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TOTAL COLECTOMY FOR RELAPSING ULCERATIVE COLITIS: A CASE REPORT

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ABSTRACT

Ulcerative colitis, UC, and Crohn's disease (CD) are the main forms of inflammatory bowel disease (IBD). Morphologically, UC differs from CD by the continuity and uniformity of the inflammation that affects the diseased mucosa, with no interspersed parts of healthy tissue, resulting from ulcerated lesions and superficial erosions, in addition to mainly affecting the final portions of the large intestine. Furthermore, this is considered a progressive disease due to the high probability of intestinal dysmotility, anorectal dysfunction, the possibility of colectomy, and colorectal cancer. The treatment of UC is based on step-up or top-down therapy, with the use of corticosteroid induction and maintenance of immunobiological. However, patients refractory to treatment still require surgery, either due to therapeutic failure or neoplastic development. A male patient, 36 years old, with a history of UC since 2010, was initially treated as CD with aminosalicylates, but with loss of response to treatment after months of therapy. Therefore, immunosuppressants were introduced, which triggered two drug-induced pancreatitis. Subsequently, the use of corticosteroids and immunobiologicals was started, with improvement of symptoms, but with loss of response to chronic treatment and development of corticosteroid dependence. During the years of follow-up with the proctologist, all annual colonoscopies presented diagnostic impressions of UC in mild to moderate activity, without remission. In 2021, the lesions were staged according to the Mayo clinical classification (score 2), the Montreal classification (E3 and S2), and the Truelove-Witts severity index (severe). Furthermore, the patient began to present extraintestinal manifestations such as dermatological lesions, further affecting his quality of life. After 13 years of progressive symptom progression and without a good response to the proposed treatments, a total proctocolectomy with an ileal pouch was performed, resulting in an improvement in the patient's quality of life. It is concluded that UC is an inflammatory bowel disease with several spectrums and that severe cases negatively affect the quality of life of patients. The patient in question has a severe case that is refractory to the use of initial therapies, with periods of relapse even after optimization of the therapy. Therefore, surgical intervention of total proctocolectomy with ileal pouch was necessary, which directly impacted the patient's quality of life. Thus, it is noted that further studies are necessary to develop medications capable of acting in severe

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cases and in those refractory to traditional treatments, in addition to new analyses regarding the use of early surgical intervention.

Keywords: Recurrent Ulcerative Colitis. Inflammatory Bowel Disease. Total Colectomy.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the main forms of Inflammatory Bowel Disease (IBD) which have significant consequences on patients' quality of life as relapses occur, whether clinical or endoscopic, mainly affecting young patients (SOUZA et al., 2002).

By definition, UC is a chronic inflammatory disease that mainly affects the final portions of the large intestine, namely the left colon, sigmoid colon, and rectum (HOULI; NETTO, 1984). Morphologically, UC differs from CD by the continuity and uniformity of the inflammation that affects the diseased mucosa, with no interspersed parts of healthy tissue, resulting from ulcerated lesions and superficial erosions (MISZPUTEN, 2009).

The etiology is not yet fully understood by epidemiologists, but it is believed that UC is caused by multifactorial components, such as environmental, ethnic, and genetic factors, the latter being the main factor, as it is an autoimmune disease and impacts the formation and composition of the intestinal microbiota of individuals in the early stages of life (CURY; MOSS, 2011). In addition, it is usually insidious and manifests itself with symptomatic periods and periods of remission, although these do not necessarily indicate control of the disease (MISZPUTEN, 2009).

Regarding the epidemiology of UC, it is observed that there are higher incidences in Europe and North America to the detriment of Asia and the Middle East, for example, which presented a person-year ratio up to 3 times lower when compared to these continents and reinforcing a tendency for it to be less frequent in underdeveloped countries, despite a global increase in the prevalence of inflammatory bowel diseases in the world. It is understood that this growth is related to the industrialization of countries, given the implication of the socio-environmental component in its etiology (Moodie et al., 2012).

In the clinical context, rectocolitis can be expressed in milder to very severe forms, ranging from intense diarrhea, presence of mucus and blood in the stool, tenesmus, incontinence, and urgency to defecate, and other symptoms of the gastrointestinal tract concomitantly such as nausea, vomiting, fever, hypoxia, pain and abdominal distension (TEIXEIRA; HOSNE; SOBRADO, 2015). In addition, this pathology can also be systemic with extra-intestinal manifestations and ocular, dermatological, hepatic, hematological, and nephropathic involvement (HOULI; NETTO, 1984) and cause acute complications, which include mild bleeding and massive hemorrhage if there is perforation of the loops; fulminant colitis and toxic megacolon in patients with a bowel movement frequency greater than 10

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times per day, local symptoms and systemic toxicity and, whether or not due to this complication, colon perforation, which may progress to acute and chronic peritonitis with colorectal cancer (PEPPERCORN; KANE, 2020). In this scenario, based on the clinical manifestations, the Montreal Classification proposed to delineate the forms of the disease in two ways, namely by the extent of inflammation of the intestinal mucosa at the histological, radiographic, or endoscope level and by severity criteria. Thus, the classification by extent includes ulcerative proctitis that is limited to the rectum, distal ulcerative colitis that affects the distal colorectal region and the left flexure, and pancolitis that affects the entire colon. Likewise, UC is also classified by severity criteria that consist of 4 categories: UC in clinical remission, that is, without symptoms; mild UC, which is the classic form of the disease; moderate UC, determined by a frequency of 4 bowel movements per day and minimal signs of systemic toxicity; and, finally, severe UC, defined by at least 6 bowel movements per day associated with fever, tachycardia, anemia, and elevated ESR. Thus, delimiting the manifestations in this way has been useful in defining the treatment and prognosis of patients, even if these classifications are limited to predicting the evolution of inflammation in the short term (SILVERBERG et al., 2005).

About treatment, there are two approaches: “step-up” therapy, which consists of gradually starting therapy with corticosteroids and salicylates and subsequently introducing immunomodulators such as azathioprine and methotrexate. Finally, biological agents should be introduced when the disease is refractory, such as the anti-TNGF Infliximab associated with cyclosporine, which has proven useful in postponing early colectomy in patients with recurrences, despite their side effects, and has reduced severe flare-ups of rectocolitis over the last 30 years. In addition, there is the therapy known as “top-down”, which consists of allocating certain types of drugs, previously intended for patients refractory to treatment, as the first line for this type of manifestation of UC. It is worth mentioning It is also known that intravenous corticosteroids are the induction treatment for severe UC, but are not indicated for maintenance treatment of IBD (BAUDET et al., 2008; TEIXEIRA et al., 2008).

In short, it is known that early treatment with immunosuppressants and biological agents reduces colectomy rates in UC patients (BURISCH; MUNKHOLM, 2013). In this sense, given the importance of the topic given the impact of clinical manifestations on the quality of life of patients, this study will elucidate a case of ulcerative colitis unresponsive to standard therapy, which culminated in a total proctocolectomy with ileal pouch. Through

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this, the aim is to reinforce the need for new studies and selective management of patients to define the best time for colectomy combined with the responsiveness or otherwise of conventional therapy (BAUDET et al., 2008).

CASE REPORT

Patient V.S.C., male, 36 years old, sought medical care in September 2022 reporting a history of ulcerative colitis (UC) for 10 years. He reports that in 2010 he had colic, diarrhea, weight loss, hematochezia, and stools with mucus, and was initially treated for Crohn's Disease (CD). He reports that he had been using sulfasalazine for around 2 years, but had lost response to treatment around the eighth month of the disease. A colonoscopy was performed in 2010 with a diagnostic impression of mild Ulcerative Colitis on the left. In 2011, a complete colonoscopy was repeated, with a diagnosis of active ulcerative pancolitis.

In 2012, it was decided to start Mesalazine, but the patient experienced side effects and stopped taking it under medical advice. The colonoscopy performed indicated moderate pancolitis. Between 2013 and 2014, he began treatment with Azathioprine for approximately 2 years, when he stopped after presenting drug-induced pancreatitis with a hospitalization lasting 15 days. Again, a colonoscopy was performed, which indicated moderately active diffuse pancolitis and ileitis.

In 2016, he presented a new case of pancreatitis, and pulse therapy was started, with corticosteroid dependence (prednisone for 4 months). After this condition, it was decided to start the biological Infliximab, with a good response during 1 year of treatment. In 2017, the colonoscopy exam was repeated, with a diagnostic hypothesis of chronic ulcerative pancolitis with moderate to severe activity. In 2018, he began to lose response to therapy again, claiming to feel cramps, with occasional bleeding around July 2018, and was started on a new therapy with Adalimumab until July 2019. Colonoscopies performed in both years gave a diagnostic impression of UC. At that time, he reported a significant weight loss of 10 kg in 6 months, associated with diarrhea, hematochezia, and bowel habits with bowel movements around 10 to 15 times per day, with a great loss of quality of life. It was decided to undergo new pulse therapy and requested application of Vedolizumab.

In September 2019, he was using 1 ampoule every 8 weeks, but due to the worsening of the colonoscopic pattern associated with corticosteroid dependence, the dose

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was optimized to 1 ampoule every 4 weeks. In November, after the medication was administered (induction dose), the patient showed an improvement in her quality of life, a decrease in the number of bowel movements, improvement in diarrhea and asthenia, and weight gain. In addition, she reported joint pain, but no dermatological lesions.

In 2021, the patient, who was dependent on corticosteroids, started a new cycle due to the recent crisis (laboratory tests indicating caprotectin protein above 800), with an improvement in the bowel movement pattern to 4 to 5 times a day. However, when the patient was weaned from the medication, the bowel habit returned to 20 times a day with diarrhea, but without hematochezia and with improvement in abdominal pain. The patient had dermatological lesions under follow-up with a dermatologist. At that time, the lesions were staged according to the Mayo, Montreal and Truelove-Witts classifications:

- Mayo clinical classification: score 2.
- Monteral classification E3 (extensive pancolitis), S2 (moderate colitis).
-Truelove-Witts severity index: severe.

Therefore, the patient was corticosteroid dependent, with loss of response to medication (Vedolizumab), no quality of life, and bowel habits of around 10-15 times per day. In addition, when corticosteroid weaning was attempted, the patient presented worsening endoscopic, clinical, and laboratory patterns, with calprotectin above 800. Therefore, a change of medication was requested to a biological that inhibits the bioactivity of human IL-12 and IL-23, preventing these cytokines from binding to their protein receptor IL-2 beta1 expressed on the surface of immune system cells Ustekinumab. The application of Ustekinumab 90 mg, 1 vial every 8 weeks was requested.

The patient returned for a consultation in September 2022, maintaining previously recommended therapy, with instructions to start budesonide for 8 weeks. If there was no clinical/endoscopic/laboratory improvement, surgery would be indicated.

The patient underwent a total proctocolectomy with an ileal pouch (Figure 2).

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Figure 1. Images from the colonoscopy performed on 05/13/2022.

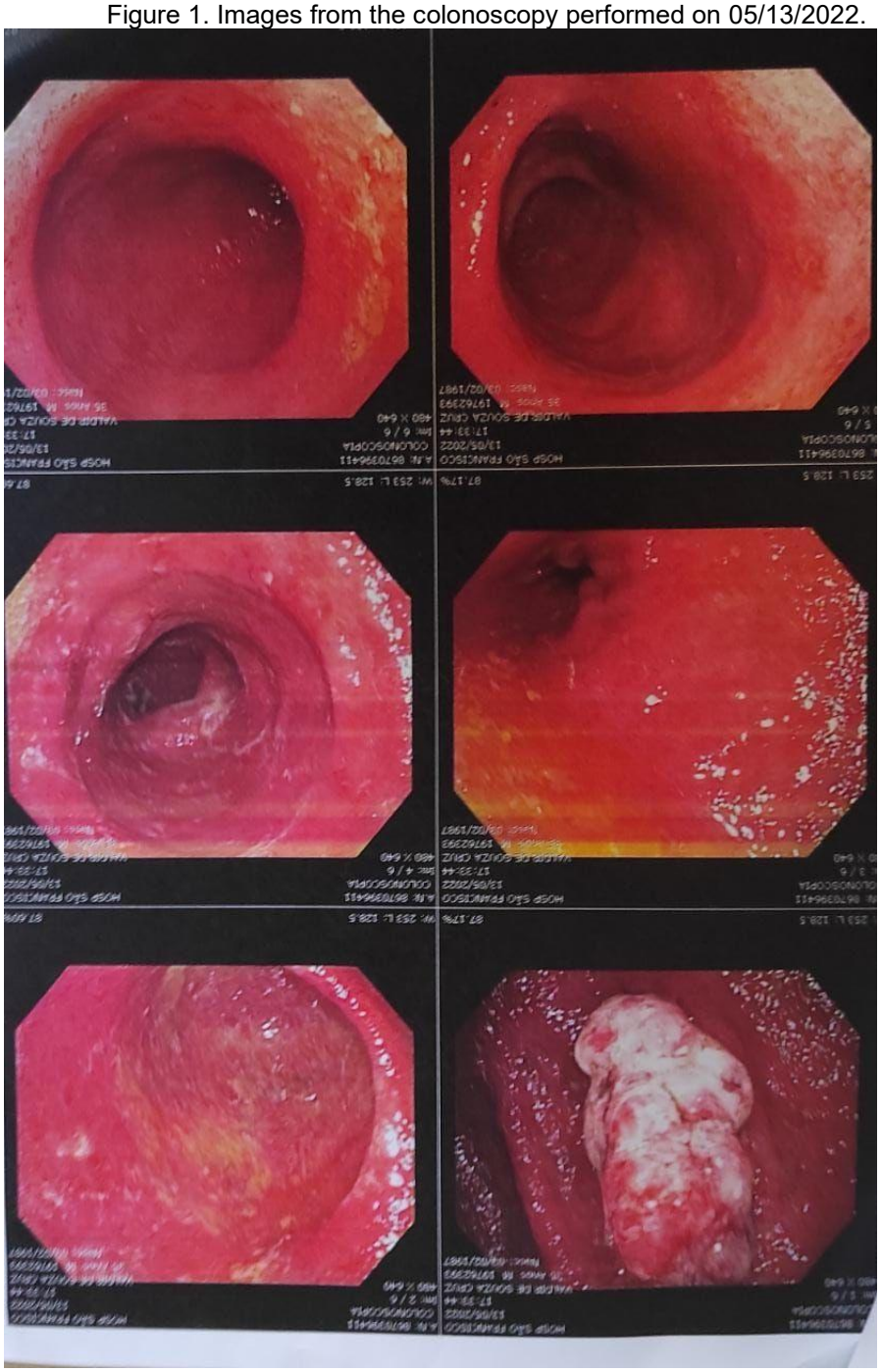

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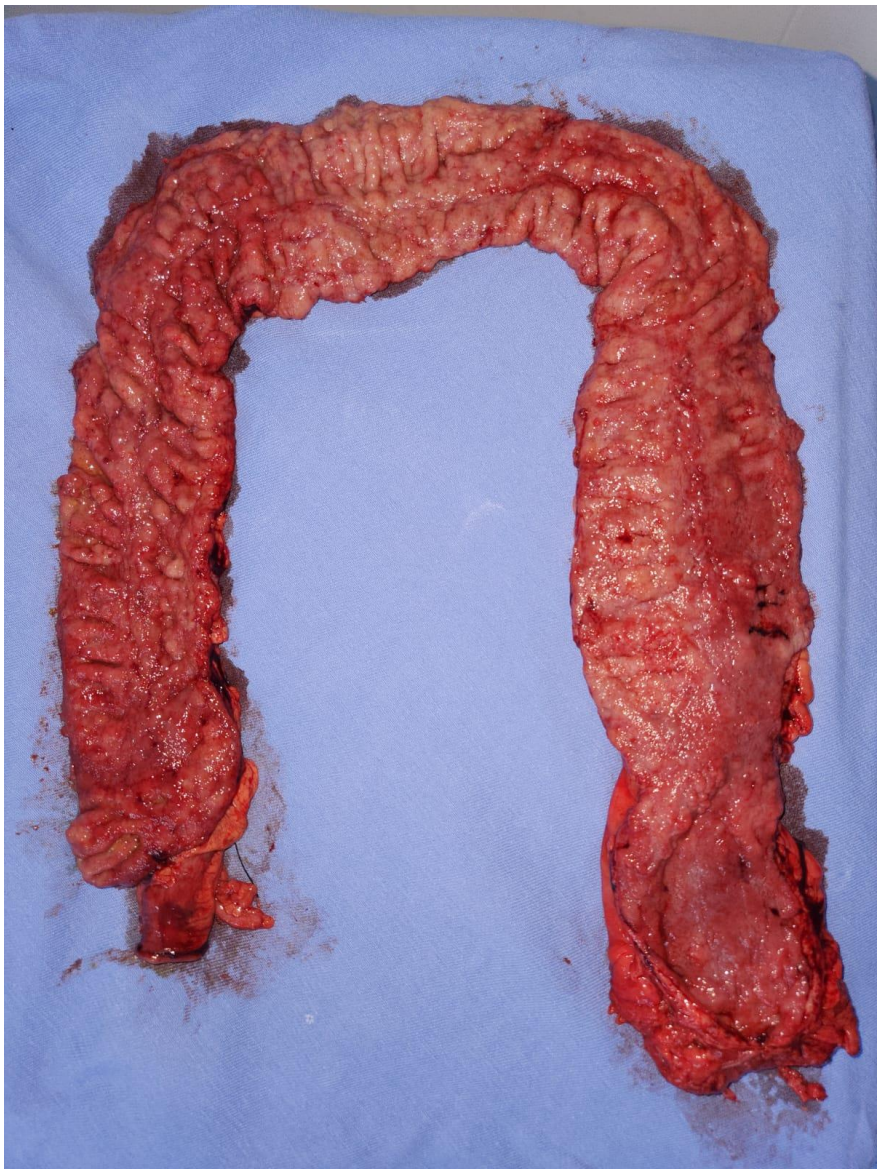
Figure 2. Product of total proctocolectomy for active and diffuse idiopathic ulcerative colitis of moderate and severe intensity.



DISCUSSION

UC begins with an epithelial dysfunction of the intestinal structure, caused by the breakdown of the intestinal barrier resulting from changes in the microbiota and the reduction of the mucus layer, which is responsible for protection against mechanical and chemical stress. This promotes the activation of defense cells, such as macrophages and neutrophils, in addition to inflammatory mediators, which promotes a cascade of inflammation and, due to the ineffectiveness of repair and constant inflammatory stimulus, a chronic rhythm is created, leading to the characterization of the disease (KOBAYASHI et al., 2020; VAN KLINKEN et al., 1999).

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The diagnosis is clinical and aided by complementary exams, such as colonoscopy, endoscopy, and histology. In UC, when explored macroscopically, chronic and diffuse inflammation is found continuously, involving the colon, mainly the rectum segment. In the mucosa, there are superficial ulcers with a granular appearance. In severe cases, ulcers can be found that go beyond the mucosa and perforate the muscularis mucosa, in addition to inflammatory polyps that grow in the injured mucosa. When there is chronic UC, fibrosis is seen in the mucosa and submucosa, forming benign stenoses at the site or not (LANGNER et al., 2014).

Regarding the microscopic section, in UC, the inflammatory cells are limited to the mucosa layer, distributed globally, and concentrated towards the rectum. Plasma cells are distributed at the base of the crypts and in the muscular mucosa, neutrophils enter the lamina propria or crypts, causing crypt abscesses, which have deformed architecture and density (CHUTKAN et al., 2002; LANGNER et al., 2014).

The mechanism of action of the drugs used to treat ulcerative colitis is to act on the damaged epithelium, aiming to reduce the progression of the disease, which, if neglected, can progress to intestinal stenosis, motor dysfunction, neoplasia, and the need for surgical intervention. In this sense, treatment has expanded over the years, initially focusing only on symptomatic control and now acting on the repair of the epithelial and connective lining, which has contributed to reducing the risk of complications, hospitalizations, and colorectal tumors (KOBAYASHI et al., 2020).

Treatment varies according to the degree of mucosal damage, distribution, and pattern of the disease, including previous episodes and use of medications, so it must be individualized for each patient, although they have the same purpose: to stop any bleeding that is occurring and accelerate the healing process of the ulceration until it is possible, later, to remain without the use of corticosteroids (BRASIL, 2021; GALLO et al., 2018).

From this perspective, pharmaceutical options include the use of aminosalicylates/5-ASA — orally or rectally —, corticosteroids, immunosuppressants, biological drugs, and Janus Kinase (JAK) inhibitors — recent and still under study. Aminosalicylates/5-ASA (sulfasalazine and mesalazine) are choices for mild to moderate UC and in diseases limited to the rectum. Only topical therapy shows results, but combined therapy is more effective, and this is the initial treatment when there is extensive involvement. In this sense, corticosteroids are used as an alternative, in inducing the therapeutic response, for patients who did not improve with aminosalicylates or who have moderate to severe UC, with

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prednisone being one of the drugs of choice initially (BRASIL, 2021; HARBORD et al., 2017). Furthermore, the use of corticosteroids in treatment was responsible for changing the natural history of the disease, and reducing mortality, previously described in the literature, by up to 50% of patients diagnosed with UC. However, the use of this class of drugs is related to the appearance of various side effects, among the most common of which are the development of orthopedic and metabolic diseases. Today, it is the gold standard drug therapy, while the introduction of immunosuppressants — azathioprine replaced by prednisone — and biologicals, for example, monoclonal antibodies are reserved for patients who did not obtain an effective therapeutic response, with monoclonal antibodies (infliximab) being recommended if a therapeutic failure occurs with the use of azathioprine. The method of progressively changing medications is known as “step-up”, while when biological drugs are the first prescribed, it is called “top-down”. (BRAZIL, 2021; BURRI et al., 2020; FRÓES, 2012; HARBORD et al., 2017; KOBAYASHI et al., 2020).

The earlier the diagnosis is made, the better the immunological responses to the proposed drug treatment, directly impacting quality of life. However, approximately 10 to 30% of individuals will require hospitalization to discuss surgical approach, the reason being severe acute colitis — whether due to a syndrome of acute perforative or hemorrhagic abdomen —, refractory ulcerative colitis, even under treatment nt with monoclonal antibodies, as was the case of the patient reported in the case, and when there is associated neoplasia (GALLO et al., 2018; UNGARO et al., 2019).

Given this, there are commonly used surgical techniques in these three situations. Reconstructive proctocolectomy with ileal-anal pouch anastomosis is one of the feasible procedures and is chosen in patients who have a functional sphincter and do not present serious risk factors for complications, since this surgical technique avoids the need for permanent colostomy. It is generally the surgery of choice in patients with refractory UC, as in the patient-reported, familial adenomatous polyposis or malignant tumors of the colon (GALLO et al., 2018; REMZI et al., 2017).

Subtotal colectomy with Brook ileostomy is another possible surgical technique in patients with refractory ulcerative colitis, mainly in those with malignant lesions in the rectum. However, two important negative points are the permanent stoma for the patient and the possibility of fistulas (GALLO et al., 2018).

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Furthermore, total colectomy with ileorectal anastomosis is generally a less used technique, but it can be performed as an alternative to reconstructive proctocolectomy. It is indicated mainly for patients with metastatic colorectal cancer (GALLO et al., 2018).

In addition, the medical and multidisciplinary team must guide possible surgical complications, such as inflammation of the small bowel loop, infertility, fecal incontinence, increased frequency of bowel movements, and sexual dysfunction (BAKER et al., 2020; KUCHARZIK et al., 2020).

Finally, to improve the prognosis of the disease, new research continues to invest in studies on the role of sphingosine-1-phosphate receptors, JAK inhibitors, anti-leukocyte integrins, new monoclonal antibodies, and even fecal microbiota transplantation. However, more experiments are still needed to consolidate the importance of these biomarkers and their effectiveness in the pathophysiology of the disease individualized for each person. These data are necessary to achieve early and more comprehensive treatment, reducing the demand for surgical intervention in patients (DANESE, 2020; SEGAL et al., 2021).

CONCLUSION

It is concluded that UC is an inflammatory bowel disease with several spectra and that severe cases, as well as refractory and long-standing cases, negatively affect the quality of life of patients, requiring medical monitoring and rigorous treatments. The patient in question has a severe case, with a progression of more than 10 years, and is refractory to the use of initial therapies such as aminosalicylates, corticosteroids, and immunosuppressants, maintaining periods of relapses even after the introduction of biological drugs. Due to this, it was necessary to perform a surgical total proctocolectomy + ileal pouch, directly impacting the patient's quality of life. Therefore, it is noted that new studies are needed to develop drugs capable of acting in severe cases and refractory to traditional treatments, through new research that addresses the benefits and harms of performing early surgical interventions, to improve the quality of life of patients..

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