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Heart failure as an adverse effect of infliximab for Crohn's disease: A case report and review of the literature

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Abstract

BACKGROUND

Anti-tumor necrosis factor agents were the first biologic therapy approved for the management of Crohn's disease (CD). Heart failure (HF) is a rare but potential adverse effect of these medications. The objective of this report is to describe a patient with CD who developed HF after the use of infliximab.

CASE SUMMARY

A 50-year-old woman with a history of hypertension and diabetes presented with abdominal pain, diarrhea, and weight loss. Colonoscopy and enterotomography showed ulcerations, areas of stenosis and dilation in the terminal ileum, and thickening of the intestinal wall. The patient underwent ileocelectomy and the surgical specimen confirmed the diagnosis of stenosing CD. The patient started infliximab and azathioprine treatment to prevent post-surgical recurrence. At 6 mo after initiating infliximab therapy, the patient complained of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea that gradually worsened. Echocardiography revealed biventricular dysfunction, moderate cardiac insufficiency, an ejection fraction of 36%, and moderate pericardial effusion, consistent with HF. The cardiac disease was considered an infliximab adverse effect and the drug was discontinued. The patient received treatment with diuretics for HF and showed improvement of symptoms and cardiac function. Currently, the patient is using

version to be submitted.

Informed consent statement:

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict-of-interest statement: The authors state that they have no conflicts of interest regarding this case report.

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anti-interleukin for CD and is asymptomatic.

CONCLUSION

This reported case supports the need to investigate risk factors for HF in inflammatory bowel disease patients and to consider the risk-benefit of introducing infliximab therapy in such patients presenting with HF risk factors.

Key Words: Heart failure; Infliximab; Anti-tumor necrosis factor therapy; Crohn's disease; Inflammatory bowel disease; Case report

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Core Tip: Anti-tumor necrosis factor agents were the first biologic therapy approved for the management of Crohn's disease (CD). While rare, heart failure (HF) is a potential adverse effect of these medications. In this report we describe a patient with CD who developed HF after treatment with infliximab. The clinical, diagnosis, imaging, and treatment details are all provided and discussed in this case report. This reported case supports the need to investigate risk factors for HF in inflammatory bowel disease patients and to consider the risk-benefit of introducing infliximab therapy in such patients presenting with HF risk factors.

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INTRODUCTION

Infliximab is a monoclonal antibody against tumor necrosis factor (TNF) and has revolutionized the treatment of Crohn's disease (CD)[1]. Despite its effectiveness in promoting clinical and endoscopic responses[2], the medication is not free from adverse events, such as anaphylactic reactions, increased risk of infections and neoplasms such as lymphomas, appearance of autoimmune diseases such as psoriasis and systemic lupus erythematosus, and more rarely, heart failure (HF)[3,4].

HF is a clinical syndrome resulting from structural and functional cardiac abnormalities, resulting in insufficient supply of oxygen and nutrients to tissues[5]. The prevalence of HF worldwide is 23 million people[5]. The role of TNF in the pathophysiology of HF is controversial. However, Levine *et al*[6] demonstrated increased serum levels of TNF in patients with advanced HF and Torre-Amione *et al*[7] showed that TNF levels correlate with disease severity. Furthermore, clinical studies of agents that promote TNF blockade were initially promising[8-10]. However, large-scale randomized studies were discontinued as the results showed no improvement in HF or mortality[11]. Moreover, the use of infliximab is associated with worse outcomes in some HF patients, showing that TNF blockers may exacerbate or even trigger HF[12]. The current case report describes a patient with CD who manifested HF after treatment with infliximab. In addition, the current relevant literature is reviewed.

CASE PRESENTATION

Chief complaints

A 50-year-old woman with previous resection of the small intestine due to a stenosing CD disease, receiving treatment with infliximab, presented in the Emergency Room complaining of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.

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History of present illness

In 2016, the patient presented with diarrhea with 10 liquid bowel movements/day associated with abdominal pain, nausea, vomiting, and weight loss of 25 kg over 6 mo. Physical examination revealed a 10-cm mass in the mesogastric region. Colonoscopy showed ulcerated stenosis of the ileocecal regions and the anatomopathological examination was consistent with nonspecific colitis with mild inflammatory activity. Abdominal ultrasound showed a segmental inflammatory process in the small intestine. Small bowel follow-through (Figure 1) and computed tomography enterography (Figure 2) showed irregularities in the mucosa consistent with ulcerations in the small intestine, stenosis and dilation in the terminal ileum, and thickening of the intestinal wall with hypervascularity of the mesentery and vascular dilatation (comb sign). Based on these clinical findings, a suspicion of small bowel CD was raised. The patient opted for an exploratory laparotomy in 2018, in which thickening of the terminal ileum was observed, and an ileocelectomy (70 cm) with ileus-ascending-anastomosis was performed (Figure 3). Anatomopathological (Figure 4) evaluation showed the presence of extensive longitudinal ulcerations, marked fibrosis of the submucosa, muscular hypertrophy, and subserous lymphoid accumulations, suggesting chronic inflammation and consistent with fibro-stenosing CD. Due to extensive resection of the small intestine and presence of residual lesions, combined treatment with infliximab (5 mg/kg) and azathioprine (2 mg/kg/d) was chosen. Colonoscopy performed 6 mo after initiation of the treatment showed four erosions in the ileocolonic anastomosis and one ulcer in the neo-terminal ileum (Rutgeerts score i2). Due to the endoscopic observed activity, the dose of infliximab was increased to 10 mg/kg. Infliximab and anti-infliximab antibody trough levels were not available. Thirty days after infliximab dose optimization, the patient complained of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. She reported the onset of mild symptoms with progressive worsening since the introduction of infliximab.

History of past illness

The patient presented a medical history of diabetes and arterial hypertension was treated with glibenclamide, losartan, and hydrochlorothiazide.

Personal and family history

There was no family history.

Physical examination

On physical examination, the patient presented with tachypnea (26 rpm), tachycardia (116 bpm), jugular venous distension, right hypochondrial pain, hepatomegaly (3 cm), and lower limb edema.

Imaging examinations

Chest radiography showed an increase in the cardiac area. Electrocardiogram findings included sinus rhythm, signs of left atrial overload, and alteration of diffuse repolarization with strain pattern of V4-V6. Echocardiography revealed biventricular dysfunction, moderate HF, and an ejection fraction of 36%. Coronary angiography was performed, and coronary artery disease was ruled out.

FINAL DIAGNOSIS

The final diagnosis was HF as an adverse effect of infliximab therapy.

TREATMENT

The infliximab was withdrawal and furosemide was prescribed. Significant improvement in symptoms was noted after 5 d of modified treatment. The patient started treatment for HF with enalapril, carvedilol, spironolactone, and amlodipine and remained asymptomatic. A new echocardiography examination showed an ejection fraction of 42%, moderate systolic dysfunction with diffuse hypokinesia, eccentric hypertrophy, significant increase of left atrium, restrictive diastolic dysfunction, mild insufficiency of aortic and tricuspid valves, and mild pulmonary arterial hypertension (42 mmHg).

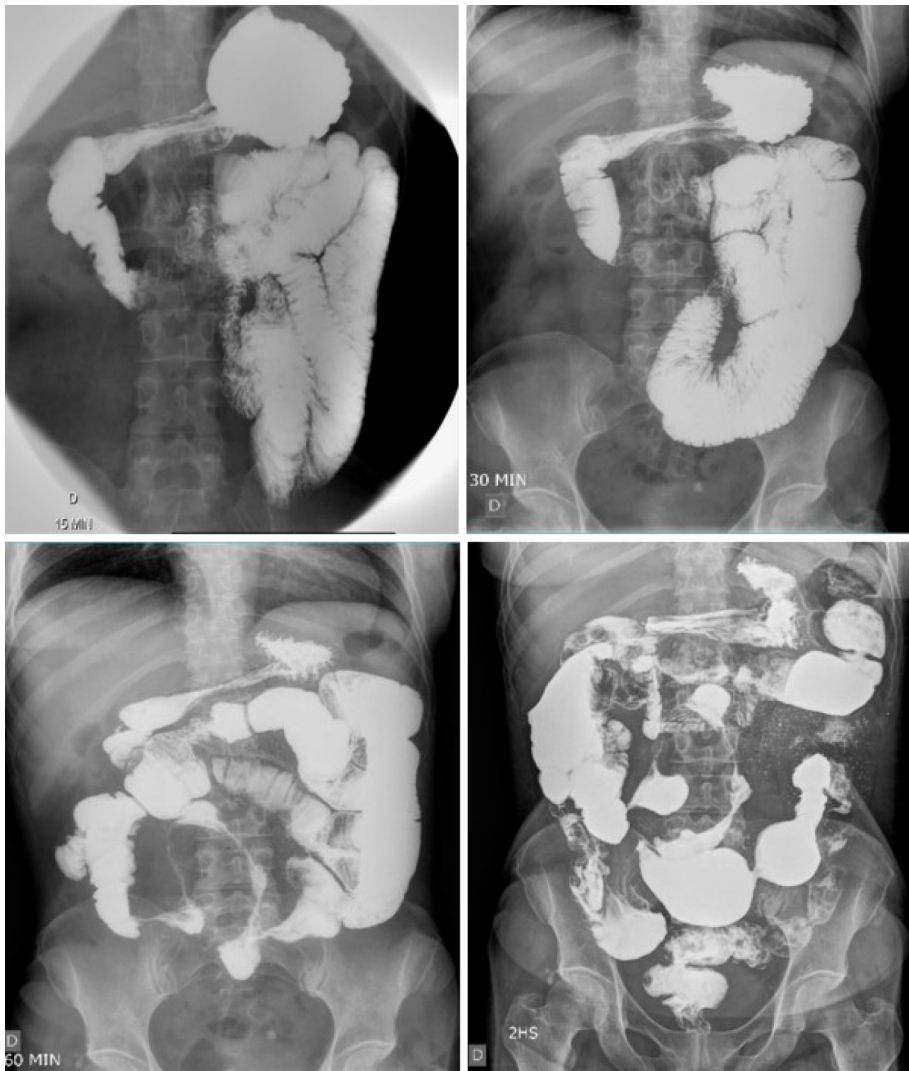


Figure 1 Small bowel follow-through showing accelerated intestinal transit. Areas of stenosis in portions of the ileum, and the ileocecal valve with filiform aspect interspersed with areas of intestinal dilation. Presence of mucous relief irregularity with "cobblestone" images due to filiform ulcerations.

OUTCOME AND FOLLOW-UP

After discontinuation of the anti-TNF therapy, the patient started exhibiting symptoms of CD activity, such as diarrhea, abdominal pain, fatigue, and weight loss. The patient then started treatment for CD with anti-IL-23 (investigational product) with significant improvement of symptoms. Currently, she has three evacuations per day with no bleeding or abdominal pain. Colonoscopy showed more than five aphthous ulcers < 5 mm each in the neo-terminal ileum without lesions in the anastomosis (Rutgeerts score i2). The patient will undergo a new colonoscopy after one year of therapy.

DISCUSSION

Treatment of CD aims for clinical and endoscopic remission and includes the use of antibiotics, steroids, immunosuppressants, and biological therapies including anti-TNF, anti-integrin, and anti-interleukin agents[13,14]. Anti-TNF agents include infliximab, adalimumab, and certolizumab[2] and are indicated in patients refractory or intolerant to corticosteroids, thiopurines, and methotrexate.

The choice of the drug should take into account the location, activity, and severity of the disease, response to previous therapies, presence of complications, medication efficacy, and development of side effects, in addition to the presence of extra-intestinal manifestations[13,15]. Individual patient characteristics, such as preference for route of administration, costs, and risk benefit of the drugs, should also be assessed[13,15]. In the current reported case, infliximab combined with azathioprine was chosen as the

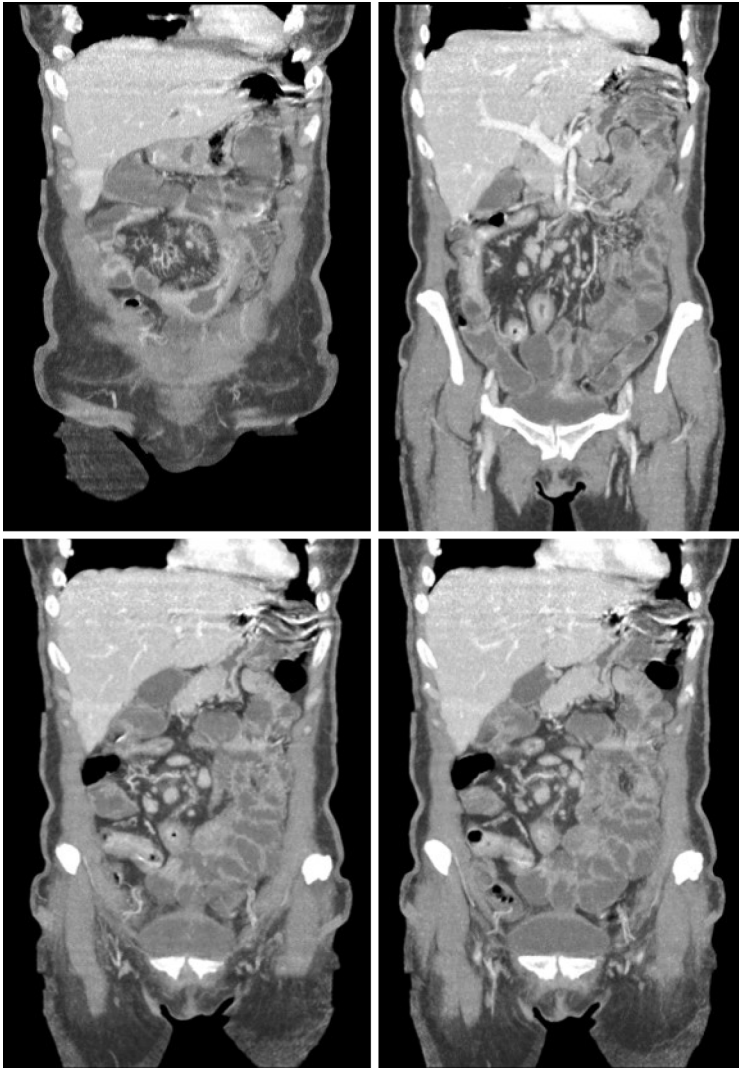


Figure 2 Computed tomography enterography. Mucosal irregularities consistent with ulcerations in the small intestine, stenosis and dilation in the terminal ileum, and thickening of the intestinal wall with hypervascularity of the mesentery and vascular dilatation (comb sign).

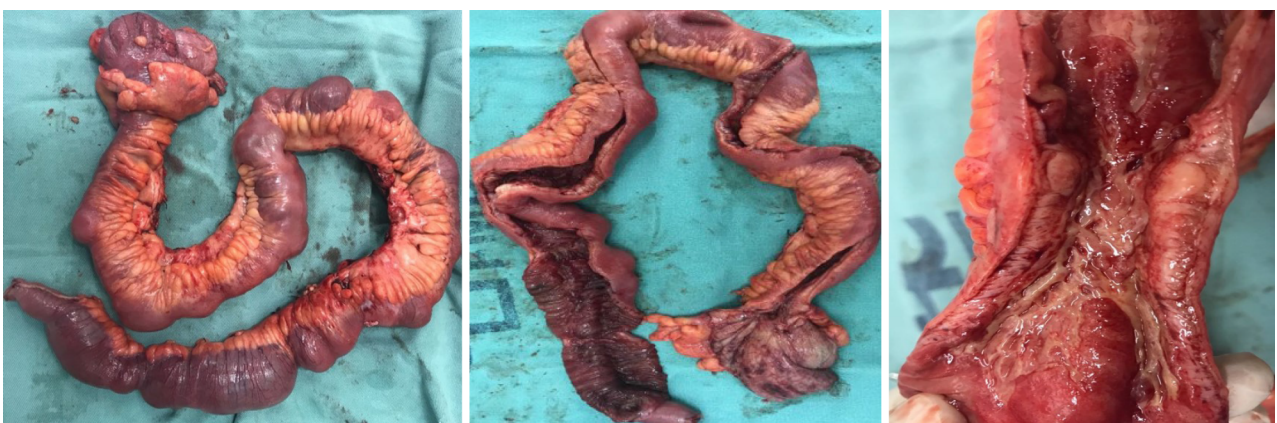


Figure 3 Surgical specimen measuring 70 cm showing severe disease with thickening of the ileum associated with ulcerations, stenosis, and dilation and mesenteric infiltration.

therapeutic option, taking into account access to medication and the patient's preference for intravenous administration. These drugs were provided by the state's high-cost drug dispensing program[16].

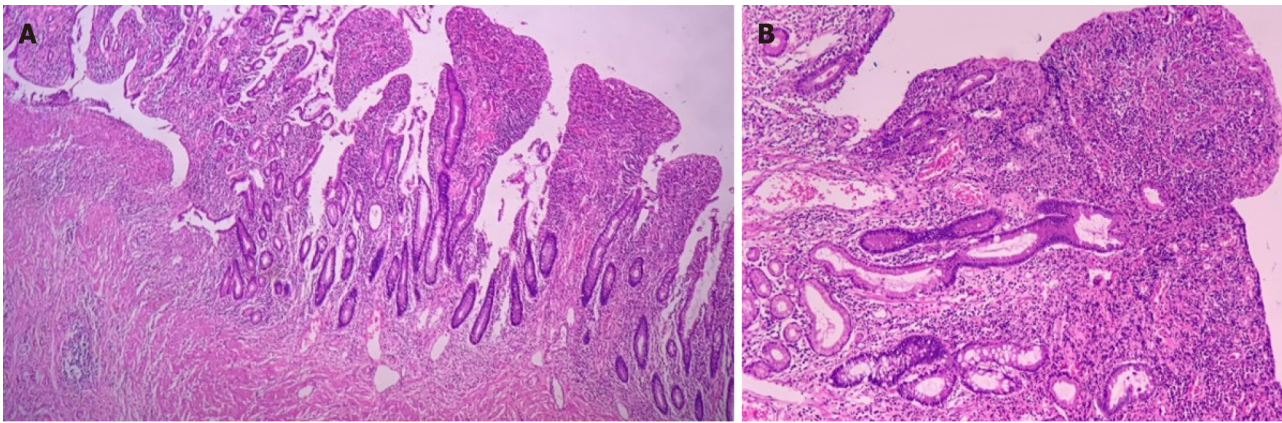


Figure 4 Histopathological diagnosis. A: Chronic transmural inflammation with ulceration, intense submucosal fibrosis, and granulation tissue formation (H&E, 40 ×); B: Chronic colitis with ulceration, extensive chronic inflammatory infiltrate with plasmacytosis, architectural distortion of crypts, and partial loss of goblet cells (H&E, 100 ×).

Anti-TNF agents have good long-term safety profiles[17]. Contraindications for their use include the presence of active infection, demyelinating disease, cancer, and HF [absolute in the New York Heart Association (NYHA) Functional Classification NYHA III-IV and relative in NYHA II][18,19]. The patient in the current report had risk factors for the development of cardiovascular disease, such as hypertension and diabetes, but had no previous diagnosis or symptoms suggesting HF at the time that infliximab was prescribed. The patient had no previous echocardiogram. The consensus regarding the treatment of inflammatory bowel disease (IBD)[14,20] does not recommend screening or assessment of cardiac function before initiating anti-TNF therapy. According to the American Heart Failure guidelines[21], there is evidence supporting the use of brain natriuretic peptides (BNP) to aid in the diagnosis or exclusion of HF as a cause of symptoms. These biomarkers are increasingly being used in population screening to detect incident HF, despite not having a formal recommendation[21] or being available for use in clinical practice.

The ATTACH (Anti-TNF Therapy Against Congestive Heart failure) trial[3] evaluated the efficacy and safety of infliximab in patients with moderate to severe HF (NYHA classes III and IV). The study found that symptoms worsened and concluded that short-term TNF- α antagonism did not demonstrate a benefit and was associated with greater occurrence of adverse events and mortality. Therefore, their use is not indicated under these conditions. Kwon *et al*[22] followed patients with rheumatoid arthritis, psoriatic arthritis, and CD that were treated with anti-TNF (etanercept or infliximab) and observed 47 patients who developed HF, of which 81% had no previous symptoms and 19% had worsening of preexisting symptoms. Among those who developed HF, 50% did not have risk factors, such as myocardial infarction, coronary disease, hypertension, or diabetes[22]. The average interval between the first anti-TNF infusion and diagnosis of HF was 3.5 mo (24 h to 24 mo)[22]. The mean age of the patients was 62 years[22], demonstrating that HF can manifest at any time during the use of the medication, even in patients without a diagnosis or previous symptoms. In our current case, we observed clinical and echocardiographic manifestations of HF 8 mo after the first infusion of infliximab, despite reports of symptoms beginning since the first infusion. However, the symptoms were mild and not considered by the patient after the first infusion. She only reported symptoms when they became disabling after the dose of the medication was increased.

Studies have sought to clarify the precise role of TNF- α in the regulation of cardiac function in patients with IBD, especially in the progression of HF[23]. The biological activity of TNF- α seems to be related to its serum concentration. At low levels, it induces local inflammation with the expression of adhesion molecules and stimulates the production of IL-1. At an increased level, systemic effects can be observed, such as fever, increases in acute phase reagents, cachexia, hypotension, and cardiovascular collapse[18]. Its intracellular effects occur by binding to two membrane receptors, TNF receptors 1 and 2 (TNFR1 and TNFR2)[24]. TNFR1 is expressed in most cells of the immune system and other systems, such as the heart, and mediates pro-inflammatory and pro-apoptotic signals[18]. In contrast, TNFR2 is found in hematopoietic and endothelial cells and is related to survival pathways[18]. There is also induction of complement-dependent and antibody-dependent cytotoxicity through the binding to

transmembrane TNF expressed in cells[25]. TNF- α contributes to the progression of HF by inducing uncoupling of the β -adrenergic receptor, increasing the reaction of oxygen species formation, promoting the synthesis of nitric oxide contributing to contractile dysfunction, and increasing IL-6 and IL-1 levels, which increase myocardial dysfunction[26]. Structural changes such as reduced left ventricular function and left ventricular dilation, in addition to severe changes such as hypertrophy, apoptosis, and cardiac fibrosis, may be observed in patients with sustained TNF- α expression in the myocardium[27].

Reverse signaling is another mechanism responsible for the cardiotoxic effects of TNF- α . Transmembrane TNF produced by cardiac cells functions as a receptor for anti-TNF agents, which serves as a signal for the production of more TNF- α in the tissue and thereby increases cardiotoxicity[28,29]. Therefore, drug-induced HF should be suspected in patients who develop HF after receiving any anti-TNF therapy and discontinuation of medication is recommended in these cases[26]. In a meta-analysis conducted by Kwon *et al*[22], ten patients under 50 years of age who developed HF after the use of anti-TNF were evaluated. Of these patients, nine discontinued the medication, three presented complete HF resolution, six presented partial improvement, and one died. In the current case, infliximab was discontinued, and diuretic therapy was initiated for HF treatment. The patient showed improvement of symptoms and echocardiographic parameters after discontinuation of the anti-TNF; however, complete recovery of cardiac function was not achieved.

The mechanism by which infliximab causes HF in patients with CD remains uncertain. As such adverse events in populations using these medications are under-reported, it is difficult to infer a causal relationship. Attention should be paid to the recent development or exacerbation of HF in patients who have started anti-TNF therapy. Should this occur, biological therapy with another mechanism of action should be considered.

We believe that the reported patient probably had previous asymptomatic cardiac structural damage, related to presented risk factors such as diabetes mellitus and arterial hypertension, characterizing stage B of AHA/ACC classification[30]. With exposure to infliximab, especially after dose optimization to 10 mg/kg, HF decompensation could be observed. Thus, we could assume that exposure to infliximab was the main causal factor related to the onset of acute HF in this patient, who probably had previous structural heart disease.

Patients with symptomatic HF are classified as having AHA/ACC C or D stage, and their symptoms are qualified according to a symptomatic score, with NYHA being the most used score of them[30]. In patients with severe symptomatic HF NYHA III and IV, the recommendation is to avoid use of infliximab[18,19]. In patients with HF and mild symptoms (NYHA I and II), who worsen after using infliximab, it is recommended to discontinue the medication to assess cardiac function and to start the adequate treatment for the cardiac condition. However, there are no recommendations for asymptomatic patients, in AHA/ACC stages A or B. Stage A of the AHA/ACC classification includes patients at increased risk of developing HF but without cardiac damage or any cardiac symptoms. Stage B comprises patients with structural or functional cardiac damage, but asymptomatic[30].

We recommend for patients in AHA/ACC stage A who are indicated to use infliximab: (1) Pre-treatment basal BNP dosage; (2) Strict control of associated comorbidities such as diabetes mellitus, arterial hypertension, and coronary artery disease; (3) Close monitoring of signs and symptoms of HF after starting treatment with infliximab; and (4) Infliximab concentration monitoring and dose correction according to the therapeutic target.

The recommendations for patients in stage B of the AHA/ACC are: (1) Pretreatment echocardiography in patients with baseline BNP levels above the reference value for outpatients; (2) If echocardiography (current or previous < 5 years) is normal or with minimal change, the recommendations are the same for patients in stage A of the AHA/ACC, as detailed above; and (3) If echocardiography (current or previous) shows signs of structural and/or functional heart disease, it is recommended to start infliximab after adequate control of comorbidities, and introduction and dose adjustment of beta-blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers. In addition, it is recommended to avoid other medications that potentially cause HF decompensation, use dose of 5 mg/kg for infliximab, other specialties medical monitoring, and strictly monitor signs and symptoms of HF. We also emphasize the need for further studies on this topic.

In the present case, other possible causal factors of HF have been ruled out. Chagasic myocarditis, an endemic disease in Latin America caused by infection by *Trypanosoma cruzi*, was ruled out by Chagas negative serology and the absence of

electrocardiographic findings of the disease such as conduction disorders, low QRS voltage, arrhythmias, and changes in the QT interval[31]. Viral myocarditis is an important differential diagnosis in the face of acute HF in an immunosuppressed patient. However, the patient did not present infectious symptoms, common in this type of infection, and there was an improvement with the suspension of anti-TNF. Endomyocardial biopsy, indicated for confirmation of viral myocarditis, was not performed due to the absence of criteria for the procedure, such as the presence of ventricular arrhythmias or atrioventricular block, hemodynamic instability, or lack of therapeutic response[32]. The acute coronary syndrome was excluded through cardiac catheterization.

CONCLUSION

The reported case supports the need to investigate risk factors for HF in IBD patients and to consider the risk-benefit of introducing anti-TNF therapy in such patients presenting HF risk factors.

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