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CLINICAL CASE

Concomitant Ulcerative Colitis and Neurofibromatosis type 1: possible common origin?

Colitis Ulcerosa y Neurofibromatosis tipo 1 concomitantes: ¿posible origen común?

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What do we know about the subject matter of this study?

Neurofibromatosis type 1 is a genetic syndrome characterized by the development of neurofibromas, with dysregulation of mast cell degranulation involved in their formation. It is postulated that this alteration could play a role in the pathogenesis of Ulcerative Colitis.

What does this study contribute to what is already known?

It is the first case report of a preschool patient with Neurofibromatosis Type 1 presenting ulcerative colitis. This case adds to the discussion the role of Cytomegalovirus in the presentation of the disease, which has not been studied in previous cases.

Abstract

In the last 15 years, 3 cases of concurrent Ulcerative Colitis with Neurofibromatosis Type 1 have been described in adults and adolescents, but not in children; although it may be a casual finding, a common pathogenic pathway between both diseases is postulated, based on mast cell dysregulation in the gastrointestinal tract. **Objective:** To report the clinical case of a toddler with onset of concomitant Ulcerative Colitis with CMV infection, with history of Neurofibromatosis Type 1, and to discuss the common origin between both diseases. **Clinical Case:** We describe the case of a 2-and-a-half-year-old toddler with history of Neurofibromatosis Type 1 who presented with bloody diarrhea. On endoscopic examination, the mucosa from the anal margin to the cecum was erythematous, with loss of vascular transparency. Biopsies of colonic mucosa showed signs of chronic inflammation, consistent with the diagnosis of Ulcerative Colitis, and CMV infection was diagnosed by PCR. **Conclusion:** Previous studies have suggested that mast cells may have a pathogenic role in the development of UC, however, the clinical significance of these findings is unknown. Future research is needed to further investigate the role of mast cells in the development of UC and to confirm a genetic association between the two diseases.

Keywords:
Inflammatory Bowel Diseases;
Ulcerative Colitis;
Neurofibromatosis 1;
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Introduction

Ulcerative colitis (UC) is one of the presentations of inflammatory bowel disease (IBD). It is defined as the chronic inflammation of the gastrointestinal tract associated with a dysregulated immune response to environmental triggers[1,2]. IBD can occur at any age, with the highest incidence occurring between 15-29 years of age. 20-25% of cases develop in the pediatric age group and between 6-15% in children under 6 years of age[3,4].

An increase in the incidence of pediatric IBD has been described, especially in the group under 6 years of age, which is classified as "very early-onset inflammatory bowel disease" (VEO-IBD)[5-7].

In the case of VEO-IBD, there are more cases of monogenic origin (monogenic IBD), reaching up to 15-20% of cases in children under 6 years of age, and the earlier ages of disease onset are more associated with genetic defects[7]. To date, approximately 60 monogenic mutations associated with IBD have been identified[3,7].

The co-occurrence of Ulcerative Colitis (UC) and Neurofibromatosis Type 1 (NF1) has only been reported on 3 occasions by Tavakkoli et al.[8], Baratelli et al.[9], and Adams et al[10]. Although it may be a chance finding, a common pathogenic pathway is postulated that would explain the relationship between both diseases, based on an alteration in mast cell signaling, which is observed in the development of neurofibromas and which would be implicated in the pathogenesis of IBD[10,11].

NF1 is an inherited syndrome caused by the alteration of the *NF1* gene[12]. It is characterized by the development of tumors mainly in the central and peripheral nervous system, associated with multisystem involvement to varying degrees, with dermatological, bone, cardiovascular, optic, and gastrointestinal alterations reported[13]. Gastrointestinal manifestations are reported in 5-25% of patients, including tumors, vasculopathy, pseudo-obstruction, and protein-losing enteropathy. The symptoms are generally nonspecific, including bleeding, abdominal pain, and symptoms secondary to intestinal obstruction, such as nausea, vomiting, and bloating[8,13,14]. The most frequent lesions are gastrointestinal stromal tumors (GIST), located mostly in the small intestine and stomach[14].

The presentation of this case was approved by the Scientific Ethical Committee of the UC Health Sciences.

The objective is to report the case of a 2-year-old patient with history of NF1, who presents with bloody diarrhea, with endoscopic study and biopsy compatible with UC and associated CMV infection.

Clinical Case

Female preschooler aged 2 years 6 months, with diagnosis of NF1. She consulted due to a 4-weeks history of bloody diarrhea (5 to 10 episodes per day). One week after the onset of the symptoms, she consulted the emergency department, where Rotavirus (+) was detected, with low inflammatory parameters, negative stool culture, and normal abdominal ultrasound. She was hospitalized for 3 days for management of dehydration and was discharged without bleeding, with persistent semi-liquid stools. Ten days after discharge, she presented again with bloody diarrhea, associated with low intake and weight loss of 1 kg referred by her parents. They consulted a pediatric gastroenterologist who requested a polymerase chain reaction (PCR) panel for gastrointestinal pathogens and PCR for *Clostridium difficile* (which were negative) and indicated hospitalization for study.

On anamnesis, the parents did not report fever, abdominal pain, vomiting, respiratory or urinary symptoms, arthralgias, or new skin lesions. They do not own pets, and there was no history of travel or recent dietary changes.

The patient had a confirmed diagnosis of NF1 at 8 months of age by genetic study, with the heterozygous pathogenic variant c.5606_5627del (p.Gly1869Valfs*28). She presented cutaneous (*café-au-lait* spots) and bone involvement. At 18 months, she required ankle arthrodesis due to tibial curvature. She has no family history of NF1 or inflammatory bowel disease.

Physical examination revealed a soft and painless abdomen, with increased bowel sounds, without masses or visceromegaly. The perianal examination was normal. She had multiple *café-au-lait* spots on her lower limbs and back. General examinations were performed, including blood count which showed moderate microcytic-hypochromic anemia (Hb 9.6 g/dL), leukocytosis with left shift (leukocytes 13,900), and slightly elevated inflammatory parameters (CRP 1.37 mg/dL, normal value up to 0.5 mg/dL).

A colonoscopy was performed, exploring the rectum, sigmoid, and the different segments of the colon up to the cecum, visualizing the ileocecal valve and the appendiceal orifice. The last centimeters of the distal ileum were also inspected. The mucosa from the anal margin to the cecum was erythematous, with loss of vascular transparency, unlike the mucosa of the cecum which was normal. No lesions were identified in the anal canal or cecum.

Biopsy samples were collected from the small intestine (ileum) and large intestine. Microscopic examination showed ileal mucosa with preserved villous architecture and adequate epithelial differentiation,

and lamina propria without inflammation. The large intestine mucosa had slight distortion of architecture and adequate epithelial differentiation, lamina propria with edema with mild mixed inflammatory infiltrate, and hyperplasia of lymphoid follicles. Isolated foci of micro-abscesses were observed. The biopsy was concordant with mild colitis, with signs suggestive of chronicity. In addition, a PCR study for Cytomegalovirus (CMV) was performed in a colonic biopsy sample, which was positive.

Given the positive PCR for CMV, CMV IgG and IgM and CMV viral load measure in blood was performed, resulting in positive IgG, negative IgM, and CMV viral load of 79.7 IU/mL. Additional laboratory studies included PCR for gastrointestinal pathogens and PCR for *Clostridium difficile* in stools, both were negative. In the colonic biopsy, microbiological studies of Gram stain were performed, which showed +++ leukocytes without bacteria; biopsy culture showed *S. gallolyticus/equinus complex* in very low quantity (interpreted as bacterial flora); acridine orange, Ziehl-Neelsen, Koch's culture, and Adenovirus PCR were negative.

Due to endoscopy findings and histology suggestive of UC, in the context of a patient with moderate symptoms (PUCAI 50), treatment was started with Mesalazine (70 mg/kg/day three times a day), and fecal calprotectin measurement was performed which showed values higher than 600 ug/gr.

The Immunology team evaluated the patient due to suspected immunodeficiency. Upon anamnesis, the parents reported no previous infectious history, up-to-date vaccination schedule, good weight gain, and no family history of immunodeficiency, autoimmunity, or early deaths. Lymphocyte subpopulations (normal), immunoglobulins (normal), HIV (negative), memory T lymphocytes (with expected alterations in the context of CMV viremia), and lymphoproliferation test (normal) were performed. In addition, a genetic panel of Primary Immunodeficiencies (Invitae) was performed, containing 429 genes, of which 68 make up the Monogenic Inflammatory Bowel Disease Panel. Seven variants of uncertain significance were obtained, none included in the Monogenic IBD Panel.

The patient received intravenous Ganciclovir for 15 days due to CMV infection. The last CMV PCR control before discharge reported an undetectable viral load.

The patient evolved favorably during hospitalization, with decreased stool frequency and increased consistency, no rectal bleeding, no nocturnal stools, no abdominal pain, and PUCAI 0 at discharge.

Subsequently, after 2 months, she presented reactivation of IBD with bloody diarrhea (PUCAI 35). A complete blood count (normal), gastrointestinal pathogens panel (-), *Clostridium difficile* PCR (+), and undetectable CMV load were performed. She was managed with oral Metronidazole, however, she persisted with bloody diarrhea, so she was hospitalized again.

A colonoscopy was performed, where diffuse erythematous mucosa was observed from the rectum to the cecum, with nodularity and loss of vascular transparency in the submucosa, more in the left and transverse colon segments. No focal lesions were observed. The ileal mucosa and anal canal were observed without lesions.

A biopsy of the terminal ileum and right and left colon was performed. On microscopic examination, the ileal mucosa maintained preserved villous architecture and adequate epithelial differentiation. The lamina propria showed no signs of inflammation. No aphthoid erosions or granulomas were observed. The large bowel mucosa showed a slight distortion of the architecture and epithelial dedifferentiation. The lamina propria was expanded by a mixed inflammatory infiltrate, with transmucosal distribution. Foci of cryptitis and crypt micro-abscesses and hyperplasia of reactive-type lymphoid follicles were found. No granulomas or cytopathic alterations of viral or parasitic type were observed. All fragments of the left colon specimen presented a similar histopathological picture.

Treatment with oral Vancomycin and Prednisone (1 mg/kg/day) was indicated with good response, presenting a favorable evolution. She was discharged with decreased stool frequency. In the outpatient check-up, she persisted with mild symptomatology (PUCAI 5), so the dose of corticosteroids was progressively reduced, and she is maintained on treatment with Mesalazine.

Discussion

NF1 is a genetic disease characterized by the development of neurofibromas, composed of Schwann cells, mast cell degranulation products, fibroblasts, and extracellular matrix. In the formation of these, Schwann cells regulate mast cell degranulation through a cytokine receptor on the cell surface, known as c-kit[10,11]. Schwann cells from NF1 patients express higher levels of c-kit compared with normal Schwann cells[11], leading to dysregulation of mast cell degranulation. Mast cells participate in the formation of neurofibromas through the release of their degranulation products and the secretion of cytokines such as TGF--, histamine, heparin, and metalloproteinases[9].

The increased recruitment and activity of mast cells would not be unique to the neurofibroma microenvironment. Baratelli et al.[9] and Adams et al[10]. demonstrated increased expression of CD117/c-kit in colonic mucosal samples in their patients with UC and NF1, indicating a local increase in the presence of mast cells.

This alteration could play a role in the pathogenesis of UC, through the release of inflammatory mediators in the epithelial barrier of the colonic mucosa that could mean an increased risk of developing UC.

One of the most widely accepted theories for the development of IBD is based on the existence of immune dysregulation that would alter the epithelial barrier, and in response to environmental triggers, a symptomatic inflammatory reaction would be activated[1]. The compromise of the immune system can lead to the reactivation of latent viruses, such as CMV. There is debate as to whether CMV infection is responsible for the severity of inflammation in UC, is a marker of disease severity, or is a consequence[15]. It is a challenge in clinical practice to distinguish whether there is viral replication without mediating disease, i.e., CMV reactivation, or CMV-mediated colitis[16]. However, it is known that adult and pediatric patients with UC and CMV infection tend to have more severe disease, resistance to corticosteroids, and are at higher risk of colectomy in the short- and long-term[15,17]. Siegmund proposed an interesting diagnostic and therapeutic algorithm to guide decisions in this scenario[16].

When comparing this case with previously reported cases, it stands out that it is the only one described in the group of children under 6 years of age. This is relevant since this age group has seen the greatest increase in the incidence of pediatric IBD in the last 10 years[7]. All reported cases begin with bloody diarrhea; however, the 39-year-old patient presented by Tavakkoli et al. had intermittent bloody diarrhea for 8 years before diagnosis[8]. The patients reported by Adams et al.[10] and Baratelli et al.[9] presented greater extension and severity of large bowel involvement, and none of the cases detailed a CMV study. In all cases, 5-aminosalicylic acid was used as part of the treatment, associated or not with the use of corticosteroids.

Finally, all patients, including our patient, present cutaneous involvement associated with NF1, and, as in this case, the patient reported by Adams et al.[10] presents bone involvement. The patient presented by Tavakkoli et al.[8] presents greater tumor involvement associated with NF1, which may be associated with her older age and the course of the disease.

In conclusion, no associated genes between IBD and NF1 have yet been described. However, as case reports of UC and NF1 increase, and thanks to advances in characterizing the microenvironment of neurofibromas in NF1 patients and the pathogenesis of pediatric IBD, the possibility that the proposed common pathologic pathway is accurate increases. Future research in the area is needed to further investigate the role of mast cells in the development of UC and to confirm a genetic association between the two diseases.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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