

Cardiac Tamponade as a Presenting Manifestation of Infliximab-Induced Lupus in Patient Treated for Crohn's Disease

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ABSTRACT

Crohn's disease is characterized by inflammation of the mucosal lining of the gastrointestinal tract. Infliximab is a tumor necrosis factor- α inhibitor that has been associated with increased remission and decreased disease flares. Biological agents such as infliximab have been associated with adverse events. We present a rare case of cardiac tamponade caused by infliximab treatment for Crohn's disease in a 30-year-old female. She was treated with emergent pericardial window and drainage of pericardial fluid. Infliximab was discontinued, and serositis was treated with steroids. The patient was later successfully rechallenged with vedolizumab.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease. It has been postulated that tumor necrosis factor (TNF)- α , a proinflammatory cytokine, plays a crucial role in the mucosal inflammation.¹ Infliximab therapy is associated with an increased likelihood of achieving and maintaining remission, preventing recurrence, and improving quality of life in Crohn's disease.²

CASE REPORT

A 30-year-old woman with a history of CD diagnosed 12 years ago presented to the emergency department with pleuritic chest pain and dyspnea that had been relapsing and remitting for the past month. The patient's pain was significantly worse the day of admission with associated shortness of breath, which prompted her to come to the hospital. Patient denied history of upper respiratory tract symptoms, headache, lightheadedness, dizziness, cough, or sore throat. There was no history of diarrhea, skin rash, joint pain, fever, or weight loss.

CD was severe at the onset and endoscopy was significant for chronic gastritis, duodenitis, and pancolitis. Previously the patient was treated with azathioprine, low-dose prednisone, and 5-ASA without adequate control of her CD, and multiple Crohn's flares. She denied any extraintestinal manifestations of CD while on these therapies. Infliximab was initiated 12 months prior to admission, at a dose of 5 mg/kg every 8 weeks, with the last dose given 1 month before presentation. The patient achieved clinical remission of her CD after infliximab therapy. Colonoscopy performed 2 months prior to presentation revealed normal appearing mucosa of the ascending and transverse colon and mild erythematous mucosa of the sigmoid colon.

At presentation the patient was hemodynamically unstable, with blood pressure 90/50 mm Hg, heart rate 130 beats per minute, and respiratory rate 41 breaths per minute. Physical examination showed increased jugular venous pressure, diminished heart sounds, and positive pulsus paradox (16–18 mm Hg). Electrocardiogram showed sinus tachycardia. Bedside echocardiogram was significant for a large pericardial effusion with severe dilatation of the inferior vena cava (3.2 cm) without any respiratory collapse, compatible with severe right

ACG Case Rep J 2017;4:e1. doi:10.14309/crj.2017.1. Published online: January 4, 2017.

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Figure 1. Computed tomography of chest showing large pericardial effusion.

atrial pressure of >25 mm Hg. Chest x-ray showed moderate to severe enlargement of the cardiac silhouette. Laboratory work-up remarkable for leukocytosis (18,200/mcL), predominantly neutrophils, elevated D-dimer of 1,339 ng/mL and 1.6 international normalized ratio. Computed tomography scan of the chest was done to rule out associated pulmonary embolism due to elevated D-dimer showed severe pericardial effusion measuring 4 cm (Figure 1).

The patient was taken for emergent surgery due to hemodynamic instability. Pericardial window was performed, and a mediastinal chest tube was inserted. Intravenous methyl prednisone was given to the patient concurrently due to suspected underlying pericarditis, and the patient subsequently received a 10-day oral prednisone steroid taper. Analysis of pericardial fluid showed 30,000 white blood cells/mm³ and 213,000 red blood cells/mm³. Pericardial fluid was negative for acid-fast bacteria, and no anaerobe or other gram-negative organisms were seen. The patient remained hemodynamically stable following the pericardial window. A biopsy of the pericardium showed fibrinous pericarditis with mixed neutrophilic, eosinophilic, and lymphocytic inflammatory infiltrate (Figure 2). It was negative for granulomatous disease or micro-abscesses, and specific microorganisms or viral inclusions were not identified. There was no evidence of neoplasm. The patient had an extensive workup to rule out causes of her pericardial effusion: C3 complement levels, C4 complement levels, human immunodeficiency virus screen, Epstein-Barr virus, cytomegalovirus, herpes simplex virus adenovirus, influenza A and B, Coxsackie B virus, and Monospot tests were negative. An autoimmune workup revealed positive antinuclear antibody (ANA) results with a titer of 1:2,560, positive anti-double-stranded DNA (dsDNA) antibody (anti-dsDNA) results (93.3), and positive anti-histone antibody results. ANA test results were negative at the time that CD was diagnosed.

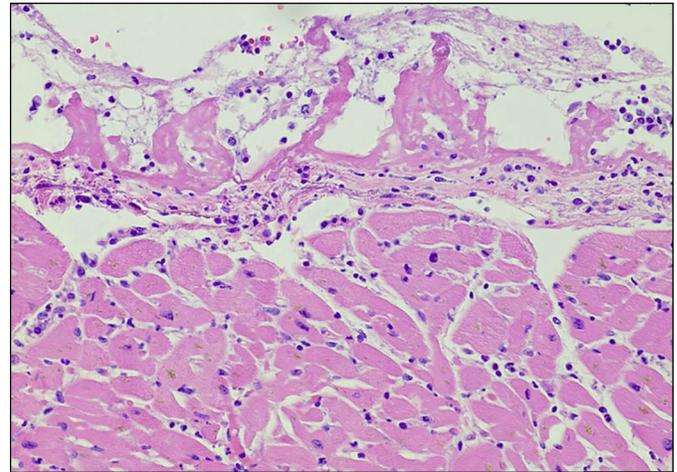


Figure 2. Histopathology of pericardial biopsy showing fibrinous pericarditis with a mixed neutrophilic, eosinophilic, and lymphocytic inflammatory infiltrate.

The patient's home medications at that time consisted only of infliximab, pantoprazole (for the last 5 years), mirtazapine, ibuprofen, and valium. Drug-induced lupus causing pericarditis and resultant pericardial tamponade secondary to infliximab was the most likely etiology for the patient's presentation. The patient was taken off the infliximab on discharge. Three months after completion of steroid therapy, the patient was rechallenged with vedolizumab (Entyvio), as patient had symptoms of Crohn's flare up. Her Crohn's disease severity index was 202 points, C-reactive protein (CRP) was 2.85 mg/L, and fecal calprotectin was 256 µg/g. Colonoscopy was significant for active inflammation at terminal ileum and descending colon. Six months later an autoimmune workup demonstrated ongoing ANA and anti-dsDNA positivity with reduced values of 1:320 and 10.3, respectively. The patient has had no recurrence of symptoms of pericarditis, pericardial effusion, or other symptoms of drug-induced lupus erythematosus (DILE) in the first year after infliximab discontinuation and vedolizumab initiation.

DISCUSSION

It has been reported that approximately 6% of the patients with CD experience serious adverse events, including infections and immunogenicity in the form of seroconversion, systemic lupus erythematosus (SLE), and drug-induced lupus following treatment with infliximab.³ The risk of ANA and anti-dsDNA seroconversion with infliximab therapy has been reported to be 41–62% and 14–85%, respectively, but only 0.6–1.6% patients develop drug-induced lupus. The prevalence of patients positive for IgG class increased to 66% at 30 weeks and 45% at 54 weeks, and of IgM class to 85% and 70%, respectively.⁴ Antinuclear antibodies usually persist for up to 1 year after the last infusion, and only a few patients become seronegative.⁵

The exact mechanisms that may cause the onset of ANA and anti-dsDNA antibodies in patients treated with anti-TNF agents are still not clear. However, it has been proposed that infliximab binds to TNF on cell surfaces and could produce apoptotic cell death, releasing nucleosomal autoantigens that then induce anti-dsDNA antibodies in a population of genetically susceptible patients. The notable downregulation of CRP that occurs after infliximab treatment may further potentiate autoimmunity by reducing the clearance of nuclear material by CRP.⁶ Another important observation is that TNF could upregulate cellular expression of the adhesion molecule CD44, which has a role in the clearance of apoptotic neutrophil by phagocytes. Impaired clearance of apoptotic cells and reduced leukocyte CD44 have been described in SLE.⁷

Although there is no recognized criteria for drug-induced lupus, criteria for the diagnosis of DILE in patients previously treated with anti-TNF therapy have been proposed.⁸ The inclusion criteria include one of the following: 1) anti-TNF- α treatment for inflammatory arthritis, 2) a temporal relationship between clinical manifestations and anti-TNF- α treatment, or 3) the presence of at least four American Congress of Rheumatology criteria of SLE.⁸ However, inflammatory bowel disease (IBD) patients often do not fulfill the American College of Rheumatology criteria for SLE. Thus, diagnosis of DILE is often based on a strong clinical suspicion. In addition, the presence of a high titer of ANA in a homogenous pattern and degree of elevation of ANA titer suggests but not confirm DILE.⁹

More than 100 cases of lupus following treatment with TNF- α inhibitors in patient with rheumatoid and psoriatic arthritis have been reported in literature. The male-to-female ratio was 0.1, and the mean age was 44.9 years with a median time to lupus onset of 11 months. Common manifestations include vasculitis, lupus-like syndrome, and interstitial lung disease.¹⁰ A recently published case series of 13 patients with infliximab-induced DILE patients showed a female-to-male ratio of 11:2.¹¹ Frequent presentations included symmetric large joint arthralgia and high titers of ANA and anti-dsDNA antibody. To date, only one case of infliximab-induced pericarditis and cardiac tamponade in an IBD patient has been reported.¹²

Management of infliximab-induced DILE involves immediate discontinuation of infliximab and treatment of serositis or arthritis with steroids. Due to life-threatening manifestations of DILE, our patient was treated with intravenous steroids followed by oral prednisone. The patient was also successfully rechallenged with vedolizumab, a humanized monoclonal antibody that selectively targets $\alpha 4\beta 7$ integrin. Vedolizumab is

approved for use in moderate to severe IBD and is effective for induction and maintenance of remission in patients, who have failed conventional and anti-TNF therapy.¹³

DISCLOSURES

Author contributions: M. Naseer drafted the manuscript. Z. Kulairi critically revised the manuscript and is the article guarantor. M. Kam reviewed the literature and edited the manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received December 25, 2015; Accepted June 23, 2016

REFERENCES

- Huoponen S, Blom M. A systematic review of the cost-effectiveness of biologics for the treatment of inflammatory bowel diseases. *PLoS One*. 2015;10(12):e0145087.
- Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: Data from the French registries. *Rheumatology (Oxford)*. 2011;50(1):222-9.
- Eriksson C, Engstrand S, Sundqvist KG, Rantapää-Dahlqvist S. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. *Ann Rheum Dis*. 2005;64(3):403-7.
- Araújo-Fernández S, Ahijón-Lana M, Isenberg DA. Drug-induced lupus: Including anti-tumour necrosis factor and interferon induced. *Lupus*. 2014;23(6):545-53.
- Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: The Mayo clinic experience in 500 patients. *Am J Gastroenterol*. 2011;106(9):1594-602.
- Ramos-Casals M, Brito-Zerón P, Muñoz S, et al. Autoimmune diseases induced by TNF-targeted therapies: Analysis of 233 cases. *Medicine (Baltimore)*. 2007;86:242-51.
- Yanai H, Shuster D, Calabrese E, et al. The incidence and predictors of lupus-like reaction in patients with IBD treated with anti-TNF therapies. *Inflamm Bowel Dis*. 2013;19(13):2778-86.
- De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: A French national survey. *Arthritis Res Ther*. 2005;7:R545-51.
- Vermeire S, Noman M, Van Assche G, et al. Autoimmunity associated with anti-tumor necrosis factor alpha treatment in crohn's disease: A prospective cohort study. *Gastroenterology*. 2003;125(1):32-9.
- Williams VL, Cohen PR. TNF alpha antagonist-induced lupus-like syndrome: Report and review of the literature with implications for treatment with alternative TNF alpha antagonists. *Int J Dermatol*. 2011;50(5):619-25.
- Subramanian S, Yajnik V, Sands BE, et al. Characterization of patients with infliximab-induced lupus erythematosus and outcomes after retreatment with a second anti-TNF agent. *Inflamm Bowel Dis*. 2011;17(1):99-104.
- Harnett DT, Chandra-Sekhar HB, Hamilton SF. Drug-induced lupus erythematosus presenting with cardiac tamponade: A case report and literature review. *Can J Cardiol*. 2014;30(2):247.e11-2.
- Shahidi N, Bressler B, Panaccione R. The role of vedolizumab in patients with moderate-to-severe Crohn's disease and ulcerative colitis. *Therap Adv Gastroenterol*. 2016;9(3):330-8.