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Case report

Refractory Very Early-Onset Inflammatory Bowel Disease to Anti-TNF Therapy

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Abstract

Background: Very early-onset inflammatory bowel disease (VEO-IBD), defined as symptom onset before the age of 6 years, presents a significant clinical challenge for healthcare teams. This case report aims to share clinical experience in managing a patient with VEO-IBD. **Case Report:** We present the case of a 3-year-old boy diagnosed with inflammatory bowel disease (IBD), Crohn's disease (CD) phenotype, with disease onset at four months of age. A comprehensive evaluation was conducted to rule out differential diagnoses such as food allergies, immunodeficiencies, and intestinal tuberculosis. Given the early onset, a genetic component was suspected, and genetic testing was performed. The patient presented with pancolitis and perianal involvement and was stratified as high-risk according to the ECCO-ESPGHAN guidelines. After therapeutic failure with infliximab and adalimumab, ustekinumab was initiated with successful clinical remission to date. This therapy has proven effective in refractory pediatric CD cases. **Conclusions:** To achieve an accurate diagnosis in suspected pediatric IBD, it is essential to follow clinical practice guidelines and apply individualized diagnostic approaches. Although most VEO-IBD cases have multifactorial etiology, genetic factors may play a significant role, particularly in children under 2 years of age. VEO-IBD is often associated with more severe disease in terms of extent and behavior.

Keywords

Inflammatory bowel diseases, pediatrics, Crohn's disease.

INTRODUCTION

Very early-onset inflammatory bowel disease (VEO-IBD), defined by symptom onset before 6 years of age, accounts for 6% to 15% of pediatric IBD cases[1,2]. VEO-IBD includes two subcategories: infant-onset IBD (IO-IBD), when disease onset occurs before 2 years of age, and neonatal-onset IBD, when symptoms appear within the first 28 days of life[3,4].

While most VEO-IBD cases result from multifactorial causes, genetic factors may play a significant role, particularly in children under 2 years (IO-IBD), where the likelihood of identifying a monogenic defect responsible for enteric inflammation is higher[1,2,5]. To date, over 70 genetic variants have been described, most commonly associated with inborn errors of immunity affecting B- and T-cell function or hyper-/autoinflammatory defects related to epithelial barrier dysfunction[1,6,7].

Selecting optimal therapy at such an early age poses a challenge for the treating team, given the nearly inevitable delay in confirming the diagnosis before initiating targeted treatment. To achieve an accurate diagnosis when pediatric IBD is suspected, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) established the Porto Criteria in 2014, con-

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solidating evidence-based recommendations for diagnostic methods and guiding a more individualized approach[8].

Key initial diagnostic tests include upper endoscopy, ileocolonoscopy with multiple biopsies from all evaluated segments, and complete small bowel evaluation. Advances in imaging modalities, serological and fecal biomarkers have improved detection and monitoring of these diseases[1,8]. This case report aims to share the clinical experience and challenges in managing a patient with this very early-onset condition.

CASE REPORT

A male infant, born to non-consanguineous parents, had no perinatal or neonatal risk factors or family history of atopy, immunodeficiencies, autoimmune diseases, or IBD. His clinical course began at 4 months of age with profuse watery diarrhea (3–30 stools per day), sometimes containing mucus but no blood, occurring day and night, accompanied by poor appetite. At 10 months, cow's milk protein allergy (CMPA) was suspected, leading to a diagnostic and therapeutic trial with extensively hydrolyzed formula (eHF) and maternal exclusion of cow's milk protein (CMP), without symptom improvement. From 12 to 16 months of age, diarrhea persisted despite multiple outpatient interventions, primarily antibiotics and antiparasitics, resulting in progressive weight loss and acute malnutrition. The diarrhea was later accompanied by oral aphthous ulcers, food refusal, intermittent fever, and lower limb edema.

At 17 months, during his first evaluation, the patient appeared in fair general condition: thin, pale, tachycardic, febrile, and hypoactive. Findings included asthenia, adynamia, brittle hair, bilateral eyelid edema, oral ulcers, and non-tender bilateral cervical, axillary, and inguinal lymphadenopathy (<1 cm in diameter). The abdomen was markedly distended, soft, depressible, and tender to palpation, without peritoneal irritation. The anus showed no lesions, but there was gluteal and lower limb hypotrophy, along with distal-predominant limb edema. Anthropometry revealed short stature and acute kwashiorkor-type malnutrition (weight: 7.84 kg, height: 74 cm, height/age: -2.7 standard deviations [SD], weight/height: -2.12 SD). Laboratory findings are presented in **Table 1**.

Table 1. Admission Laboratory Results

Hematologic	- Complete Blood Count: Hb: 7.7, Hct: 23.8, MCV: 93.9, MCHC: 32.5, RDW: 28%, RBC count: 2.53 (low), WBC: 15,700, Neutrophils: 3,600 (23%), Lymphocytes: 9,800 (62%), Monocytes: 1,800 (11%), Eosinophils: 300 (2.2%), Platelets: 516,000. - Reticulocyte Count (corrected): 2.8 (reticulocyte percentage: 5.2%).
Acute Phase Reactants	- CRP: 2.24 mg/dL (Ref.: 0.01–0.82) elevated - ESR: 97 (Ref.: 0–20) elevated
Liver Function Tests	- ALT: 11 - AST: 15 - Alkaline Phosphatase: 78 - GGT: 11.5 U/L - Total Bilirubin: 0.19 - Direct Bilirubin: 0.05 - PT: 11.9 (control: 11.4) - INR: 1.05 - Albumin: 2.3 g/dL (Ref.: 3.8–5.4) - Prealbumin: 8 (Ref.: 11–34)
Renal Function	- Creatinine: 0.15 mg/dL - BUN: 10.8
Gastrointestinal Infection	- Stool Analysis: No mucus/blood, pH 7, >5 WBC/hpf, no parasites observed. - Adenovirus/Rotavirus: Negative. - FilmArray GI Panel: Negative.
Other Infection Workup	- Urinalysis: Normal, urine culture negative. - Blood cultures (x2): Negative. - Chest X-ray: Normal.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GGT: γ-glutamyl transferase; GI: gastrointestinal; Hb: hemoglobin; Hct: hematocrit; INR: international normalized ratio; CRP: C-reactive protein; PT: prothrombin time; MCV: mean corpuscular volume; Ref.: reference range; ESR: erythrocyte sedimentation rate. Table prepared by the authors.

The patient presented with chronic diarrhea and severe nutritional compromise, requiring evaluation for multiple differential diagnoses. A multidisciplinary diagnostic workup was initiated, including an upper endoscopy (normal findings) and colonoscopy with the findings described in **Figure 1**.

Histopathology reported two completely ulcerated mucosae (cecum and transverse colon), increased eosinophils in descending colon, and scarce chronicity signs (occasional crypt branching). Findings were nonspecific but could represent either an infectious process or early-stage IBD (**Figure 2**). Special stains: Ziehl-Neelsen (ZN) and modified ZN were negative for acid-fast bacilli. Periodic acid-Schiff (PAS) and methenamine silver stains were negative for fungal structures (**Figures 3A**, **C** and **D**). CMV immunohistochemistry was negative (**Figure 3B**).

Initial management consisted of maintaining exclusive enteral nutrition with an elemental formula to ensure adequate caloric intake for nutritional recovery, while also serving as a management strategy for both cow's milk protein allergy (CMPA) and Crohn's disease (CD) induction therapy - two primary differential diagnoses. The patient additionally received multivitamin supplementation, folic acid, zinc, ferrous sulfate, albumin replacement, and packed red blood cell transfusion.

During hospitalization, the patient tolerated oral enteral formula well, with reduced diarrhea episodes, weight gain, improved abdominal distension, and resolution of

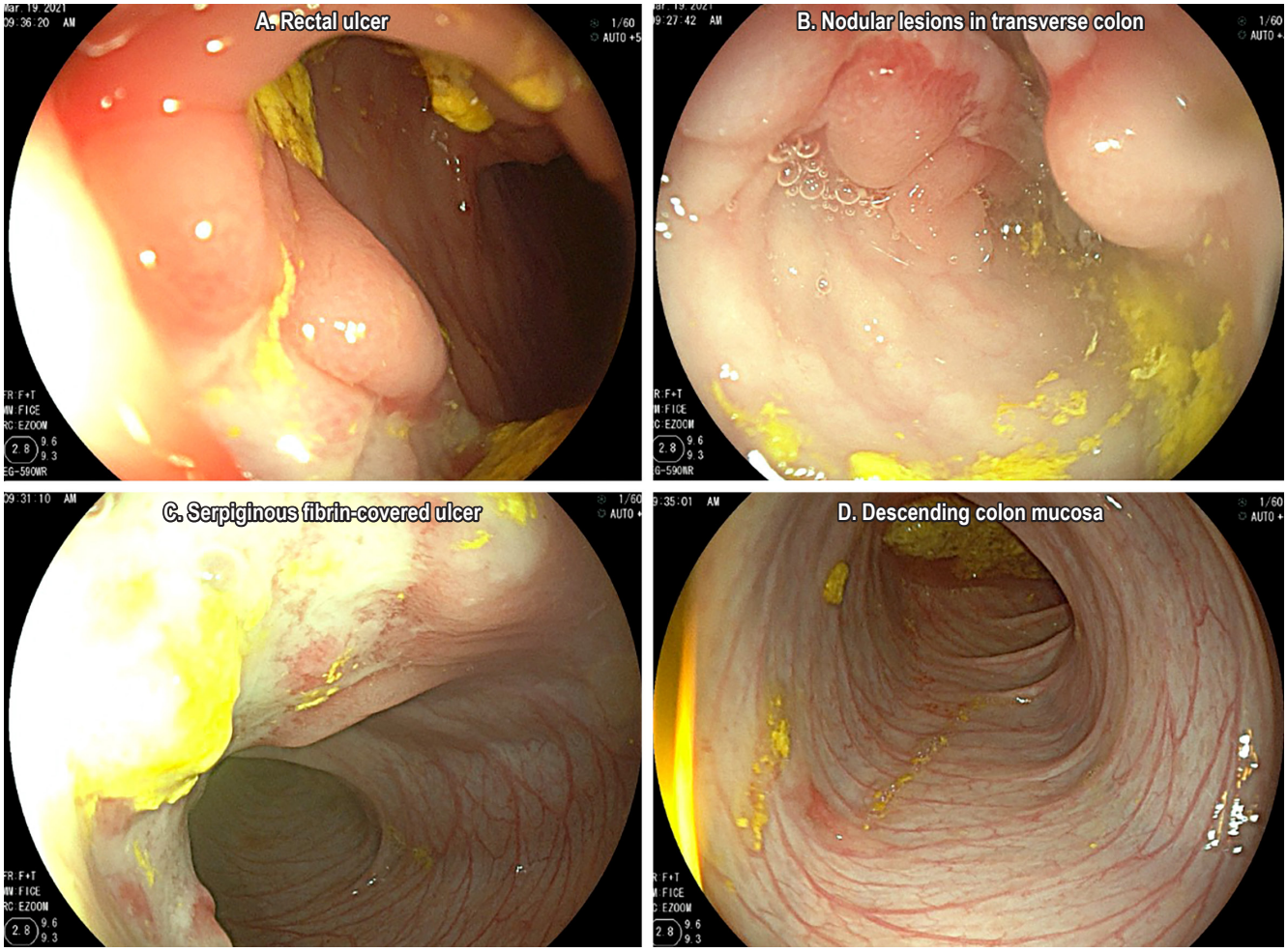

Figure 1. Initial colonoscopy. **A.** Anus and perianal region without lesions; poor preparation. At 5 cm from the anal margin, a large deep rectal ulcer covered with fibrin is observed. **B** and **C.** Rectosigmoid with edema and nodularity. The transverse colon shows multiple ulcerated nodular lesions forming a conglomerate causing partial circumferential stenosis. **D.** The remaining mucosa up to the cecum appears normal. Ileocecal valve could not be cannulated. Staged biopsies were taken, along with a transverse colon (nodular lesion) sample for mycobacterial PCR. Diagnosis: Inflammatory and ulcerated nodular lesions in rectosigmoid and transverse colon. Image property of the authors.

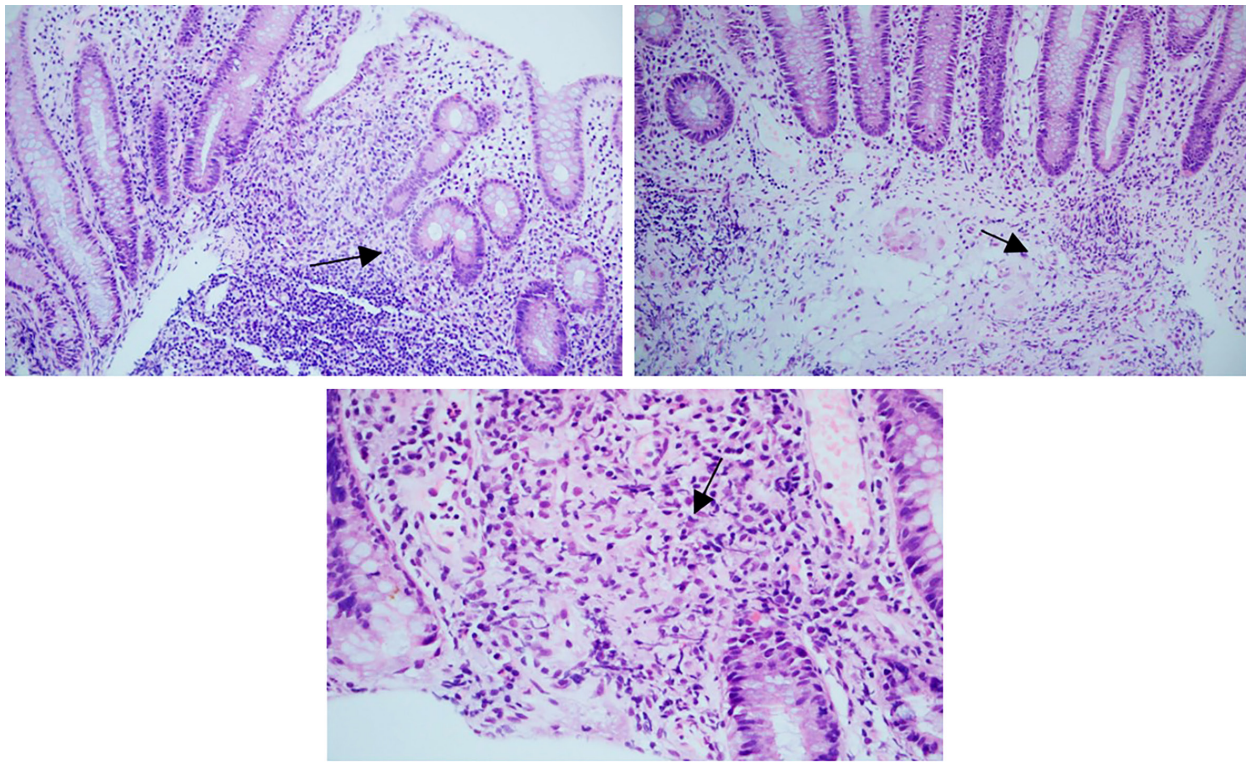

Figure 2. Conventional histology. Mixed inflammatory infiltrate with crypt architectural distortion (occasional branching indicating chronicity). Poorly defined granuloma present. Images property of the authors.

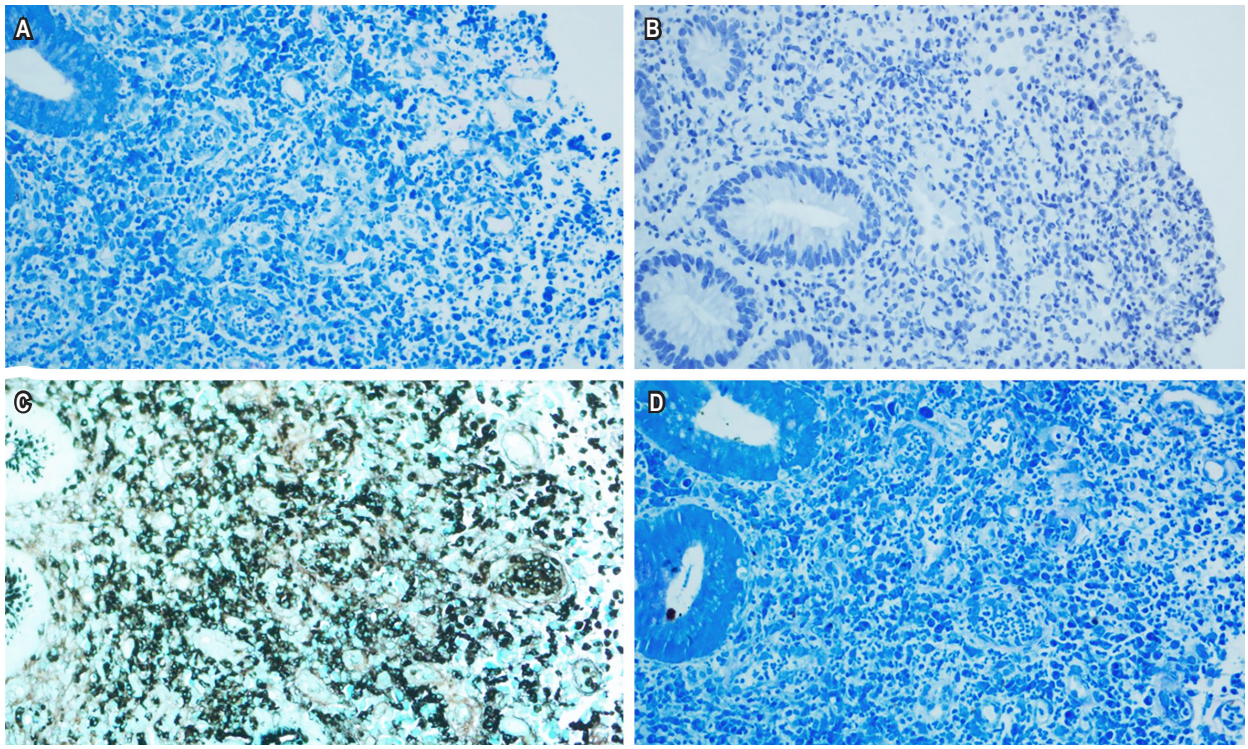

Figure 3. Special stains. **A.** Negative Ziehl-Neelsen (ZN) stain. **B.** Negative CMV immunohistochemistry. **C.** Negative periodic acid-Schiff (PAS) and methenamine silver stains. **D.** Negative modified ZN stain. Images property of the authors.

edema. However, isolated febrile spikes persisted. Given the endoscopic findings, comprehensive infectious workup was imperative - particularly for gastrointestinal tuberculosis (TB) and non-infectious causes of persistent fever (e.g., immune defects or intestinal barrier integrity disorders) - prompting whole exome sequencing.

Over the 27-day hospitalization, management followed a multidisciplinary approach (**Table 2**). Upon achieving clinical stability, gastrointestinal symptom improvement, and weight recovery (weight/height -0.95 SD), discharge was planned for outpatient follow-up and testing. Unfortunately, adequate adherence could not be maintained.

Follow-up evaluation during an IBD flare at 2 years of age (approximately 12 months after initial management) revealed persistent diarrhea (6-8 stools/day, some nocturnal) without mucus or blood, accompanied by abdominal pain/distension, food refusal, vomiting, left knee edema, bilateral conjunctival injection, oral aphthous ulcers, new perianal lesion, and intermittent fever. Physical examination showed the patient in fair general condition, febrile, with bilateral conjunctival injection, oral ulcers, distended abdomen tender to palpation (no masses or organomegaly), no peritoneal irritation, and perianal region demonstrating a skin tag with scant purulent discharge. Anthropometry confirmed persistent short stature with maintained weight-for-height adequacy.

Admission tests revealed severe anemia, elevated acute-phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]), hypoalbuminemia, thrombocytopenia, negative gastrointestinal FilmArray panel, and elevated fecal calprotectin. Given the presumptive diagnosis of early-onset IBD during a severe disease flare (PCDAI score: 60), a comprehensive workup was performed, including follow-up endoscopic studies (**Figure 4**), enterography to assess small bowel involvement, and pelvic MRI to evaluate perianal disease extent (**Figure 5**). A renewed

Table 2. Extended Workup

Test Category	Results
Infectious Profile	- PPD: 0 mm - COVID-19 RT-PCR: Negative - Mycoplasma pneumoniae IgM: Negative - PANFUNGAL PCR (colon biopsy): Negative - Mycobacterial PCR (colon biopsy): Negative (report received 04/06/2021)
Metabolic/Hormonal	- Venous blood gases: No acid-base imbalance - Ammonia: 22.3 (normal) - Glucose: 108 mg/dL - Iontophoresis: 33 (normal; previous Sept/2020: 31 - negative), ruling out cystic fibrosis - TSH: 4.23 (Ref.: 0.5-4.9) - normal - Fecal alpha-1 antitrypsin: 0.44 mg/g (normal ≤0.3) - elevated
Gastrointestinal	- Fecal calprotectin: 1251 µg/g - ASCA: IgA: 172.3 U, IgG: 64.6 U (Ref.: 0-20) - positive - ANCA: MPO: 1.8 (Ref.: 0-20), PR3: 2.6 (Ref.: 0-20) - negative - CT scan: Wall thickening in transverse/descending colon. No small bowel involvement.
Hematologic	- Serum iron: 40 (Ref.: 50-150) - low, Transferrin: 90 (Ref.: 186-388) - low - Ferritin: 90.8 (Ref.: 7-140) - normal, LDH: 160 U/L (Ref.: 145-345) - normal
Immunologic	- Protein electrophoresis: - Hypoalbuminemia, Alpha-1 region elevation, and Mild beta-1 region reduction. Faint nonspecific band in gamma region. IgA: 234 mg/dL (Ref.: 21-294) - normal IgG: IgG: 772 mg/dL (Ref.: 475-1210) - normal IgM: 319 mg/dL (Ref.: 41-183) - mildly elevated IgE: <25 (Ref.: 0-60) - normal

ANCA: Anti-neutrophil cytoplasmic antibody; ASCA: Anti-Saccharomyces cerevisiae antibody; COVID-19: Coronavirus disease 2019; IgA: Immunoglobulin A; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IgM: Immunoglobulin M; LDH: Lactate dehydrogenase; PCR: Polymerase chain reaction; PPD: Purified protein derivative; PR3: Proteinase 3; RT-PCR: Reverse transcription polymerase chain reaction; CT: Computed tomography; TSH: Thyroid-stimulating hormone; Ref.: Reference range. Table prepared by the authors.

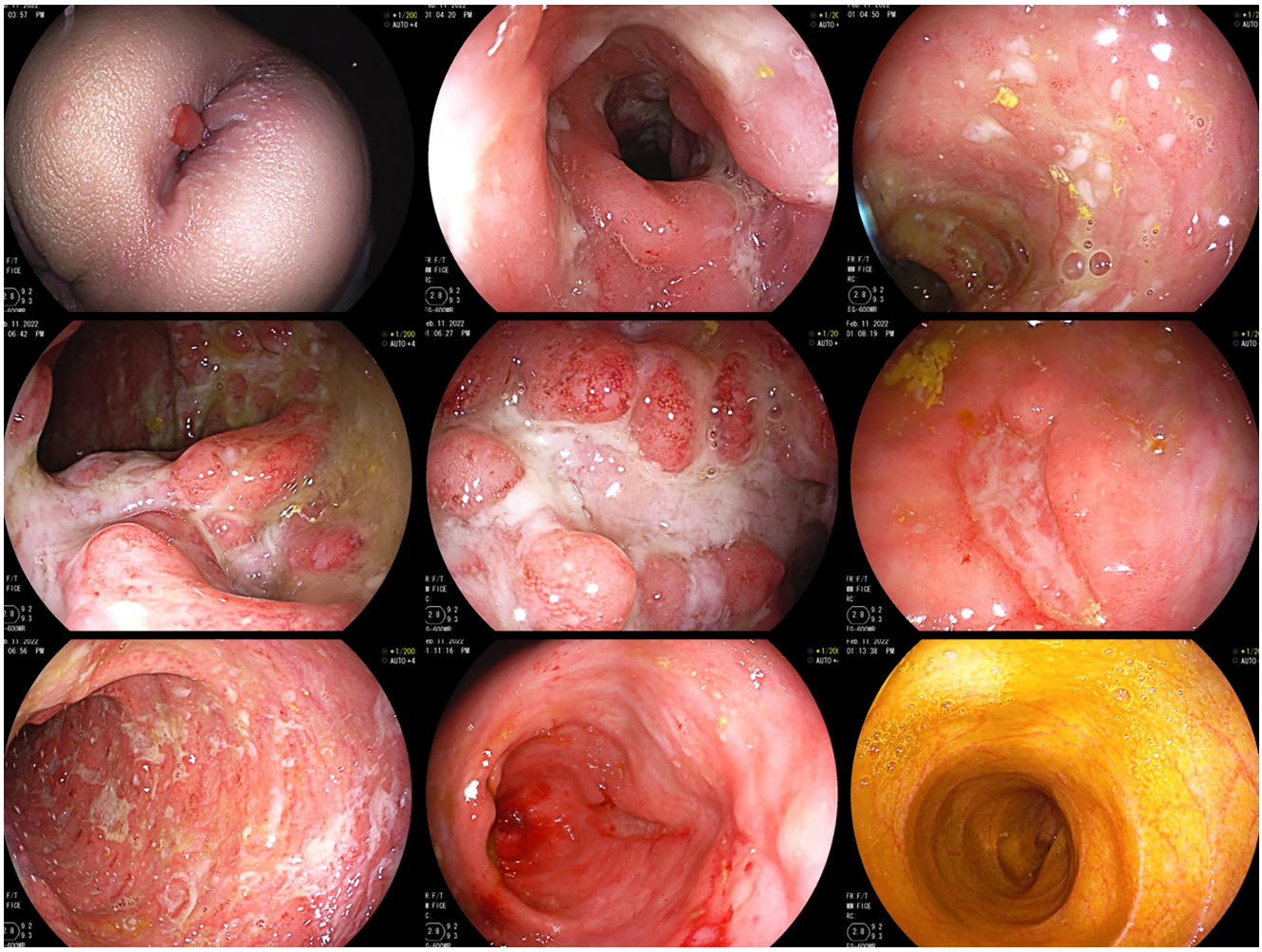

Figure 4. Follow-up ileocolonoscopy during disease flare. Images property of the authors.

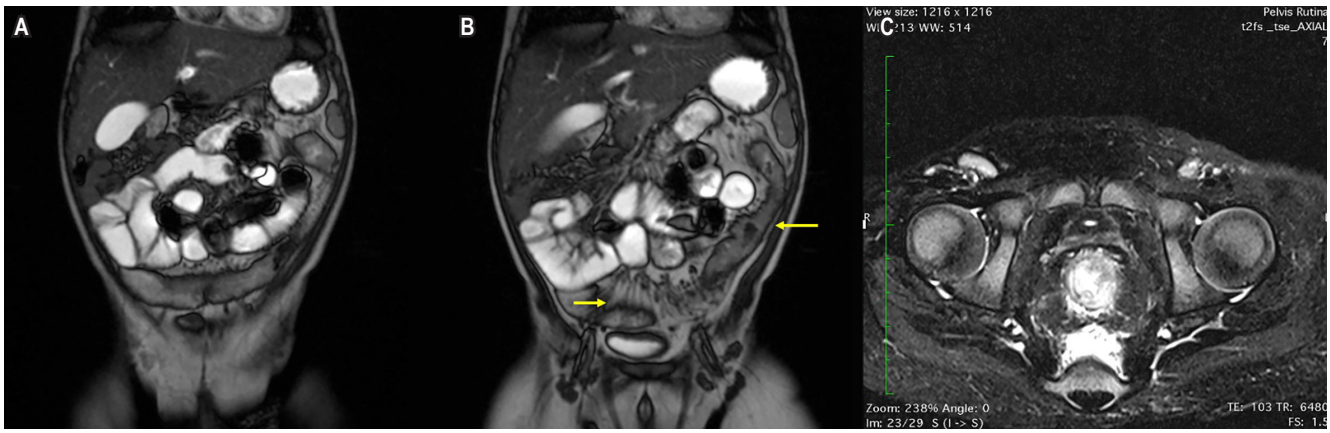

Figure 5. Enterography and pelvic MRI. **A.** Adequate small bowel distension with normal appearance - no pathological enhancement/wall thickening, stenosis, or dilatation. **B.** Pathological enhancement and wall thickening throughout the colon (predominantly left/transverse colon) consistent with colitis and vascular engorgement. **C.** Intersphincteric perianal fistula tract with associated right-quadrant abscess. Images property of the authors.

multidisciplinary approach was implemented with emphasis on addressing the patient's social context contributing to prior non-adherence.

After ruling out the most likely differential diagnoses through comprehensive clinical, endoscopic, histological, and radiological reevaluation, we classified our patient according to the Paris criteria as having very early-onset IBD of the Crohn's disease (CD) type in the infant subcategory (A1a), with colonic + perianal involvement (L2p), inflammatory and stenosing phenotype (B2), and growth failure (G1).

The patient exhibited multiple risk factors predicting a complicated disease course: Non-response to exclusive enteral nutrition induction therapy, Age <2 years at onset, Pancolonic involvement, Positive anti-Saccharomyces cerevisiae antibodies (ASCA), and Perianal disease requiring biologic therapy. Infliximab was selected as first-line treatment at 5 mg/kg/dose on an intensified frequency schedule (weeks 0-1-4), targeting serum trough levels >12.7 µg/mL before the fourth dose - the recommended pharmacological approach for perianal involvement. All management decisions followed ECCO/ESPGHAN pediatric CD guideline recommendations. This therapy was combined with azathioprine initiation (2 mg/kg/day) as an immunomodulator and dual therapy with salicylates.

For perianal disease management, in addition to intensified anti-TNF-α dosing, an antibiotic regimen (metronidazole + ciprofloxacin) was initiated along with surgical intervention consisting of fistulectomy with seton placement. This combined strategy achieved clinical improvement and partial endoscopic response.

Unfortunately, during infliximab therapy, the patient developed immunomediated loss of response manifested by anaphylaxis during infusion, necessitating biologic switching to adalimumab with induction dosing (80 mg) followed by maintenance (40 mg every two weeks).

Despite adherent maintenance therapy with adalimumab, the disease followed an unfavorable course with rapid progression and failure to achieve clinical/endoscopic remission. Subtherapeutic adalimumab levels (<0.2 µg/mL) with elevated antibodies (>200 ng/mL) confirmed secondary immunologic failure to this second-line anti-TNF. Having exhausted available pediatric therapeutic options for severe perianal CD, we transitioned to ustekinumab (anti-IL-12/IL-23 biologic) for induction (6 mg/kg) and maintenance (3 mg/kg every 8 weeks), which has been well-tolerated without adverse events to date.

Concurrently with ustekinumab initiation, due to high-risk perforating perianal disease, a multidisciplinary team recommended surgical management. Attempted seton placement for the perianal fistula failed due to anal stenosis and severe rectal inflammation, prompting concurrent diverting ileostomy creation.

Following ileostomy and ustekinumab induction, clinical improvement was evidenced by PCDAI=20 (from previous 55), representing a >20-point decrease indicating adequate treatment response, with restored appetite, pain reduction, sustained weight gain, normalized serum albumin, and decreased acute-phase reactants. Trio exome sequencing identified no pathogenic variants associated with very early-onset disease.

DISCUSSION

We present the case of a 3-year-old male patient who developed infant-onset IBD at 4 months of age, with a CD phenotype according to the Porto Criteria[8] and classified as A1aL2pB2G1 under the Paris Classification[9]. These VEO-IBD patients demonstrate significant differences compared to pediatric IBD occurring in children under 18 years or adults (**Figure 6**). The condition is notably distinct due to its predominantly colonic involvement, more severe disease course, reduced response to conventional therapy (59% vs 85%, p=0.003), higher need for surgical interventions (32% vs 14%, p<0.001), and association with monogenic defects[1,2,4].

When evaluating a patient with symptom onset at such an early age and presenting with the clinical conditions we observed at 17 months, it was crucial to conduct a comprehensive assessment to rule out differential diagnoses. In this case, given the initial endoscopic findings, it was particularly important to exclude immunodeficiency and intestinal tuberculosis (ITB)[3]. ITB can mimic Crohn's disease (CD) in several aspects, including clinical presentation, radiological features, endoscopic appearance, and histological findings[10]. For this patient, establishing an accurate diagnosis was essential to provide appropriate treatment.

Pediatric studies comparing ITB and CD remain limited; however, certain clinical and endoscopic features show significant associations with CD: chronic diarrhea (82% vs 40%, p=0.006), bloody stools (74% vs 10%, p<0.001), extraintestinal manifestations (21% vs 0%, p=0.02), and left-sided colonic involvement with deep longitudinal ulcers (87% vs 40%, p=0.003). In contrast, ITB cases predominantly present with intestinal obstruction (20% vs 0%, p=0.02), ascites (30% vs 0%, p=0.005), and isolated ileocecal involvement (40% vs 8.7%, p=0.03). Although evidence remains scarce, these findings align with adult-reported data[10]. Given our inability to isolate mycobacteria and the clinical, endoscopic, histological, and radiological features suggestive of CD, we proceeded with CD management.

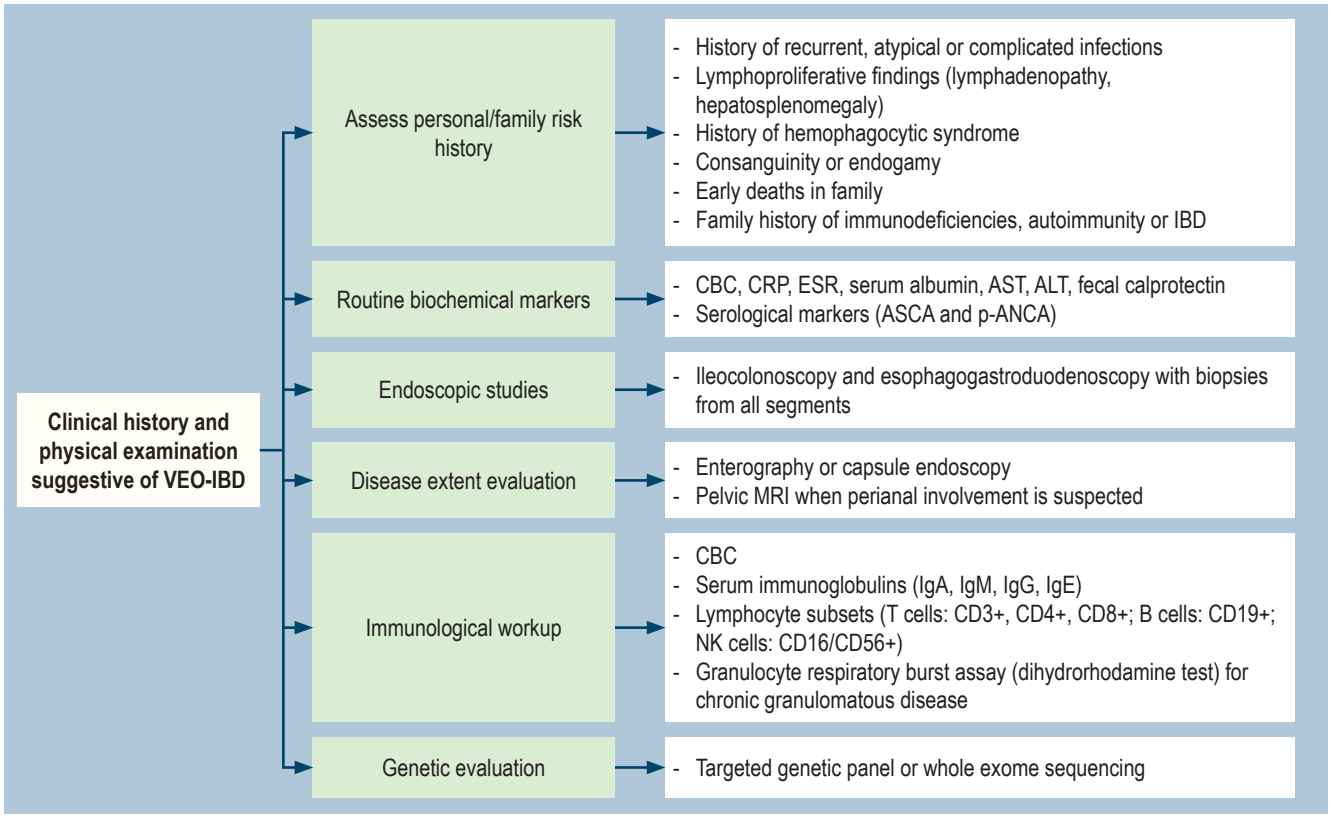

Figure 6. Diagnostic algorithm for suspected VEO-IBD. ALT: alanine aminotransferase; ASCA: anti-Saccharomyces cerevisiae antibodies; AST: aspartate aminotransferase; CD: cluster of differentiation; IBD: inflammatory bowel disease; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; CRP: C-reactive protein; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibodies; ESR: erythrocyte sedimentation rate; VEO-IBD: very early-onset inflammatory bowel disease. Image property of the authors.

Accurate differentiation between phenotypes, particularly ulcerative colitis (UC) and CD, carries significant implications for defining disease natural history, induction/maintenance therapeutic strategies, and surgical considerations[8,11].

For disease monitoring, we employed the Pediatric Crohn's Disease Activity Index (PCDAI), where clinical remission is defined as a score <10 points and clinical response requires at least a 20-point reduction. Our patient's hospitalization scores >40 indicated severe disease activity[2,12]. Beyond clinical and endoscopic follow-up, we monitored inflammatory biomarkers (fecal calprotectin) and imaging (MRI)[12,13].

Our management strategy followed the 2020 ECCO-ESPGHAN guidelines[12], incorporating risk stratification - a critical step for identifying patients at high risk of complicated disease progression. Early pediatric stratification guides optimal therapy selection to minimize bowel damage. Our patient met high-risk criteria due to extensive stenosing colonic involvement, perianal disease, severe growth impairment, and lack of clinical/biochemical response after 12 weeks of exclusive enteral nutrition[12,14]. After excluding immunodeficiency[1,3] and considering the severe clinical course, we initiated anti-TNF biologic therapy with immunomodulator combination - a decision requiring evidence-based, systematic deliberation.

For perianal disease assessment, we performed detailed pelvic MRI (with/without contrast) and thorough examination under general anesthesia. Perianal CD complications (fistulae/abscesses) represent severe, treatment-resistant manifestations[15,16], occurring in 8-15% of pediatric patients. Risk factors include male sex (3-fold higher vs females) and systemic corticosteroid induction therapy (2-fold increased risk)[17].

Current recommendations for perianal CD advocate anti-TNF therapy as first-line induction/maintenance treatment, combined with antibiotics and surgical intervention[16,18]. Intensified infliximab regimens (dose/inter-

val optimization targeting pre-fourth-dose serum levels >12.7 μg/mL) significantly improve mucosal healing and fistula closure rates[15,19,20]. Additional criteria for intensified biologic therapy include low body weight (<30 kg), extensive disease, and hypoalbuminemia.

Regarding the surgical management of perianal disease, once the perianal involvement has been classified and characterized through pelvic magnetic resonance imaging, any identified abscess should be drained, typically through partial fistulectomy with seton placement[16,18]. When deep perianal ulcers, purulent discharge, and adjacent tissue inflammation accompany fistulae, diverting ostomy may be a recommended therapeutic option, particularly in cases refractory to medical therapy[15], as described in this case. Due to the refractory nature of the disease, surgical interventions are frequently required in the clinical course of VEO-IBD patients; studies have shown this group requires surgical procedures (diverting ostomies or colectomy) more frequently, with surgical intervention rates of 32% in VEO-IBD cases with symptom onset before one year of age compared to 14% when symptoms begin after one year ($p<0.001$)[1,2].

In our patient with severe, treatment-refractory disease and perianal involvement associated with significant rectal inflammation, a multidisciplinary team including pediatric surgery and coloproctology specialists decided to perform a diverting ileostomy to promote colonic rest and reduce inflammatory burden[1].

We combined infliximab with azathioprine as maintenance therapy to reduce immunogenicity risk[21]. Regarding infliximab maintenance dosing, adjustments should ideally be guided by proactive therapeutic drug monitoring. Unfortunately, during the fifth infliximab infusion, the patient developed an anaphylactic reaction with immunologic anti-TNF failure, prompting a switch to the second pediatric-approved biologic, adalimumab, whose effectiveness for perianal disease management has been validated in multiple clinical trials[13,22,23].

Our patient's clinical course highlights the concept of immunologic failure to first- and second-line anti-TNF therapy. Few studies evaluate anti-TNF use in VEO-IBD; however, available data suggest reduced durability of these biologics (90% anti-TNF persistence at 1 year, 75% at 3 years, and 55% at 5 years), with the most frequent reasons for discontinuation being loss of response (57% of cases) and adverse reactions (24%)[21,24,25].

Therapeutic drug monitoring is essential to guide treatment modifications rather than empirical anti-TNF dose adjustments. Optimal outcomes depend on close monitoring of treatment response with timely therapy adjustments when clinical and endoscopic targets are not met[12,26]. Unfortunately, this patient's sociodemographic circumstances and insurance status created barriers to adequate specialized follow-up.

During the most recent hospitalization, after multidisciplinary review, extensive literature analysis, and consultation with international referral centers, the decision was made to transition to ustekinumab (anti-IL-12/IL-23 biologic) for induction and maintenance therapy.

Ustekinumab is a monoclonal antibody targeting the p40 subunit shared by proinflammatory cytokines IL-12 and IL-23. Its mechanism of action involves blocking these cytokines' interaction with the IL-12 receptor on Th1 and Th17 lymphocytes - cells implicated in CD pathophysiology[27]. Ustekinumab has demonstrated efficacy in adults with anti-TNF refractory CD and UC[28].

Emerging evidence suggests ustekinumab may effectively induce and maintain remission in pediatric patients with anti-TNF failure, with documented improvements in clinical scores, biochemical parameters, and growth metrics[12,29,30].

A study of 50 children with IBD who discontinued anti-TNF therapy due to primary failure or adverse events showed 48% clinical response rate at 3 months in CD phenotype, increasing to 90% in biologic-naïve patients, with good tolerability and no serious adverse events reported[30].

Although emerging evidence supports ustekinumab use in pediatric populations, this medication is not yet approved for pediatric IBD in Colombia. Consequently, we lack local pediatric experience with this agent, making our patient the first pediatric VEO-IBD case receiving this treatment in Colombia. Selecting optimal therapy at such a young age presents both clinical and administrative challenges for the treatment team.

From a pediatric perspective, the significant nutritional impairment at disease onset warrants emphasis. Our patient presented with severe malnutrition that showed rapid weight recovery with appropriate enteral support; however, failure to thrive persisted throughout the disease course, reflecting greater systemic inflammatory burden in pediatric patients - a finding present in 46% of pediatric CD cases at diagnosis[31].

After two years of follow-up in this patient with very early-onset disease demonstrating aggressive progression and failure of multiple conventional therapies, genetic exome sequencing becomes crucial for early detection of monogenic defects[1] that may guide targeted therapy, as some patients may respond successfully to bone marrow transplantation[5,6]. Conversely, when no specific genetic or immunologic defect is identified (as in our case), treatment follows standard pediatric IBD protocols, recognizing these cases typically show poorer response to conventional therapies[1].

CONCLUSIONS

- VEO-IBD cases exhibit more severe disease in terms of extent and behavior.
- While most VEO-IBD cases are multifactorial, genetic factors play a significant role, particularly when symptom onset occurs before two years of age. Therefore, genetic exome sequencing is critical in the initial evaluation.
- Perianal involvement in pediatric IBD is a marker of more severe disease and a predictor of poor long-term outcomes.
- Intestinal tuberculosis (ITB) mimics Crohn's disease (CD) in clinical, radiological, endoscopic, and histological presentations.
- To achieve an accurate diagnosis in suspected pediatric IBD, adherence to clinical practice guidelines for diagnostic and individualized management is essential.
- Correct differentiation between IBD phenotypes has significant implications for defining disease natural history, therapeutic strategies, and surgical considerations.
- Selecting optimal therapy at such an early age presents a challenge for the treatment team. Thus, following management guidelines, expert recommendations, and a multidisciplinary approach is crucial.
- Therapeutic drug monitoring is fundamental to guide treatment adjustments rather than empirically modifying anti-TNF dosing.
- Ustekinumab represents a treatment alternative for CD patients who fail anti-TNF biologics.
- Patients with VEO-IBD frequently require more surgical interventions. In this population, diverting ostomies may promote colonic rest, reduce inflammatory burden, and improve quality of life when conventional therapy fails and severe colonic involvement progresses.

Author Contributions

All authors contributed to the design, development, and writing of the manuscript.

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Conflicts of Interest

None declared by the authors.

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