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Unique Immediate Postoperative Management of Crohn's Disease in a Patient with Autoimmune Hepatitis-Like Drug-Induced Liver Injury from Infliximab Requiring Liver Transplantation

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Abstract Drug-induced autoimmune hepatitis (DI-AIH) is a poorly defined, underreported liver disorder. This report describes a rare case of anti-TNF DI-AIH in a patient with Crohn's disease resulting in acute liver failure requiring orthotopic liver transplantation in which a novel technique of leveraging a delayed abdominal fascial closure to perform ileocolonic anastomotic revision was used.

Keywords: *Crohn's disease, drug-induced liver injury (DILI), inflammatory bowel disease (IBD), infliximab, orthotopic liver transplantation*

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1. Introduction

Drug-induced autoimmune hepatitis (DI-AIH) is a poorly defined, underreported liver disorder. It comprises acute and chronic liver injury accompanied by the development of autoantibodies, a hepatocellular pattern of serum enzyme elevation and liver biopsy features suggestive of idiopathic autoimmune hepatitis (AIH). Unlike AIH, it typically resolves completely once the medication is withdrawn; recovery can be slow and may require a limited course of corticosteroid therapy [1].

Cases of significant liver disease associated with infliximab (IFX) treatment have been reported in patients with rheumatoid arthritis, Crohn's disease (CD), and psoriatic arthritis [2]. This report describes a rare case of anti-TNF DI-AIH in a patient with CD resulting in acute liver failure requiring orthotopic liver transplantation (OLT) in which a novel technique of leveraging a delayed abdominal fascial closure to perform ileocolonic anastomotic revision was used.

2. Case Report

A 45-year-old female with longstanding ileocolonic CD status post four small bowel resections had previously failed adalimumab based on persistent symptoms and a nontraversable ileocolonic inflammatory anastomotic stricture on colonoscopy with limited neo-terminal ileal disease on radiographic imaging. She started IFX with minimal improvement, and five months later she was admitted to an outside hospital with 3 days of abdominal pain and hematochezia thought to be secondary to a CD flare. On admission she was noted to have markedly elevated liver chemistries (AST 1048 IU/l, ALT 1222 IU/l, bilirubin 4.9 mg/dL); three months prior to presentation after IFX induction, liver chemistries were normal (AST 17 IU/l, ALT 10 IU/l, total bilirubin 0.4 mg/dL).

Over the next week, aminotransferases remained elevated with rising bilirubin and INR without encephalopathy or renal failure; she was then transferred to our center for further management. Hepatic imaging had no mass lesion, hepatic/portal vein flow abnormalities, or biliary dilation.

Toxin assays were negative (including acetaminophen), as was an infectious workup (viral hepatitis A-E, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, varicella zoster virus). Ceruloplasmin was normal, as were smooth muscle and liver kidney microsomal type 1 antibodies (<20.0), but ANA (speckled, 1:320), dsDNA antibody (133 IU/mL), and serum IgG (1938 mg/dl) were noted to be mild to moderately elevated with normal serum IgM. She had no reported hypotension in her previous hospital course. As her bilirubin and INR continued to climb to peaks of 21 mg/dL and 3.3 mg/dL respectively, with the development of hepatic encephalopathy (confusion and lethargy), a workup for liver transplantation was under-taken. N-acetylcysteine was given empirically. Hepatic and portal venous pressures and gradient were normal on transjugular liver biopsy, which revealed marked inflammatory infiltrate and parenchymal collapse with both necroinflammatory and cholestatic patterns of injury most consistent with drug-induced liver injury (DILI); there was no advanced fibrosis (Figure 1 & Figure 2). On hospital day 15, with a biologic MELD of 31, she underwent OLT; explant histology was consistent with DI-AIH. Skin was closed but fascial closure was delayed due to large donor liver, bowel edema, and prolonged operating time.

Four days later the patient returned to the operating room for a delayed abdominal fascial closure. To avoid need for repeat surgical intervention soon after OLT, a decision was made to use her delayed fascial closure as an opportunity to perform a resection of her tight ileocolonic anastomotic stricture. Fifteen centimeters of neo-terminal ileum in addition to the anastomotic stricture was resected with primary ileocolonic anastomosis followed by abdominal fascial closure; pathology was consistent with CD.

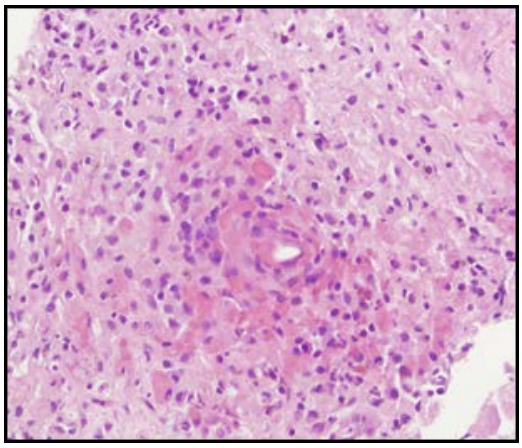

Figure 1. Portal tract inflammatory infiltration with abundant plasma cells, lymphocytes, and eosinophils with interface hepatitis

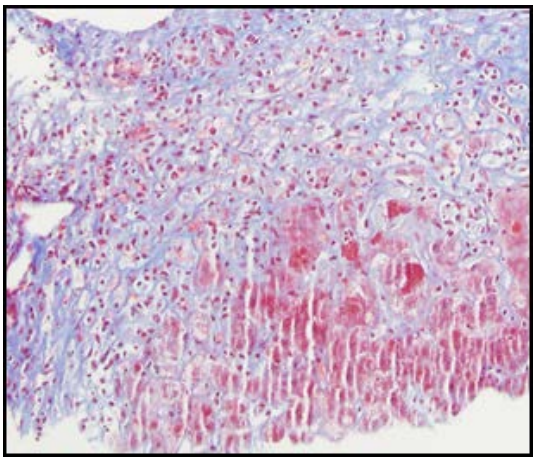

Figure 2. Portal tract inflammatory infiltration with abundant plasma cells, lymphocytes, and eosinophils with interface hepatitis

3. Discussion

IFX is a human-murine chimeric antibody directed against tumor necrosis factor alpha with well-established efficacy in the treatment of several autoimmune diseases [3]. Since the introduction of IFX in 1999, twenty-eight cases of DILI related to it have been described in the English literature [4]. As in our case, a number of these patients have been found to have positive ANA and dsDNA [4]. In a recent study by Shelton et al. looking at ALT elevation in 1753 IBD patients initiating anti-TNF therapy, 6% developed new onset ALT elevation within 5 months of initiation of anti-TNF therapy [5].

The role of corticosteroids in modifying outcome continues to be controversial. A study by Yeoman et al. characterized a cohort of patients with acute severe AIH (AS-AIH); although untreated patients had a higher MELD score at presentation (34 vs 28, p=0.01), there was no difference in sepsis or mortality observed between corticosteroid untreated or treated patients (11% vs. 26% [p=0.6] and 22% vs. 17% [p=0.99] respectively) [6]. We did not institute corticosteroid therapy in our patient given the timing of her presentation to our institution and her rapid decompensation. N-acetylcysteine (NAC) was given empirically as studies have shown that treatment with NAC may benefit patients with non-acetaminophen related acute liver failure. In 2009, Lee WM and his colleagues demonstrated that transplant-free survival was better for NAC patients (40%) than for those given placebo (27%, p=0.043) [7]. This improvement may be via improved systemic hemodynamics, tissue oxygen delivery, or other favorable effects on the injured liver [7,8].

Table 1. Cases of Fulminant Liver Failure Associated with Infliximab Treatment Resulting in Hepatic Transplantation

Patient	Age	Sex	Disease	Infusions	AST	ALT	Autoimmune Markers	HBV Markers
1 [Tobon]	39	F	RA	6	1690	2250	ANAs	No
2 [Michel]	28	F	Still	2	1350	1200	ANAs	Anti-Hbc IgG, anti-Hbe
3 [Rowe]	40	F	SLE	---	292	---	---	---
4 (present report)	45	F	CD	4	1048	1222	ANAs, Anti-dsDNA, antimitochondrial	No
5 [Rowe]	51	F	UC	---	568	140	Anti-actin	---

ALT alanine-aminotransferase (UI/I), ANA antinuclear antibody, AST aspartate-aminotransferase (UI/I), CD Crohn's Disease, F female, Hbc hepatitis B core antibody, Hbe hepatitis b e antibody, IgG immunoglobulin g, RA Rheumatoid arthritis, Still adult onset Still disease, UC Ulcerative colitis.

Only 4 other documented cases of IFX-related acute liver failure have been reported (Table 1) [2,3,9]. This is the first reported case in the literature using the delayed fascial closure of the abdominal wall after liver transplantation as an opportunity for surgical management of CD.

Liver edema can result in a tight primary abdominal wound closure resulting in various complications including wound dehiscence, partial liver necrosis, intra-abdominal hypertension, subcapsular hepatic necrosis, vascular compression or thrombosis, and abdominal compartment syndrome [10]. In order to prevent these complications, our surgical transplant team used a delayed abdominal fascial closure technique. Primary abdominal wall closure is delayed and a temporary prosthetic closure is performed instead. By using a prosthetic closure, the surgical team is able to avoid the risk of infection and minimize fluid loss while allowing time for the bowel and liver edema to improve in order to maximize the chances of a successful abdominal wall closure.

The delayed primary closure of liver transplantation has been reported in the pediatric population and has been shown to be safe with no significant long-term is-sues and was not associated with higher incidence of wound related complications [10,11]. Because the patient had a tight anastomotic stricture and focal distal ileal inflammation for which medical treatment for CD would need to be delayed, and since she would likely need surgical anastomotic revision despite optimal medical therapy, we leveraged our center's delayed fascial closure technique to perform concomitant anastomotic revision. Resection at the time of her delayed fascial closure, instead of at the time of her initial liver transplantation procedure, allowed us to optimize her coagulation parameters, temperature, and blood supply to a new anastomotic connection; these factors might have been comprised at the time of her initial liver transplantation, which required more than five hours of operating time.

Here we report the first case of IFX causing DI-AIH that led to OLT in a CD patient and the first case of using a delayed fascial closure technique to be able to safely perform other surgeries in the peri-OLT period for management of CD.

Acknowledgements and Statement of Competing Interests

The authors of this manuscript have no acknowledgments and no competing interests.

List of Abbreviations

DI-AIH Drug-induced autoimmune hepatitis, AIH autoimmune hepatitis, IFX infliximab, CD Crohn's disease, OLT Orthotopic liver transplantation, DILI Drug-induced liver injury, AS-AIH Acute severe autoimmune hepatitis, NAC N-acetylcysteine.

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