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Case Report

Etanercept-Induced Crohn's Disease in Ankylosing Spondylitis: A Case Report

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Abstract

We present the case of a young male patient who developed Crohn's disease (CD) following Etanercept (ETN) treatment for ankylosing spondylitis (AS). After 1 month of abdominal pain, diarrhea, fever, and weight loss ETN treatment was stopped and treatment with infliximab (IFX) begun. The patient responded well and was discharged from the hospital. New-onset CD is an immune-mediated injury induced by ETN treatment. However, a definitive causative link between ETN and CD has not yet been established.

INTRODUCTION

Etanercept (ETN) is a dimeric fusion protein comprised of the extracellular portion of the human soluble P75 tumor necrosis factor-alpha (TNF-α) receptor and the Fc portion of human immunoglobulin G1. ETN binds TNF-α with high affinity, inhibiting TNF-α biologic activity. Because commercialization of ETN, it has been approved for the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) [1,2]. Previously published data has shown ETN to have no treatment benefit for patients with Crohn's disease (CD) [3,4].

For AS, ETN reduces disease activity, functional disability, and joint damage [2,5,6]. However, with the increasing use of ETN and other TNF-α inhibitors, the number of new-onset CD diagnoses in AS patients has increased [7-11], even though such a diagnosis is still relatively rare. It is possible that CD is an immune mediated injury induced by ETN, but no causative link has been definitively established. Herein, we report a case of CD due to ETN therapy of an AS patient.

CASE PRESENTATION

In January 2013, a 34-year-old man with a 9-year history of unregulated AS was treated with subcutaneous injections of ETN (25 mg twice a week) because of high disease activity scores. He responded well to ETN, and the disease was well-controlled. The patient had no personal or familial history of inflammatory bowel diseases (IBD). In January 2020 the patient underwent total hip replacement arthroplasty and had an excellent recovery with no complications.

In February 2021, the patient was hospitalized with 1 month of abdominal pain, diarrhea, fever, and weight loss. Blood analysis found elevated inflammatory markers; leukocytosis (9.3×10^9/L, with 76.80% neutrophilic granulocytes), C-reactive protein (CRP) 28.76 mg/L, and an erythrocyte sedimentation rate (ESR) of 39 mm/h.

He underwent a colonoscopy that revealed deep ulceration of the terminal ileum as well as scattered superficial ulcers extending from the cecum to the sigmoid colon (Figure 1). Histological analysis identified signs of severe acute and chronic colitis with non-caseating granulomatous ulcerations, as well as polymorphonuclear leukocytes, and crypt destruction (Figure 2). Infectious etiology was ruled out. Based on the clinical presentation, endoscopic and histological findings, as well as the absence of infection, a diagnosis of CD phenotype A2L3B1 (Vienna classification) was made. ETN was stopped and the patient was successfully treated with 300 mg infliximab (IFX). He went into clinical AS remission after 3 IFX treatments. Currently, AS and CD are in remission.

DISCUSSION

With extensive use of TNF-α inhibitors, adverse events related to the inhibitors have been reported, including paradoxical adverse events (PAEs). PAEs are defined as the occurrence during biological agent therapy of chronic immune-mediated disorders such as RA, JIA, AS, and PsA. These are pathological conditions that usually respond to biological agent therapy but are surprising predominant in response to TNF-α inhibitors [12,13]. PAEs incidents include new onset psoriasis or

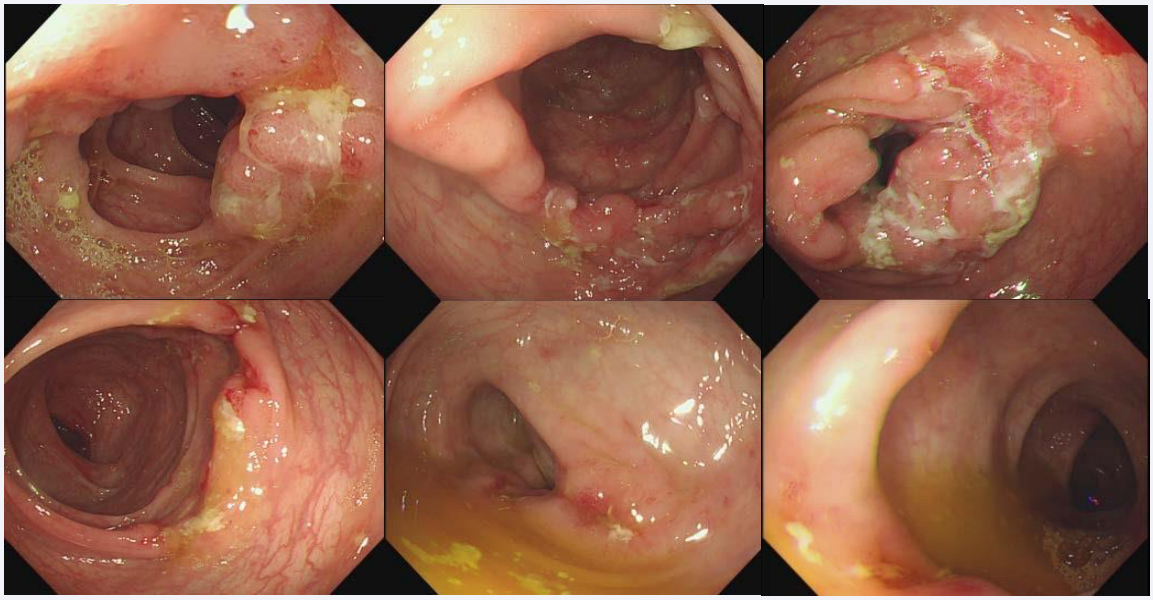

Figure 1 During colonoscopy, deep ulcerations of the terminal ileum and scattered superficial ulcers extending from the cecum to the sigmoid colon were observed.

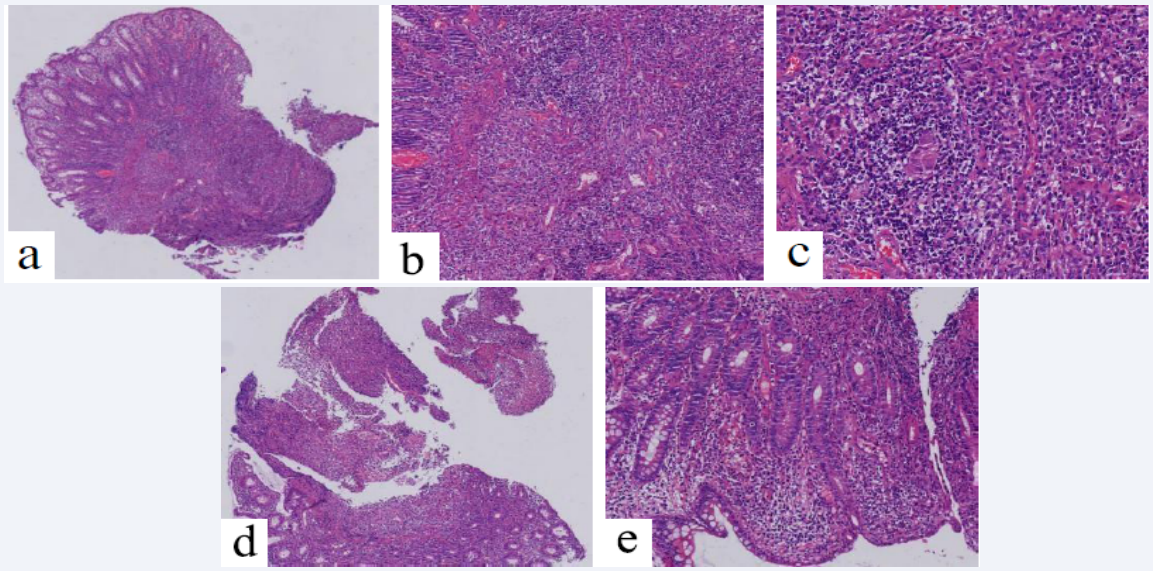

Figure 2 Histological features. (a) 40×, non-caseating granulomas. (b) 100×, non-caseating granulomas, polymorphonuclear leukocytes. (c) 200×, non-caseating granulomas, polymorphonuclear leukocytes. (d) 40×, Fissures, ulcerations, and cellulose-like necrosis. (e) 100×, Distortion of the crypt architecture.

hidradenitis suppurativa, development of aseptic granulomatous disease, and the appearance of uveitis or IBD [13-15].

Currently, five TNF-α inhibitors are available for AS clinical use; adalimumab (ADA) and golimumab (GLM) are fully human monoclonal antibodies, IFX is a chimeric human-murine monoclonal antibody, certolizumab pegol (CZP) is a humanized Fab fragment conjugated to polyethylene glycol, and ETN. Although other anti-TNF-α agents may increase the risk of IBD in patients with AS, ETN is reported to be of greatest risk [15], which may be attributed to structural and functional differences among TNF-α inhibitors [16]. Joshua Korzenik et al., conducted a population-based cohort study in Denmark of 17,018 autoimmune disease patients who received anti-TNF-α therapy. The majority of the patients received IFX, ETN, and ADA. A cohort of 63,308 individuals without exposure was also examined. Patients treated

with ETN had an increased risk for CD and ulcerative colitis (UC) while receiving treatment, with an adjusted hazard ratio of 2.0 [95% CI:1.4–2.8]and 2.0 [95% CI:1.5–2.8], respectively [10]. In contrast, another study found no significant difference between three anti-TNF agents (ETN, INF, ADA) with regard to the risk of IBD onset in AS patients [17].

Because chronic systemic, immune-mediated inflammatory disorders are complex diseases involving multiple immune factors and pathways, the occurrence of PAEs is not surprising. The mechanisms underlying these PAEs remain unknown. TNF-α inhibitors may predispose to PAEs by changing the cytokine milieu, creating a conducive immune environment that drives specific known pathological pathways or possibly new or unknown pathways [12]. ETN, and other TNF-α blockers, differ in their mechanisms of action. Indeed, ETN does not fix complement and does not activate antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), which would induce cellular apoptosis within the gastrointestinal mucosa [18]. Monoclonal antibody TNF-α blockers produce profound TNF-α inhibition, whereas ETN partially preserves the production of the cytokine. ETN is associated with IFN-α production, and this process contributes to granuloma formation, while monoclonal antibody TNF-α blockers inhibit IFN-γ release [12,19]. These differences explain why ETN has limited CD efficacy.

Herein, we report a case of new onset CD after 8 years of ETN therapy of an AS patient. During the period of ETN treatment, new onset CD likely resulted from either extra-articular manifestations (EAMs) of AS [20], or a TNF-α inhibitor-related PAE. Other studies have also demonstrated an increased risk for IBD among patients with AS who were not treated with TNF-α inhibitors. Although most studies reported the prevalence of clinically diagnosed IBD in AS patients of less than 10%, approximately 60% of those patients did exhibit intestinal inflammation based on endoscopic or histological examination of intestinal tissue [20-24]. Furthermore, it is estimated that 5%~20% of patients develop CD within 5 years [25,26]. The prevalence of AS is 5% to 10% among IBD patients who are HLA-B27-positive [27]. Temporal associations between ETN exposure and the occurrence of CD have been reported to range from 5 months to 10 years [8]. As a consequence, there is no uniform recommendation for appropriate timing of endoscopy for AS patients, although careful follow up within the first 2 years of therapy, to assess IBD development, has been suggested. In this report, we consider the occurrence of CD in this patient to be a TNF-α inhibitor-related PAE based on; the lack of personal or family history of CD, an asymptomatic bowel for 9 years prior to ETN treatment, and the absence of other medication during treatment with ETN. As such, there was a temporal relationship between new-onset CD and ETN therapy, which resolved following discontinuation of ETN and treatment with IFX.

There have been few published studies of IBD among patients with AS. Serum CRP and fecal calprotectin levels can be used to monitor IBD [28-30]. In the Netherlands, the use of the Dudley Inflammatory Bowel Symptom Questionnaire (DISQ) in patients with spondyloarthritis has been validated and can be a useful tool for disease monitoring. However, the questionnaire needs to be validated in other populations [31]. A family history of IBD, HLA-B27 positivity, and TNF-α inhibitor use are significant predictive factors for the development of IBD in AS. Patients suffering from AS who have family or personal history of IBD, or are HLA-B27 positive, should not undergo ETN treatment [32]. Endoscopy is recommended prior to initiation of TNF-α inhibitor treatment. IBD should be taken into consideration when ETN treatment of the patient results in clinical symptoms such as abdominal pain, chronic diarrhea, rectal bleeding, perianal disease, weight loss, malnutrition, and fever.

To summarize, apart from efficacy, TNF-α inhibitor-related PAEs need to be considered as a possible outcome of treatment for chronic immune-mediated disorders. Patients receiving ETN should be carefully evaluated for family or personal history of IBD. Colonoscopy should be completed before ETN treatment of AS patients and regularly thereafter in those with risk factors. In most reported cases, if the cause of CD is suspected to be ETN, ETN must be stopped immediately, switching to therapy with a monoclonal TNF-α antibody [12,33].

Author Contributions

Zhengyang Li and Miao Jiang: research concept, data analysis and interpretation, drafting of the manuscript; Haiyan Wang: participant enrolment, drafting of the manuscript. All authors read and approved the final manuscript.

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