Successful treatment of ulcerative colitis with anakinra: a case report

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Abstract

Currently the effect of IL-1 blockade on ulcerative colitis (UC) is still ambiguous. This case report describes a patient with UC who developed severe complications after an episode of azathioprine-induced pancytopenia including cytomegalovirus pneumonitis, hemophagocytic lymphohistiocytosis, and probable pulmonary aspergillosis. Imaging after the hospitalization revealed a severe disseminated chronic candidiasis and persisting inflammation was seen. Genetic testing revealed heterozygous variants in NOD2 and NLRP12, and cytokine testing showed an increase in IL-1Ra, IL-18, CXCL9, and CXCL10. Consequently an IL-1 mediated autoinflammatory syndrome was suspected. Simultaneously, the patient developed a corticosteroid dependent UC flare-up. Treatment with anakinra was initiated for the IL-1 mediated disease which quickly induced remission of both the inflammatory syndrome and the UC. (Acta gastroenterol. belg., **2023,** 86, **573-576**).

Keywords: Inflammatory bowel disease, IL-1, chronic disseminated candidiasis, azathioprine.

Introduction

In ulcerative colitis (UC) a chronic inflammation of the colonic mucosa is seen, thought to be caused by a dysregulated mucosal immune response to the commensal gut flora, typically in genetically susceptible individuals (1). Interleukin 1 (IL-1) is a proinflammatory cytokine that is associated with inflammasome activation and plays an important role in the host response to noxious stimuli. Excessive inflammasome activation and IL-1 signaling is at the heart of immunopathology of autoinflammatory syndromes and evidence exists for a role of IL-1 in the pathogenesis of inflammatory bowel diseases (IBD) (2). Anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra), shows promising results in the treatment of inflammatory syndromes, but the effect on IBD is still unclear (3). This report describes the case of a patient with UC who was diagnosed with an IL-1 mediated inflammatory disease for which anakinra was initiated.

Results

A female patient was diagnosed with UC in 2014 at the age of 22. Initially she was treated with salicylates and due to multiple flare-ups azathioprine (AZA) was initiated in January of 2017 and gradually increased until 175 mg (2.5 mg per kg bodyweight). However in May 2017, the patient developed pancytopenia and neutropenic fever, requiring hospitalization. The AZA was stopped and she was transferred to a tertiary hospital due to the severity of the complications. She developed progressive respiratory insufficiency and a CMV pneumonitis was diagnosed for which ganciclovir was started until serum CMV DNA titers remained undetectable. Subsequently, a hemophagocytic lymphohistiocytosis (HLH 2004 criteria: 6/8 +), secondary to the CMV infection, was diagnosed. Treatment consisted of etoposide, dexamethasone, and cyclosporin. Moreover, she was diagnosed with a probable pulmonary aspergillosis which was consecutively treated with voriconazole, caspofungine, liposomal amphotericin B (all stopped due to hepatotoxicity) and posaconazole. After three months of hospitalization the patient was discharged. Genetic testing confirmed thiopurine S-methyltransferase (TPMT)-deficiency (heterozygosity for the c.460G>A and c.719A>G *TPMT* gene polymorphism). The patient received no further maintenance treatment for UC.

In November 2017, still under treatment with posaconazole, a PET-CT showed diffuse PET-positive lesions in the liver, lymph nodes, bones, muscles, and one lesion intracerebral. There was splenomegaly with extensive PET-positive lesions in the spleen. Despite these diffuse lesions the patient had no symptoms. Even though the patient had no maintenance treatment for UC, there were no symptoms matching an active UC nor signs of active disease on the PET-CT. Several investigations (BAL, bone marrow examination, lumbar puncture, and liver biopsy) revealed no diagnosis. Finally, a lung biopsy showed granulomatous inflammation with fungal hyphae. The panfungal PCR was positive for *Candida albicans*. Routine blood analysis during this episode showed persistent systemic inflammation (Figure 1a-b). Anti-Candida antibodies and Candida antigen were negative, while β-D-glucan test was positive (100 pg/ml). In January 2019 the control ultrasound confirmed per-

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Submission date: 24/10/2022
Acceptance date: 02/03/2023

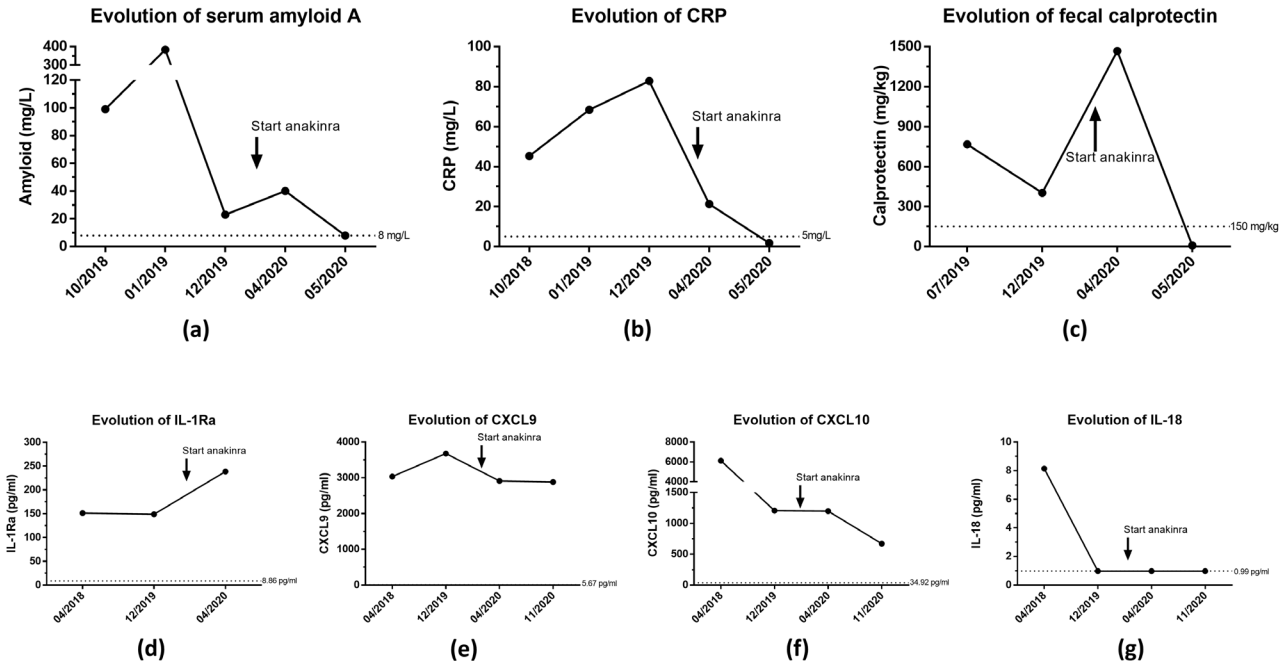
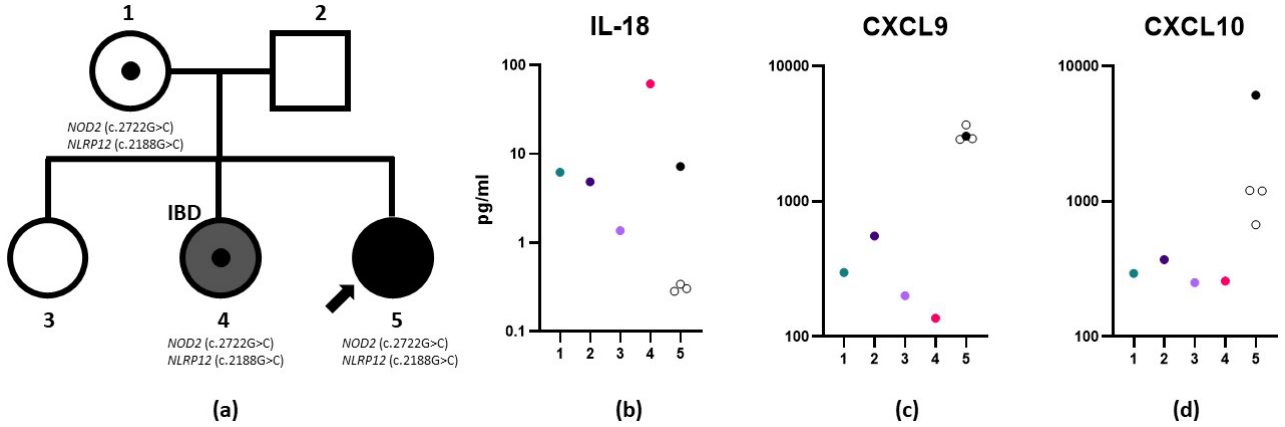


Figure 1. — Shortly after the start of anakinra in 03/2020 a good biochemical evolution was seen. The serum amyloid A (A), the CRP (B) and the fecal calprotectin (C) all normalized within two months after start of anakinra. An increase in serum IL-1Ra (D), CXCL9 (E), CXCL10 (F) and IL-18 (G) was seen before anakinra initiation, suggesting inflammasome activation and downstream interferon signaling. A clear decrease of CXCL10 was seen under treatment. After the patient was initiated on anakinra, IL-1Ra was above the upper limit of detection. The dashed lines indicate the reference value for each analysis.



Supplementary Figure 1. — Family tree of the index patient (indicated with arrow); her mother was a healthy carrier, her sister was a carrier of both mutations and also had IBD (which was well-controlled with salicylates), both the father and other sister were unaffected (A). Cytokine analyses in the index patient and her relatives. (B): IL-18 levels were increased both in the index patient as well as in the sister with IBD. The levels of CXCL9 (C) and CXCL10 (D) were clearly elevated in the patient compared to her relatives. ●: cytokine levels in index patient before treatment; ○: cytokine levels in index patient after treatment.

sistence of the multiple infiltrating lesions in the spleen. A splenectomy was performed and the histopathological evaluation showed multiple necrotizing granulomatous regions with Candida colonies. *Candida albicans* was again confirmed by panfungal PCR. She was diagnosed with a proven chronic disseminated candidiasis (CDC).

In May 2019 the patient developed an UC flare-up: she had diarrhea (20x/day), rectal blood loss, and abdominal pain. The endoscopy showed extensive UC Mayo 1-2, with backwash ileitis (Figure 2a). The biopsies reveal few granulomas, suggestive for cryptolytic granulomas related to UC (Figure 2b). The Periodic Acid-Schiff staining showed no signs of fungal organisms in the colon. Treatment included mesalamine in combination with beclomethasone. A clinical response was seen with persisting Mayo 1-2 colitis on endoscopy in December 2019. She remained steroid-dependent and a step-up of treatment was considered.

The functional tests at baseline showed an increase in several cytokines (Figure 1d-g), which suggests inflammasome activation. In the meantime whole exome sequencing revealed heterozygous variants in NOD2

Table 1. — **Different genetic variants identified**

Gene	Mutations	Pathogenicity score (16)
NOD2	c.2722G>C p.(Gly908Arg)	Uncertain significance
NLRP12	c.2188G>C p.(Gly730Arg)	Uncertain significance

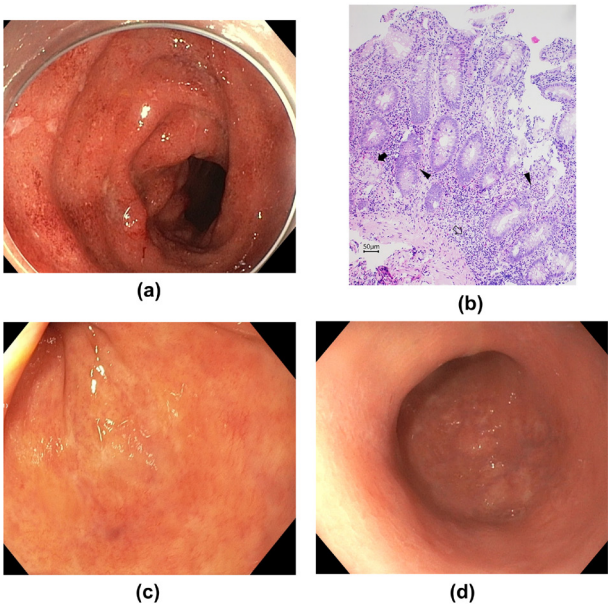


Figure 2. — Endoscopic evaluation at the different time points. (A): Ileocolonoscopy in May 2019 showed a pancolitis Mayo 1-2. (B) The biopsy showed active chronic colitis with crypt distortion, basal plasmacytosis (open arrow) and cryptitis (arrowheads) and a cryptolytic granuloma (filled arrow) (C): Five months after start of anakinra (August 2020) the ileocolonoscopy showed a clear endoscopic response (Mayo 0-1). (D): The control endoscopy in September 2021 revealed endoscopic (and histological) remission.

and NLRP12 (Table 1). Genetic and functional testing was also performed in the relatives of our patient (Supplementary figure 1).

Based on the clinical presentation, persistent inflammation, and the cytokine profile an IL-1 mediated disease was suspected. Treatment with anakinra (once daily 100 mg subcutaneous) was started in March of 2020 due to the persisting inflammation and increased risk of secondary amyloidosis, this in combination with posaconazole to prevent a possible flare-up of the invasive fungal disease. Around the start of anakinra the patient had a fecal calprotectin of 1467 mg/kg (Figure 1c). Two months after the start of anakinra the patient was in clinical remission and there was a reduction of calprotectin to 8.7 mg/kg. The PET-CT in July 2020, showed overall a reduction in the volume of the lesions in lung, liver and lymph nodes. Endoscopic evaluation after five months of treatment showed an endoscopic response Mayo 0-1 (Figure 2c). In October of 2020 beclomethasone and mesalamine were stopped after which the patient remained in stable clinical corticosteroid free remission. The systemic inflammation was fully controlled with anakinra treatment (Figure 1a-c), which was continued, and no side effects were noted. The systemic candidiasis lesions remained stable, also after a dose reduction of anakinra to 100 mg three times a week. Posaconazole was stopped in March of 2021, six months later the PET-CT did reveal an increase in the volume and metabolic activity of the lesions in lung, liver and lymph nodes. The last control colonoscopy in September 2021 revealed clear endoscopic and histological remission (Figure 2d). In January 2022 the patient was readmitted to the hospital with hepatic candida abscesses, for which anakinra was temporarily stopped and treatment with echinocandins followed by posaconazole was started. In October of 2022 anakinra was restarted. Throughout this period, her UC remained in stable remission.

Discussion

The current case report highlights the potential serious side effects of AZA, including bone marrow depression leading to severe neutropenia in this patient, indicating the importance of TPMT-deficiency screening (4). After recovering from neutropenia the patient was diagnosed with a proven CDC, which has been recognized as an immune reconstitution inflammatory syndrome (5). During the CDC, the activation of the immune signaling is thought to have subsequently triggered an inflammatory syndrome (5). Despite fluconazole treatment and splenectomy, the CDC remained a persisting chronic infection in this case, however, the patient was asymptomatic. Genetic and functional analyses were performed and mutations in *NOD2* and *NLRP12* were found in the patient. Monoallelic mutations in *NOD2* have been associated with IBD, although mainly Crohn's disease, and Blau syndrome (6). Even though *NOD2* mutations are not associated with an increased risk of UC onset, they have been associated with a more aggressive course of the colitis (7). Mutations in *NLRP12* have been associated with auto-inflammatory diseases such as atopic dermatitis and *Nlrp12*$^{-/-}$ mice have shown increased susceptibility to chemically induced colitis (8,9). These variants might have been predisposing factors in our patient. Based on the cytokine analyses an IL-1-mediated disease was suspected, which can explain both the refractory UC relapse and the chronic inflammation following the systemic candidiasis. Imbalance between IL-1 and the regulatory IL-1Ra has been implied in numerous inflammatory syndromes, including IBD and an association between UC and the *IL-1RN* gene has been identified (10,11). However, the effect of IL-1 blockade on IBD is still ambiguous. It is thought IL-1 plays an important role in colonic inflammation by the local activation of neutrophils and downstream inflammatory mediators and IL-1 has been identified as a therapeutic target in UC (12). This his led to the initiation of the IASO trial which studied the safety and efficacy of IL-1 blockade in acute severe UC (12). In our case clinical, biochemical and endoscopic remission was reached shortly after initiation of anakinra treatment.

On the other hand, several case reports have described de novo IBD development or flare-up of existing IBD after anti-IL-1 treatment (13-15).

Additionally, the IASO trial was recently discontinued for futility as anakinra did not reduce the need for rescue therapy or colectomy (16). While more research is necessary into the role of IL-1 in IBD pathogenesis and the effect of IL-1 inhibitor treatment on IBD disease course, the clinical and biochemical evolution of our case demonstrates a potential beneficial effect of IL-1 blockade in UC (17).

Conflicts of interest

The authors have no conflicts of interest to report.

Funding

This research received no external funding

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the GHENT UNIVERSTIY HOSPITAL (BC-08226 date: 11.AUG.2020).

Informed Consent Statement

Informed consent was obtained from the subject involved in the study.

Acknowledgements

The authors would like to thank Lore Pottie and Marieke De Bruyne from the Center for Medical Genetics of the Ghent University Hospital and Prof. Dr. Frank van de Veerdonk from the Department of Internal Medicine of the Radboud UMC for their contribution.

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