient underwent a GI endoscopy as part of the investigation into a possible diagnosis of IBD. Whereas gastroesophageal endoscopy was unremarkable, colonoscopy revealed severe pancolitis with rectal sparing, characterized by multiple, linear, deep ulcers interspersed with normal mucosa, and an IBD-like pattern was diagnosed. A recent CMV infection was documented but no evidence of CMV colitis was found at histology. After steroids and azathioprine therapy, clinical remission was achieved. Repeat endoscopy at 2 and 5 years of age,

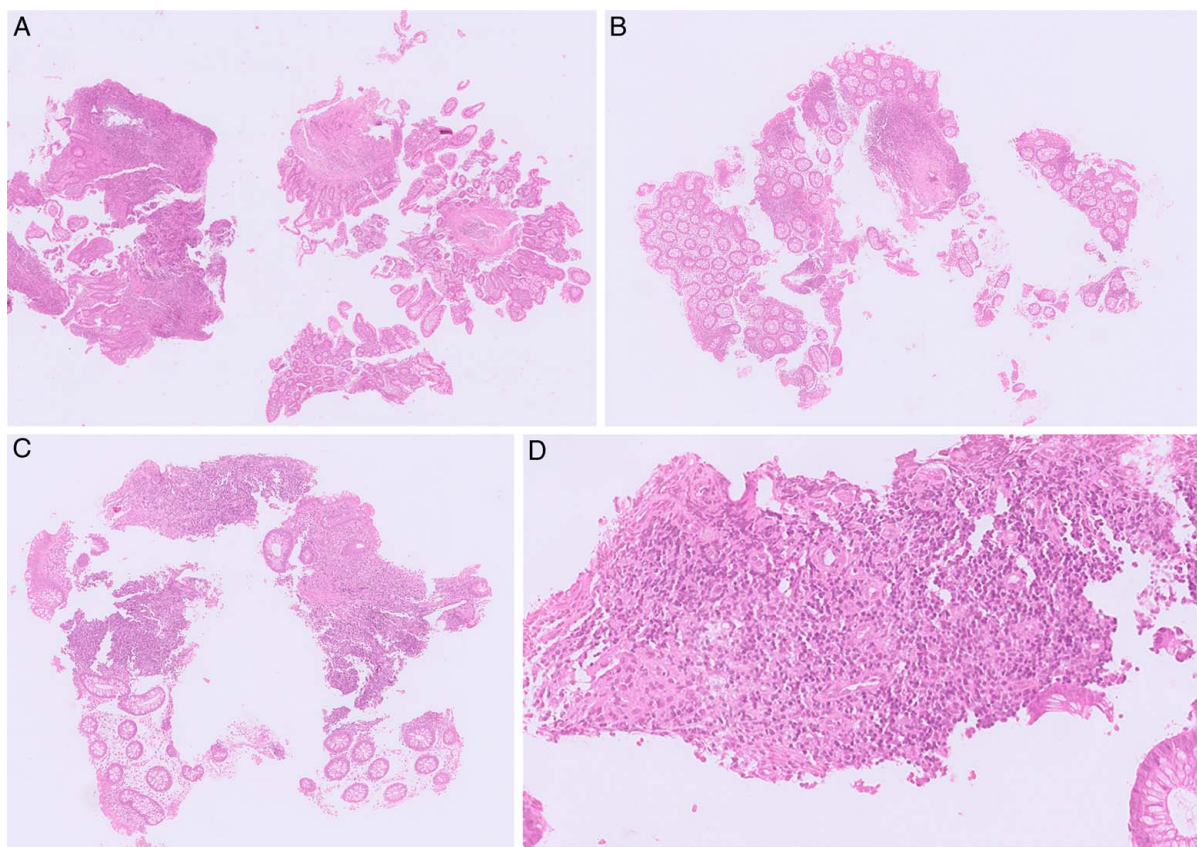


FIGURE 2. Case 2: Mild atrophy and glandular distortion with discontinuous plasma cells and eosinophilic infiltrate in the lamina propria in the biopsies from ileum (A, H&E, $\times 5$), transverse (B, H&E, $\times 5$) and descending colon (C, H&E, $\times 5$) was observed, with non-necrotizing granuloma (D, H&E, $\times 15$) (Crohn-like pattern). Please see this image in color online.

respectively, demonstrated inactive CD and complete mucosal healing, allowing thiopurine suspension. Following the clinical diagnosis of VEO-IBD, whole exome sequencing was carried out, which documented compound heterozygosity of one *LoF* variant (p. Leu679IlefsTer3) and a partially functioning variant (p. Cys565Phe) in the *IFIH1* gene.

Histologically, mild glandular distortion and atrophy were documented in biopsies obtained from the right, transverse, descending colon, and sigma-rectum, with moderate lymphoplasmacytic and eosinophilic infiltrate in the lamina propria. Inflammation was homogenous in the descending colon and sigma-rectum, while it was discontinuous in the right and transverse colon. Focally, cryptitis was observed. Moreover, Paneth cell metaplasia was documented in the sigma-rectum (Fig. 1). An IBD-U-like pattern of colitis was assigned.

Case 2

A 3-year-old girl was admitted to the Emergency Department with a medical history of bloody diarrhea and fever persisting for over 3 weeks and not responding to broad-spectrum antibiotic treatment. Her medical history was notable for recurrent respiratory infections and failure to thrive since the age of 1 year. According to the clinical suspicion of VEO-IBD, a digestive endoscopy was performed. Upper endoscopy revealed no lesions, while colonoscopy showed multiple aphthous erosions associated with a fragile, hyperemic mucosa involving the sigmoid colon, ileocecal

valve, and terminal ileum, with rectal sparing. Treatment with systemic steroids and azathioprine was commenced, with rapid relief of symptoms and growth recovery. Whole exome sequencing was performed and 2 variants in trans were identified in the *IFIH1* gene: one *LoF* (c.2807+1G>A) and one (p.Thr702Ile), the latter without functional consequences.

Histologically, villous blunting was documented in ileal biopsies, with ulceration and severe glandular distortion and atrophy as well as a severe lymphoplasmacytic and eosinophilic inflammation in the lamina propria. All intestinal biopsies showed mild glandular atrophy and distortion with typical discontinuous lymphoplasmacytic and eosinophilic inflammation as well as an isolated non-necrotizing epithelioid microgranuloma (Fig. 2). A CD-like pattern of colitis was assigned. Duodenal mucosa was unremarkable, while neutrophilic inflammation was observed in a single gland in the antral mucosa (ie, focally enhanced gastritis).

Case 3

A 1-month-old infant girl was taken to the Emergency Department with persistent vomiting and severe, watery diarrhea since 20 days of life. VEO-IBD was clinically suspected and GI endoscopy was performed. Upper endoscopy showed absent duodenal folds with mucosal atrophy, whereas lower endoscopy documented reduced haustral folds and a bleeding ulcer surrounded by mucosal inflammation in the left colon. Methylprednisolone and sirolimus were administered with rapid and complete relief of GI symptoms.

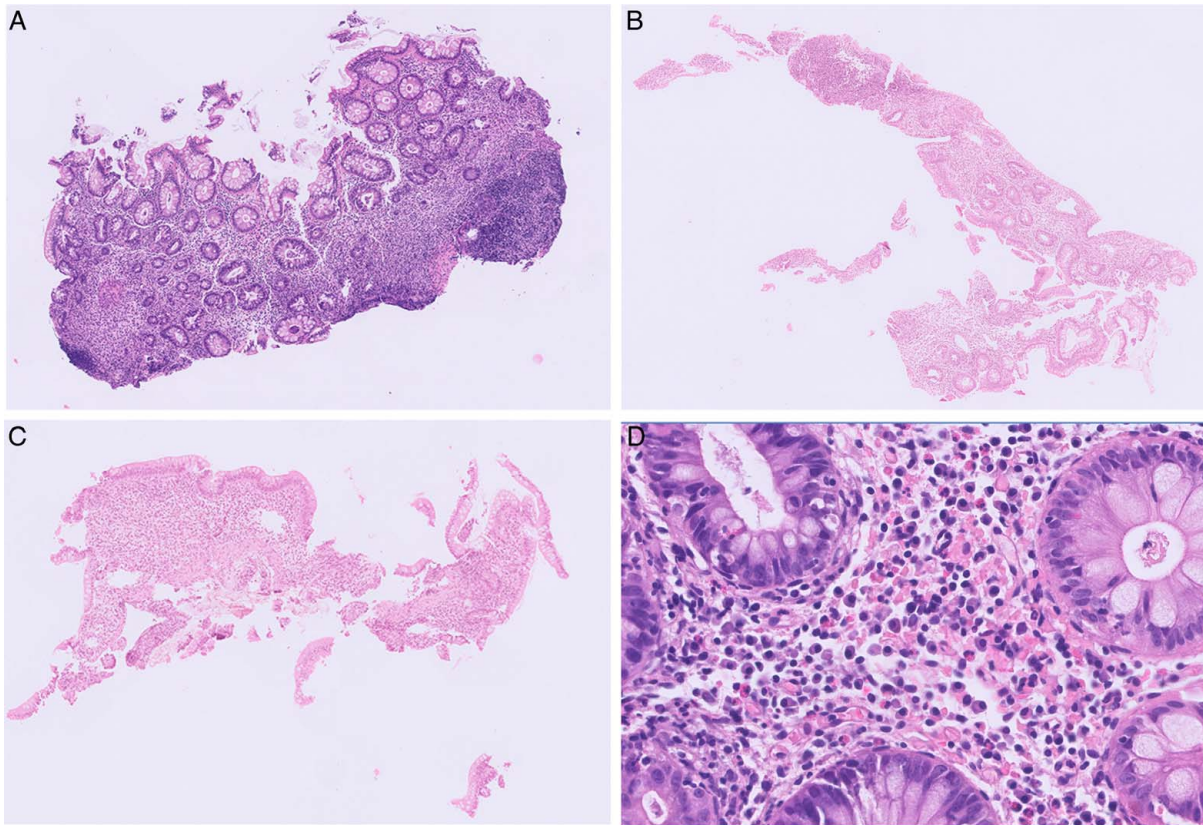


FIGURE 3. Case 3: Severe atrophy and moderate glandular distortion in the intestinal biopsies (A–C, H&E $\times 5$); polymorphous inflammatory infiltrate with basal plasma cells and eosinophils (D, H&E $\times 40$). Please see this image in color online.

Repeat endoscopy at 4 years of age demonstrated resolution of inflammation with mucosal healing, while on sirolimus treatment. During the first year of life, the patient also experienced multiple infections (neonatal sepsis, postnatal CMV infection, urinary infections due to *Pseudomonas aeruginosa*, interstitial pneumonia due to Parainfluenza virus type 3, and a central venous catheter-related sepsis due to *Enterococcus faecium* and *Staphylococcus epidermidis*). On the basis of the clinical history, a primary immunodeficiency was suspected, and whole exome sequencing was performed. The latter identified a homozygous frameshift deletion (rs773033563, c.2016delA) in *IFIH1*, resulting in impaired MDA5-mediated IFN β 1 production and increased cell susceptibility to viral infection.

Histologically, moderate glandular distortion and severe atrophy were documented in all colorectal biopsies, with mucous depletion and severe, diffuse, and homogenous lymphoplasmal and eosinophilic inflammatory infiltrate in the lamina propria. Cryptitis and crypt pseudo abscesses were observed (Fig. 3). After histologic revision and discussion, a UC-like pattern of colitis was assigned. On duodenal biopsies, villous blunting with glandular atrophy and moderate lymphoplasmal and eosinophilic inflammation were documented. Interestingly, isolated apoptotic bodies (ie, immune mediate-like duodenitis) with CMV infection were documented. Gastric biopsies were unremarkable.

Case 4

A 3-month-old infant boy was admitted to the Gastroenterology Department, suffering from persistent

bloody mucous diarrhea unresponsive to treatment. All routine stool-based microbiological tests resulted negative for bacterial and viral infections, and a clinical diagnosis of VEO-IBD was proposed. Upper endoscopy was unremarkable, while colonoscopy revealed a diffuse cobblestone appearance of the intestinal mucosa. Following initiation of treatment with 5-aminosalicylic acid (5-ASA), rapid and progressive resolution of the diarrhea and normalization of calprotectin were seen. Mesalazine was suspended after 2.5 years. Repeated endoscopy at 6 years of age showed complete mucosal healing without any sign of intestinal inflammation. Whole exome sequencing identified a monoallelic *LoF* variant (p.Gln230Ter) in *IFIH1*.

Histologically, focal glandular distortion was documented in biopsies from the right, transverse, descending colon, and the sigma-rectum, with discontinuous lymphoplasmal and eosinophilic inflammatory infiltrates in the lamina propria. Moreover, Paneth cell metaplasia was documented in the sigma-rectum (Fig. 4). An IBD-U-like pattern of colitis was assigned in agreement.

DISCUSSION

Primary immunodeficiency monogenic diseases-related VEO-IBD are characterized by heterogeneity in the genetic landscape, inflammatory pathway alterations, clinical findings, and therapeutic approach. On the other hand, histologic pattern of GI damage is not specific and, moreover, is often indistinguishable from a “true” IBD. Although the prevalence of monogenic diseases in

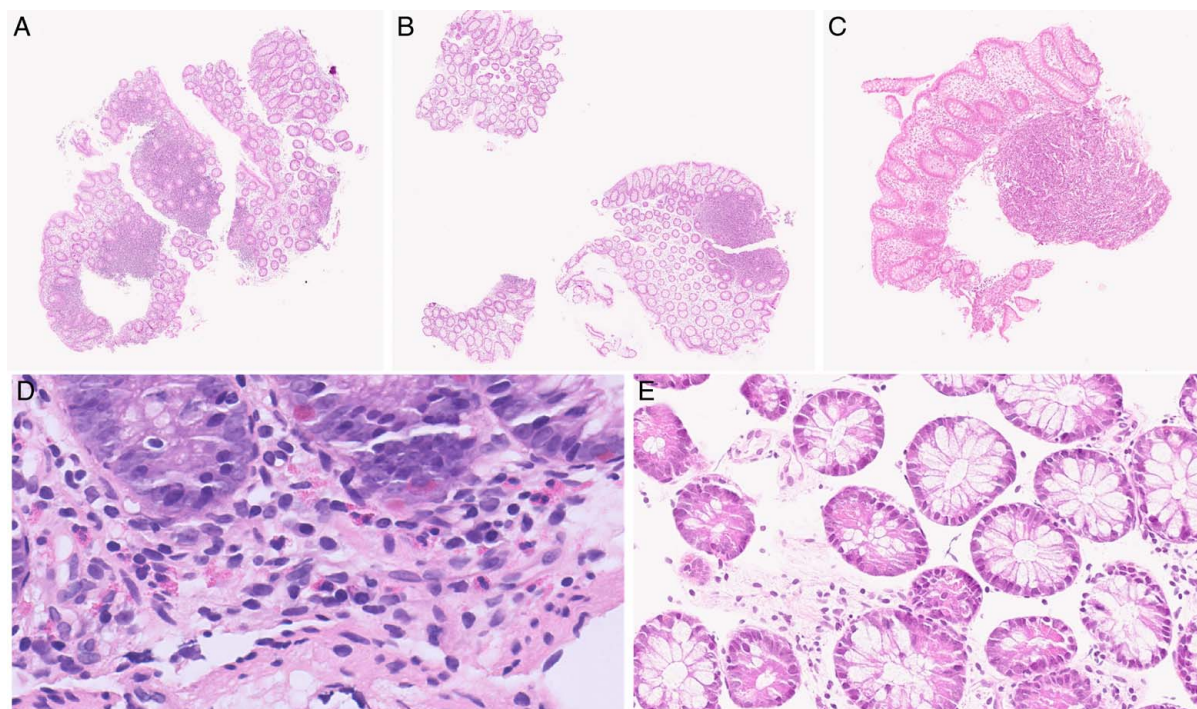


FIGURE 4. Case 4: Discontinuous inflammation in the biopsies from the right (A, H&E ×5), transverse (B, H&E ×5), and rectum (C, H&E ×5) with plasma cells and eosinophilic infiltrate (D, H&E ×40) and Paneth cells metaplasia in the rectum (E, H&E, ×20) (IBD-U like pattern). Please see this image in color online.

VEO-IBD is not well established, almost 15% to 20% of VEO-IBD is caused by monogenic diseases. This association must not be forgotten in daily clinical practice and requires prompt and appropriate clinical management.¹

The most frequent primary immunodeficiency monogenic disease gene alterations with related syndromes and GI manifestations have been recently described^{11–13} with new pathogenetic gene alterations being discovered. Interestingly, GI manifestations have seldom been reported in patients with *IFIH1* LoF variants.

Previously, in a cohort of 93 children with a clinical diagnosis of VEO-IBD, we identified 13 monogenic diseases, 3 of which were associated with *IFIH1* LoF variants.²⁴ All cases, which were also previously described in a study focusing on *IFIH1* deficiency,¹⁹ presented with IBD-like symptoms (chronic diarrhea, vomiting, haematochezia, abdominal pain, rectal bleeding, etc.), leading to a clinical diagnosis of VEO-IBD with subsequent GI endoscopy for histologic confirmation.

In the present study, we provide a more detailed description of GI histologic features in 4 children with *IFIH1* LoF variants, emphasizing the need to be aware of monogenic diseases in children with a clinical diagnosis of VEO-IBD. Indeed, in this context, the importance of avoiding an IBD histologic diagnosis in clinically suspected VEO-IBD is reaffirmed. In fact, in all our patients, we documented intestinal histologic IBD-like damage (2 IBD-U, 1 CD-like, and 1 UC like) that cannot be ascribed to a “pure” IBD, and, in case 3, immune-mediated-like duodenitis.

Although 3 of the *IFIH1* genetic variants described (case 1, case 2, and case 4) cannot be properly attributed to Mendelian inheritance, they still represent risk factors for the development of primary immunodeficiency. Indeed, as

IFIH1 mutations are related to alterations of type I IFN function, leading to a “syndromic” immune dysregulation, a primary immunodeficiency syndrome can be considered in these cases, as also suggested in a previous study.¹⁹ This approach is especially relevant in those patients in whom GI symptoms precede extraintestinal comorbidities, potentially masking the underlying syndromic immune-altered habitus. In fact, in three cases (case 1, case 3, and case 4), GI symptoms were the first clinical presentation, whereas in one case (case 2), the patient initially presented with growth failure and recurrent respiratory infections and, only later, with GI symptoms. Most importantly, failure to consider a monogenic etiology in IBD symptoms may delay the correct therapeutic approach, as steroid and immunomodulatory drugs may be ineffective or even dangerous in patients with primary immunodeficiency.^{3,4,9,10} In this setting, a multidisciplinary approach is recommended,^{1,2} as also underlined in the recent position paper from the Paediatric IBD Porto Group,⁷ focusing on an in-depth clinical investigation including family history, immunologic and laboratory data, extraintestinal manifestations, necessary to select cases needing molecular investigation and genetic counseling.

CONCLUSIONS

Primary immunodeficiency monogenic diseases-related VEO-IBDs need to be included in the pathologist’s daily practice when evaluating GI histologic slides in children. Histologic patterns of intestinal damage are heterogeneous, lack pathogenic elements, and may be completely indistinguishable from those seen in “true” polygenic IBD cases, thus confirming the need to avoid a histologic diagnosis of IBD in clinically suspected VEO-IBD, especially when other red flags such as recurrent or severe infections are present.

Besides the most frequent monogenic diseases, gene alterations in *IFIH1*, such as complete and partial deficiency, secondary to mono- or biallelic LoF variants, are also associated with VEO-IBD with variable penetrance and expressivity. The peculiar genetic landscape of *IFIH1* mutations requires the evaluation of non-Mendelian inheritance variants linked to primary immunodeficiency among causes of VEO-IBD.

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