

# Delayed Hypersensitivity Reactions to Infliximab Infusion: Case Report

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Case Report

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## Abstract

*Inflammatory Bowel Disease is a chronic, relapsing disease that occurs with acute flare ups and remissions. Among the existing therapies, biological agents have revolutionized the management and the natural progress of the disease, but without lacking side effects. Infliximab, a chimeric monoclonal antibody that suppresses the activity of TNF- $\alpha$ , plays a significant role in the therapeutic management of the disease. However, there are some concerns about the safety of Infliximab because it can trigger acute and delayed hypersensitivity reactions. Delayed hypersensitivity reactions are mostly attributed to the development of antibodies to Infliximab. In this report we present three cases of patients with Inflammatory Bowel Disease treated with Infliximab that developed a delayed hypersensitivity reaction after years of regular treatment.*

**Keywords :** Infliximab; Anti-TNF; Hypersensitivity Reactions; Delayed Infusion Reactions.

## Introduction

Inflammatory Bowel Disease (IBD) is a chronic, relapsing disease that occurs with acute flare ups and remissions [1]. Over the last two decades, biological agents have revolutionized the management and the natural progress of Crohn's disease and ulcerative colitis providing long term remission [2].

Infliximab (IFX), a chimeric monoclonal IgG1 antibody that suppresses the activity of TNF- $\alpha$ , has significantly changed the current treatment strategies [1]. However, there are some concerns about the safety of IFX and TNF inhibitors because they can trigger immunization and different types of hypersensitivity, causing acute (more frequently) and delayed reactions [2]. IFX has been reported to have a higher frequency and severity of hypersensitivity reactions than other anti-TNFs [3].

The most common adverse events include dermatological conditions, such as erythema, eczema and psoriasis and infusion reactions, both acute and delayed [4]. Acute infusion reactions tend to occur in about one third of subsequent IFX infusions [5]. The most frequent manifestations of immediate infusion reactions are pruritus, flushing, dyspnoea, chest discomfort, hypertension, myalgia, nausea, urticaria, headache, rash and dizziness [5]. The management of these adverse events includes conservative therapy with use of corticosteroids and discontinuation of IFX therapy [4].

Adverse reactions have been categorized into different types, including a complement-mediated reaction with immediate IgE or delayed IgG antibody formation [2]. Pathophysiological mechanisms that have been postulated to contribute to infliximab-induced adverse events are believed to be mediated through the immune system [4]. Pathogenesis may include the development of antibodies to IFX (ATI), either immunoglobulin IgE resulting in a hypersensitivity type reaction or IgG resulting in the formation of antibody/antigen complexes [4].

In this report we present three cases of patients with IBD treated with IFX that developed a delayed hypersensitivity reaction after years of regular treatment.

## Case presentation

We report a 76-year-old female patient with a medical history of primary sclerosing cholangitis and liver cirrhosis that developed a delayed hypersensitivity reaction during an IFX infusion. The patient was diagnosed with Crohn's disease in 2005 and was initially treated with Budesonide. After several years the patient received treatment with Azathioprine until 2012 when she received an IFX infusion for the first time, without adverse events. She was treated with IFX therapy for about five years and in 2017 she developed the first infusion reaction manifesting angioedema, resulting in IFX discontinuation. Today the patient is being treated

with Ustekinumab.

We report a 40-year-old male patient that developed a delayed hypersensitivity reaction during an IFX infusion. The patient was diagnosed with Crohn's and perianal disease in 2004 and was initially treated with Mesalazine and Azathioprine. In 2008 he received an IFX infusion for the first time, without adverse events. He was treated with IFX therapy for about nine years and in 2017 he developed the first infusion reaction manifesting shortness of breath and tachycardia, resulting in IFX discontinuation. Today the patient is being treated with Adalimumab.

We report a 35-year-old female patient with a medical history of Turner's syndrome that developed a delayed hypersensitivity reaction during an IFX infusion. The patient was diagnosed with Crohn's in 2018 and was initially treated with IFX without adverse events. She was treated with IFX therapy for about three years and in 2021 she developed the first infusion reaction manifesting shortness of breath, laryngeal edema, paroxysmal cough and itchy rash, resulting in IFX discontinuation. Today the patient is being treated with Adalimumab.

All of the three patients manifesting with IFX-associated infusion reaction were treated with immediate cessation of IFX, followed by administration of intravenous corticosteroids and antihistamines with immediate response. After 1 day hospitalization for follow-up they were discharged without further events.

### Discussion

Anti-TNF therapies and especially IFX have markedly changed the treatment course and the clinical outcomes of patients with IBD. Although, IFX use and its indications are in the spotlight, drug safety should be prioritized. Long term efficacy and adverse events of IFX are poorly investigated.

During the last decade, large retrospective investigations attempted to study adverse events in patients suffering from IBD who were treated with IFX. Several studies showed that production of IFX antibodies resulted in a decrease in the clinical response and an increase in the risk of infusion reactions.

There is still scarce data about the risk and management of infusion reactions to IFX. Working algorithms based on systematic review of the available data and more randomized-controlled trials are needed in order to investigate the pathological mechanisms and the safety of Anti-TNF therapies.

In the present study, we report three patients receiving stable maintenance IFX therapy that experienced an IFX-associated infusion reaction adverse event. To the best of our knowledge, there are not many reported cases of patients receiving IFX treatment for such long time and developing a delayed infusion reaction.

### Conclusion

Concluding, the generation of novel and safe treatments and combinations of existing therapeutic agents for patients suffering from IBD, should trigger future research. IFX is quite effective in the treatment of IBD and results in partial or complete remission in the majority of patients. However, several adverse events may occur in one-third of subjects, mostly in the initial infusions, but also delayed reactions have been reported, indicating the

physicians to be highly alert. This case highlights the importance of awareness of the atypical presentation that medication-induced side effects may have.

### Ethical considerations

All procedures performed in this case report were in accordance with all the ethical standards and an informed consent was obtained from the patients included in this case reports.

### Conflict of interests

Nothing related to this work.

### Funding information

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