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Application of a pattern-based approach to histological diagnosis in very early onset IBD (VEO-IBD) in a multicentric cohort of children with emphasis on monogenic disease with IBD-like morphology

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Application of a pattern-based approach to histological diagnosis in very early onset IBD (VEO-IBD) in a multicentric cohort of children with emphasis on monogenic disease with IBD-like morphology

Aims: Very early-onset inflammatory bowel disease (VEO-IBD) is a clinical umbrella term referring to IBD-like symptoms arising in children before the age of 6 years, encompassing both 'pure' IBD, such as ulcerative colitis (UC) and Crohn's disease (CD) and monogenic diseases (MDs), the latter often involving genes associated with primary immunodeficiencies. Moreover, histological features in gastrointestinal (GI) biopsies in MD can also have IBD-like morphology, making differential diagnosis difficult. Correct diagnosis is fundamental, as MDs show a more severe clinical course and their inadequate/untimely recognition leads to inappropriate therapy.

Methods and results: Biopsy samples from the lower and upper GI tract of 93 clinically diagnosed VEO-IBD children were retrospectively selected in a multicentre cohort and histologically re-evaluated by 10 pathologists blinded to clinical information. Each case was classified according to morphological patterns, including UC-like; CD-like; enterocolitis-like; apoptotic; eosinophil-rich; and IBD-unclassified (IBD-U). Nine (69%) MD children showed IBD-like morphology; only the IBD-U pattern correlated with MD diagnosis ($P = 0.02$) (available in 64 cases: 51 non-MD, true early-onset IBD/other; 13 MD cases). MD patients showed earlier GI symptom onset (18.7 versus

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26.9 months) and were sent to endoscopy earlier (22 versus 37 months), these differences were statistically significant ($P < 0.05$). Upper GI histology was informative in 37 biopsies.
Conclusions: The diagnosis of the underlying cause of VEO-IBD requires a multidisciplinary setting, and pathology, while being one of the fundamental puzzle pieces, is often difficult to interpret. A pattern-based histological approach is therefore suggested, thus aiding the pathologist in VEO-IBD reporting and multidisciplinary discussion.

Keywords: apoptotic colitis, Crohn's disease, enterocolitis, eosinophilic colitis, IBD, monogenic disease, ulcerative colitis, VEO-IBD

Introduction

Very early-onset inflammatory bowel disease (VEO-IBD) refers to a clinical presentation with IBD-like symptoms, such as chronic diarrhoea, vomiting, perianal lesions, haematochezia, abdominal pain and rectal bleeding, arising in children before the 6th year of life. These clinical features are found both in 'pure' IBD, such as Crohn's disease (CD) and ulcerative colitis (UC), and in causative monogenic or digenic defects, often involving genes associated with primary immunodeficiencies (PID).[1] 'Pure' IBD represents the multifactorial result of a dysregulated immune response to environmental factors in a genetically susceptible host and, in older paediatric patients and adults, is most often polygenic, involving more than 200 risk loci spanning more than 300 genes. Conversely, monogenic disease (MD) has mendelian inherited transmission and involves genes crucial to the immune system network, although they can be classified into six main (and sometimes overlapping) immune dysregulation categories: (i) general immune dysregulation, (ii) T and B cell defects, (iii) phagocytic defects, (iv) hyper- and autoinflammatory conditions, (v) epithelial barrier dysfunction and (vi) other conditions.[2] For this reason, MD leads to a variety of conditions including gastrointestinal (GI) and extra-GI symptoms, such as pulmonary and/or upper airway and/or urinary recurrent infections starting in the first months of life and unresponsive to conventional therapy, early-onset tumours, endocrine dysfunction, hepatosplenomegaly, cytopenia, high ferritin levels (macrophage activation syndrome) and somatic defects in skin, hair, teeth and various other ectodermal elements. Non-immune syndromic aspects, such as facial malformations and delays in psychophysical development, are very common in MD, but they appear after 2–3 years of life.[3] Moreover, GI symptoms in MD are characterised by a more severe clinical course, reduced responsiveness to conventional IBD therapy, intense treatment regimens involving extensive surgery, and more intensive medical treatment; most importantly, inadequate recognition of underlying MDs may lead to inappropriate therapy. Indeed, immunosuppressive therapy, used to treat IBD, can be fatal in children with MD/PID with IBD-like symptoms.[1] With this in mind, consultation by an expert immunologist for in-depth immune deficiency evaluation and testing is recommended, especially in infants, before initiation of therapy. Moreover, as MDs follow mendelian transmission, patients and their families should be referred to geneticists for analysis of first-degree family members.[4]

Unfortunately, histological features in GI biopsy samples from children with MD can overlap with true IBD and various other conditions.[5–10] Erroneously labelling the process as 'IBD' in the histology report early in the disease course will prevent the physician from considering further conditions as well as initiating inappropriate clinical management and therapy.[11] Moreover, lesions such as colitis without chronic damage, with eosinophilic-rich inflammation or apoptotic bodies, usually observed in infections, autoimmune disorders, allergic and/or food intolerance, have also been described in MDs.[12] In real clinical practice, the pathologist is often asked to report on histological findings before the diagnostic process is completed with no clinical or, sometimes, endoscopic details. The use of term 'VEO-IBD' in the histological report could be confounding and possibly lead to inappropriate and dangerous treatment.[11]

The aim of the study was to collect a large multicentric case series of lower GI (and any available upper GI) biopsy sets from children with a clinical diagnosis of VEO-IBD, with a review of histological aspects by a panel of experienced pathologists, using a morphological pattern-based approach, blinded to clinical information, and comparison of histology with the final multidisciplinary diagnosis (including true IBDs and MDs).

Materials and methods

Histological slides from gastrointestinal biopsy sets of clinically diagnosed VEO-IBDs in children younger than 6 years were retrospectively selected from January 2015 to July 2022 from the archives of the Pathology Units of Fondazione IRCCS Casa Sollievo della Sofferenza (San Giovanni Rotondo), Ospedale San Camillo Forlanini (Rome), Azienda Ospedaliera-Universitaria Meyer (Firenze), Università degli Studi Federico II (Napoli), Università degli studi di Padova (Padova), IRCCS Ospedale Gaslini (Genova), Ospedale Pousillipon (Napoli), Università degli Studi di Pavia (Pavia), Ospedale Pediatrico Bambino Gesù (Rome). Ten pathologists with experience in gastrointestinal paediatric and adult pathology jointly re-evaluated all cases during monthly meetings and blinded to clinical information. All available original haematoxylin and eosin-stained slides were reassessed and categorised according to the histological pattern in four previously described VEO-IBD categories:[5–7] (a) UC-like pattern, characterised by a continuous marked inflammatory infiltrate with eosinophils, monocytes, plasma cells and lymphocytes with or without cryptitis, Paneth cell metaplasia, ulcerations and architectural gland atrophy/distortion (Figure 1A, B); (b) CD-like pattern, characterised by a discontinuous inflammatory infiltrate with eosinophils, neutrophils and plasma cells, transmural inflammation, deep ulceration of mucosa, non-necrotising granulomas, pronounced lymphoid hyperplasia, aphthous lesions over lymphoid aggregates and, in the small bowel, villous atrophy (Figure 1C,D); (c) enterocolitis-like pattern, characterised by focal detachment of colonic

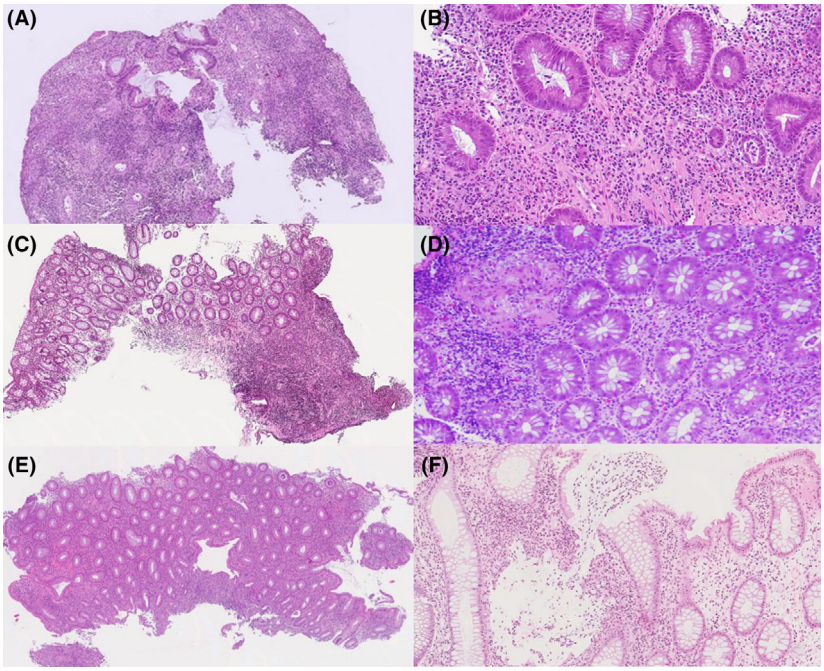

Figure 1. **A,B,** Ulcerative colitis-like pattern. **C,D,** Crohn's disease-like pattern. **E,F,** Enterocolitis-like pattern.

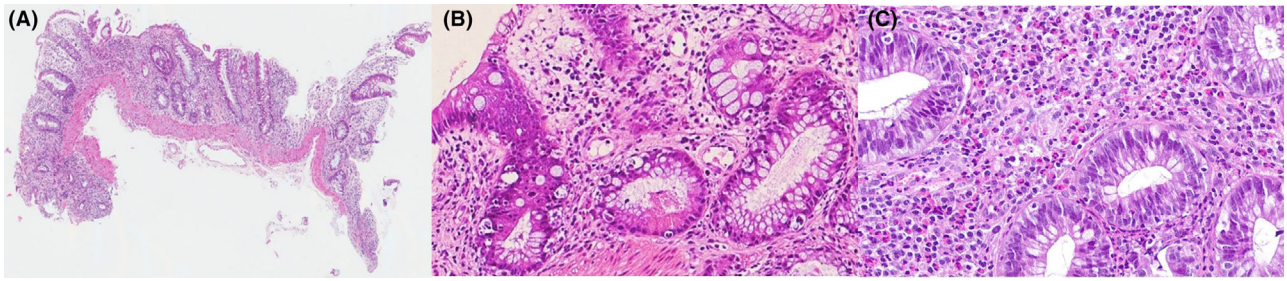

Figure 2. **A,B,** Apoptotic pattern. **C,** Eosinophil-rich pattern.

Table 1. Clinicopathological findings in the total cohort and in the non-monogenic disease and monogenic disease groups (total 93 cases; in 64 cases a definitive diagnosis was reached, including 51 cases of non-MD causes and 13 cases of MD)

	Total cases (with known diagnosis at follow up) 93 (64)	Non-monogenic disease (%) 51 (80%)	Monogenic disease (%) 13 (20%)	*P*
Males	37 (26)	21	5	NS
Females	56 (38)	30	8	
Mean age of onset GI symptoms to diagnosis (months)	32.7 (1–78)	37.2 ± 22.5 (1–78)	22.1 ± 18.9 (2–72)	*P* = 0.028
Mean age of onset of extra GI symptoms to diagnosis (months)	23.6 (1–72)	27.0 ± 22.7 (1–72)	18.7 ± 20.5 (1–60)	NS
Mean age of first endoscopy with biopsy (months)	35.4 (2–78)	39.7 ± 21.4 (3–78)	24.3 ± 19.8 (2–72)	*P* = 0.027
Lower GI histological patterns				
UC-like pattern	36 (24)	21	4	NS
CD-like pattern	9 (8)	6	2	
Enterocolitis-like pattern	16 (12)	9	3	
Apoptotic pattern	4 (1)	0	1	
Eosinophil-rich colitis-like pattern	7 (3)	3	0	
IBD-U-like pattern	4 (4)	1	3	*P* = 0.0241
Mixed patterns	9 (7)	6	0	
Normal mucosa	7 (5)	5	0	
Lower GI histological findings				
Histological activity	71 (50)	41	9	NS
Ileo-pancolic damage	9 (7)	6	1	
Pancolic damage	52 (41)	31	10	
Ileal-restricted damage	2	0	0	
Distal damage	14 (6)	6	0	
Segmental damage	11 (4)	2	2	
Rectal sparing	7 (8)	6	2	
Ulcers	3 (2)	1	1	
Sovra-infection	4 (1)	2	0	
Ileal blunting	2 (2)	0	2	NS
Upper GI histological findings	59	27	10	

Table 1. (*Continued*)

	Total cases (with known diagnosis at follow up) 93 (64)	Non-monogenic disease (%) 51 (80%)	Monogenic disease (%) 13 (20%)	*P*
Normal oesophageal mucosa	13 (9)	8	1	NS
Oesophagitis	5 (2)	2	0	
Candida	1 (1)	1	0	
Normal gastric mucosa	32 (21)	18	3	
Focally enhanced gastritis	10 (8)	5	3	
Non-atrophic gastritis	7 (3)	2	1	
Non-necrotising microgranuloma	1	0	0	
Normal duodenal mucosa	33 (17)	12	5	
Duodenal blunting	8 (6)	4		
Increased CD3 IEL	4 (3) (1 coeliac disease)	2 (1 coeliac disease)	1 (with duodenal blunting)	
Tufting enteropathy	3 (3)	3	0	
Apoptotic duodenitis	1 (1)	0	1	
Other lesions*	4 (3)	2	1 (CMV and isolated apoptotoses)	

CD, Crohn's disease; CMV, cytomegalovirus; GI, gastrointestinal; IBD-U, inflammatory bowel disease unclassified; IEL, intra-epithelial lymphocytes; MD, monogenic disease; non-MD, non-monogenic disease; NS, not significant; UC, ulcerative colitis.
*Other lesions include: erosions, ulcerations, eosinophilic-rich infiltrate and isolated apoptoses.

epithelium, extensive, widespread continuous marked inflammatory infiltrate with eosinophils, monocytes, plasma cells and lymphocytes with minimal architectural distortion in the absence of chronic damage (Figure 1E,F); (d) apoptotic pattern, characterised by severe gland loss/dropout and atrophy, increased mononuclear cells in the lamina propria, frequent crypt-based apoptoses (more than five apoptosis/gland) and 'exploding crypts' (Figure 2A,B); (e) eosinophilic pattern, eosinophilic diffuse and dense infiltration in the crypts, lamina propria and surface epithelium without chronic damage (Figure 2C); and (f) IBD-like pattern not otherwise specified/unclassified (IBD-U) when biopsy showed chronic inflammatory and structural crypt alterations, but it was not possible to specify IBD. Any increased frequency of apoptoses (presence of more than one but fewer than five apoptotic bodies/10 crypts) was also noted.

When available, biopsy samples from the upper GI tract were also re-evaluated and all changes in mucosal architecture and inflammation were reported.

Clinical data on gender, age at diagnosis, GI and extra-GI symptoms and time of their onset, endoscopic report, final clinical outcome with definitive diagnosis (when available) were collected.

The diagnosis of MD was reached with molecular tests, in particular investigating gene panels [targeted next-generation sequencing (NGS) or panel NGS testing].

All information regarding human tissue was managed using anonymous numerical codes, and all samples were handled in compliance with the Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). Informed consent was signed by the legal guardians at the time of clinical diagnosis.

Results

A total of 93 children (37 males and 56 females) with a clinical diagnosis of VEO-IBD and available endoscopic biopsy sets were reviewed. The mean age of GI symptom onset of the total case series was 32.7 (range = 1–78) months while extra-GI symptoms, known in 40 patients, presented earlier (mean = 23.6 months; range = 1–72).

Lower GI sampling protocols were complete with samples from the ileum and different sites of the colon in 72% of cases (67 of 93), while 11% (10 cases) had no ileal sample, 15% (14 cases) of samples were limited to the left colon and rectum and in 2% (two cases), only one left-sided site was sampled. Most cases (81%, 75 cases) had complete endoscopic reports attached and the majority (76%, 57 of the 75 cases) of these showed various endoscopic alterations. Upper GI sampling was performed in 63% (59 cases) with variable biopsy sets including both stomach and duodenum samples (46%), with the addition of oesophageal samples in 25%, and other combinations of just one site in a third of cases (29%).

Histologically, the most frequent pattern was the UC-like colitis pattern seen in 39%, while the least was the apoptotic pattern and IBD-U pattern both seen in 4%; see Table 1. Mixed patterns were present in nine cases and histology was unremarkable in seven cases; in one case, no agreement was reached in the assignation of a histological pattern (five pathologists for CD-like pattern and five pathologists for an enterocolitis-like pattern).

HISTOLOGICAL DIFFERENCES BETWEEN MD AND NON-MD CASES

In 64 patients (69%), follow-up and final outcome were available (see Table 2) and 51 patients were diagnosed with UC (33), CD (eight) or other causes (10) (non-MD group), while in 13 patients a final diagnosis of MD was made. No differences were seen in the male : female ratio between MD and non-MD; however, MD patients tended to show earlier onset of GI symptoms (18.7 versus 26.9 months) and were sent to endoscopy earlier (22 versus 37 months), and these differences were statistically significant ($P < 0.05$).

No significant differences in histological patterns were seen between groups except for the IBD-U pattern, which was significantly correlated with MD cause ($P = 0.02$). No significant differences in the topographic distribution of lesions were seen between non-MD and MD cases.

UPPER GI HISTOLOGICAL FINDINGS

Upper GI findings, in part, reflect the variability in sampling protocols (see above). Most cases showed no histological lesions, and 72% (13 of 18), 64% (32 of 50) and 70% (33 of 47) of cases from the oesophagus, stomach and duodenum, respectively, were diagnosed as normal. Histological lesions in the oesophagus, stomach and duodenum are shown in Table 1 and Figure 3. No statistically significant differences in histological features were seen between non-MD causes and MDs.

Table 2. Correlation between histological pattern at onset and final clinical diagnosis inVEO-IBD

		Final diagnosis			
Histological pattern of onset	No.	UC	CD	Other	Monogenic disease
UC-like pattern	25	19	0	2 (IE)	4
CD-like pattern	8	0	6	0	2
Enterocolitis-like pattern	12	7	0	2 (1 IBD-U; 1 IE)	3
Apoptotic pattern	1	0	0	0	1
Eosinophil-rich pattern	3	1	0	2 (1 IL; 1 IE)	0
IBD-U pattern	4	1	0	0	3
Mixed patterns					
Enterocolitis-like + eosinophil-rich patterns	2	1	0	1 (EE)	0
CD-like + enterocolitis-like patterns	1	0	1	0	0
Enterocolitis-like + apoptotic patterns	1	1	0	0	0
UC-like + apoptotic patterns or isolated apoptoses	2	1	1	0	0
Normal mucosa	5	2	0	3 (CTE)	0
Total	64	33	8	10	13

CD, Crohn's disease; CTE, congenital tufting enteropathy; EE, eosinophilic enterocolitis; IBD-U, inflammatory bowel disease unclassified; IE, infectious enterocolitis; IL, intestinal lymphangiectasia; UC, ulcerative colitis.

DESCRIPTION OF MD CASES

Table 3 describes in detail the 13 cases of diagnosed MDs in our series, showing that IBD-like morphology is frequent in MD cases (69%). Indeed, four cases

presented with a UC-like pattern, two cases with a CD-like pattern and three cases with an IBD-U pattern, while four cases showed non-IBD-like morphology (three cases with an enterocolitis-like pattern, one case with an apoptotic pattern).

Although, at first endoscopy, no clinical information/suspicion was given, the case (case 9) with an apoptotic pattern was identified as suspicious for MD in the pathology report, and a recommendation for in-depth clinical study and genetic evaluation on the basis of the peculiar morphology, including numerous apoptotic bodies, dramatic, diffuse glandular atrophy, Paneth cell metaplasia (Figure 1E,F) and mild inflammation, in the whole intestinal tract.

A further three cases presented as an IBD-U histological pattern showing mild and focal glandular architectural damage; mild, occasionally discontinuous, lymphomonocytic inflammation; and ulcers and granulation tissue. One child had also undergone upper GI endoscopy with diffuse duodenal blunting with increased CD3 intra-epithelial lymphocytes (coeliac disease-like in the absence of serological and genetic tests positive for coeliac disease), isolated apoptotic bodies and focally enhanced gastritis.

Discussion

VEO-IBD is a clinical umbrella term used to describe IBD-like symptoms in children aged fewer than 6 years and comprises a heterogeneous spectrum, both phenotypically and genetically, of diseases with GI and extra-GI symptoms.[1] Numerous studies concerning the clinical manifestations of VEO-IBD identified up to 15% of patients suffering from MD, often involving genes associated with PID.[1,2,13]

Due to the wide phenotypical and genetic heterogeneity of these conditions and the lack of specific clinical, endoscopic or histological findings, it is often difficult to reach a final diagnosis.[14] In this context, very few studies, mostly case reports, have described IBD-like histological features in MD and, more specifically, in PID.

One approach to simplifying the broad array of histological findings in VEO-IBD is to group them into patterns and use these to describe morphological features without reaching a pathology-based definitive diagnosis.[5–7] In our study, differences in disease onset (MD children tend to be sent to endoscopy earlier, probably due to earlier onset of symptoms and more severe disease) were found between non-MD and MD cases in our cohort; however, no significant differences in histological patterns were found. Our findings are similar to the study by Conrad *et al.*, who evaluated a mono-institutional retrospective case series comprising 57 cases, and found no statistical differences in histological features between 'pure' IBD (46 patients) and MD (11 patients).[15] In particular, the authors analysed 11 histological features [active inflammation (neutrophil-predominant cryptitis and crypt micro-abscesses), chronic architectural changes, apoptoses, granulomas, lymphoid aggregates, intra-epithelial lymphocytes, plasma cell infiltrates in the lamina propria, eosinophils in the lamina propria or crypts or surface epithelium, mucus and goblet cell depletion, small bowel villous blunting and colonic villous surface transformation] in all cases, and

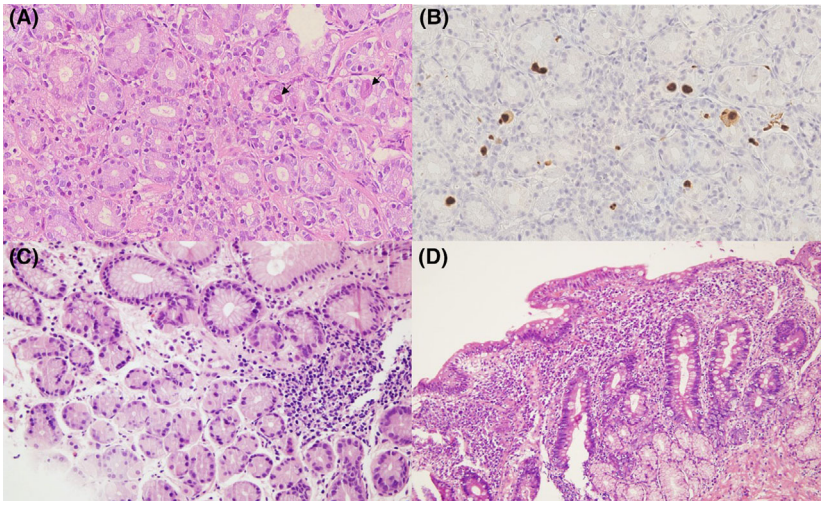

Figure 3. **A,** Cytomegalovirus inclusions in gastric mucosa. **B,** Immunohistochemistry using anti-CMV antibodies. **C,** Focally enhanced gastritis. **D,** Duodenal blunting with increased intra-epithelial lymphocytes.

Table 3. Clinical and histological findings in monogenic disease

	GI symptoms (time to onset)	Extra-GI symptoms (time to onset)	Ileo-colic endoscopic findings	Pattern at lower Gi histology	Oesophago-gastroduodenal endoscopic findings (biopsy sampling)	Upper GI histology	Monogenic disease
Case 1	Bloody diarrhoea (2 months)	Height-weight growth delay, recurrent multi-visceral infections, sepsis (1 month)	Pancolic oedema and erythema	UC-like pattern	Normal (stomach and duodenum)	CMV-related gastritis	*IFIH1* mutation
Case 2	Bloody diarrhoea, portal hypertension (24 months)	NR	Mild pancolitis	UC-like pattern	NR (sampling not performed)	–	*NOX1* deficit in Turner's syndrome
Case 3	Bloody diarrhoea (24 months)	Hearing loss (55 months)	Pancolic oedema with rectal sparing	UC-like pattern	NR (oesophagus, stomach and duodenum)	Normal	*PIK3CD* mutation
Case 4	Bloody diarrhoea (3 months)	NR	Polyposis and stenosis	UC-like pattern	Normal (stomach and duodenum)	Haemosiderin in gastric mucosa, normal duodenal mucosa	*DUOX2* mutation
Case 4	Bloody diarrhoea, greenish stools (72 months)	Lung parenchymal alterations (60 months)	Aftous colitis in left colon and sigma	CD-like pattern	NR (stomach and duodenum)	Focally enhanced gastritis; normal duodenal mucosa	*XIAP* mutation
Case 5	Bloody diarrhoea (34 months)	Upper respiratory airway and recurrent ear infections (NR)	Ileal and right-sided segmental colitis	CD-like pattern	Normal (stomach and duodenum)	Focally enhanced gastritis; normal duodenal mucosa	*IFIH1* mutation
Case 6	Bloody diarrhoea (24 months)	Recurrent multi-visceral infections, hearing loss, cardiac, uveal and cerebral malformations documented after MD diagnosis (12 months)	Pancolitis	Enterocolitis-like pattern	NR (stomach and duodenum)	Normal	*6p24* terminal deletion

Table 3. (*Continued*)

	GI symptoms (time to onset)	Extra-GI symptoms (time to onset)	Ileo-colic endoscopic findings	Pattern at lower Gi histology	Oesophago-gastroduodenal endoscopic findings (biopsy sampling)	Upper GI histology	Monogenic disease
Case 7	Watery diarrhoea (2 months)	Height-weight growth delay (2 months)	Normal mucosa	Enterocolitis-like pattern	Normal (stomach and duodenum)	Normal gastric mucosa, Villous blunting in duodenum	*TTC37* mutation; trichohepato-enteric syndrome.
Case 8	Watery diarrhoea (39 months)	Rash (4 months)	NR	Enterocolitis-like pattern	NR (stomach and duodenum)	Non-atrophic gastritis; normal duodenal mucosa	*PIEZO1* mutation
Case 9	Diarrhoea (20 months)	Height–weight growth retardation and delay in psychomotor stage acquisition, microencephaly documented at imaging after MD diagnosis (20 months).	Ileal damage; colic mucosa normal.	Apoptic pattern with glandular atrophy, Paneth cell metaplasia and mild inflammation	Normal (duodeum)	Normal	*DKC1* mutation; Dyskeratosis X-linked
Case 10	Diarrhoea (2 months)	Recurrent multi-visceral infections, height–weight growth delay (2 months)	Right-sided moderate colitis	IBD-U like pattern	NR (sampling not performed)	–	*IL-10* receptor mutation
Case 12	Muco-haemorrhagic diarrhoea (12 months)	Recurrent multi-visceral infections, anaemia (11 months)	Segmental pancolitis	IBD-U like pattern	NR (sampling not performed)	–	*IFIH1* mutation
Case 13	Abdominal pain and distention, alvum alternum (29 months)	Height–weight growth delay, hypothyroidism (20 months)	Normal mucosa	IBD-U like pattern	Scalloped duodenal mucosa (stomach and duodenum)	Focally enhanced gastritis; in duodenum - blunting of villi, isolated apoptoses and increase of intra-epithelial $CD3^+$ T lymphocytes	*FOXP3* mutation in HIPEX syndrome

CD, Crohn's disease; CMV, cytomegalovirus; GI, gastrointestinal; IBD-U, inflammatory bowel disease unclassified; NR, not reported; UC, ulcerative colitis.

similar histological features were found between the two groups.[15]

In our cohort, a final diagnosis of MD was made in cases showing all morphological features, including IBD-like features (UC, CD, IBD-unspecified) as well as enterocolitis-like and apoptotic patterns, with no significant statistical differences, even though other studies in the literature have proposed some diagnostic clues to a correct MD diagnosis.[12,15] These include increased frequency of apoptoses, severe and diffuse gland loss in the absence of inflammation (as seen in our case 9), villous atrophy (cases 6 and 13), diffuse eosinophilic infiltrates and lack of plasma cells in the mucosa. Of note, a poorly defined IBD-U pattern of injury in our cohort was statistically correlated with MD, meaning that ill-defined aspects of IBD-like damage should prompt suspicion. Furthermore, while upper GI findings are often normal, some features such as focally enhanced gastritis[17] and the aforementioned villous blunting/atrophy should again be looked for and mentioned in the pathology report.

We did not find some patterns in our cohort which have been described, such as the lymphocytic (with lymphocytosis and nodular lymphoid hyperplasia) or the granulomatous patterns,[15] and this may be due to the low number of diagnosed MD cases. The rarity of this disease entity is highlighted by the fact that in 7 years and more than five tertiary paediatric gastroenterology centres, 93 children were biopsied and only 13 definitive cases of MDs were found, making it difficult to accrue sufficient numbers for statistically sound interpretation.

This study, which essentially underlines the difficulty in reaching a differential diagnosis between true IBD and MD-associated VEO-IBD on histological grounds alone, may appear to not completely resolve this issue; however, it quantifies the true impact of IBD-like morphology in MDs (69.2%), thus substantiating important points made in the recent literature.[5–7,11]

First, a 'definitive' diagnosis of UC/CD/IBD-U should be avoided in a clinically suspected VEO-IBD, without appropriate multidisciplinary work-up. Secondly, as morphological lesions can be found in endoscopically healthy mucosa, biopsy sampling should always be performed at all intestinal sites (according to IBD guidelines[16]). Thirdly, upper GI histological findings can sometimes lead to unexpected diagnoses. Indeed, three cases of congenital tufting enteropathy were documented in clinically suspected VEO-IBD, two cases showing a UC-like pattern in intestinal biopsies. In this context, it would be useful to always acquire a whole upper GI biopsy set [including oesophageal, gastric (both body and antrum) and duodenal (I and II portion) biopsies].[6] Finally, clinical information should always be made available to the pathologist, and discussion of cases in a multidisciplinary context is imperative.

Our study has some limits, such as its retrospective nature and the absence of a definitive diagnosis for some children (molecular profiling to investigate MD was not available in all cases). A further limitation is that we did not perform a concordance study for pattern recognition between the participating pathologists due to the need for standardisation of reporting at the start of the study. A future concordance analysis will be important to help in identifying key issues with this pattern-based approach, but will require the collection of a large international series of cases.

In conclusion, our results show that IBD-like morphology is frequent in MD (69%), and that no single pathological feature is able to predict the true nature of VEO-IBD; a pattern-based approach is very much advised, so that the multidisciplinary team can perform more in-depth clinical, laboratory or genetic investigations to correctly diagnose these young patients.

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Conflicts of interest

M.F. has been involved in consulting/advisory roles in Astellas Pharma, Pierre Fabre, MSD, AstraZeneca, Janssen, GlaxoSmithKline, Amgen, Lilly, Novartis and Roche, and received research funding from Astellas Pharma, QED Therapeutics, Diaceutics and Macrophage Pharma. P.P., M.C.M., A.M.B., L.S., B.C., D.B., J.F., A.V., R.A., L.M., M.D.M., F.G. and P.F. have no conflicts of interest to disclose.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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