

Fulminant Herpes Simplex Hepatitis Secondary to Adalimumab in Crohn's Disease: A Case Report

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ABSTRACT: Herpes simplex virus (HSV) hepatitis is an uncommon cause of fulminant hepatic failure, seen mostly in immunocompromised patients. Conventional treatment modalities for inflammatory bowel disease (IBD), such as steroids and azathioprine, have been known to cause HSV hepatitis. However, the reported incidence of HSV hepatitis in IBD patients undergoing tumor necrosis factor (TNF)- α inhibitor therapy is very rare. In this case report, we describe a rare case of fulminant HSV hepatitis that developed in a patient with Crohn's disease after treatment with the TNF- α inhibitor, adalimumab.

KEYWORDS: herpes simplex virus, hepatitis, inflammatory bowel disease, TNF- α inhibitor, Crohn's disease, adalimumab

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Introduction

Herpes simplex virus (HSV) hepatitis is an uncommon cause of fulminant hepatic failure, accounting for approximately 1% of all cases.¹ It was first described in adults by Flewett et al in 1969.² It is most commonly associated with impaired cell-mediated immunity due to immunosuppressive medications, or conditions such as malnutrition, pregnancy, or malignancy.^{3–7} There are a few reported cases of HSV hepatitis that developed in patients with inflammatory bowel disease (IBD) who were treated with steroids, with or without azathioprine.^{3,5,7–14} The incidence of HSV hepatitis in IBD patients undergoing tumor necrosis factor (TNF)- α inhibitor therapy is, however, extremely rare. In fact, our extensive literature review revealed only 2 such published cases.^{3,13} In this report, we describe a rare case of fulminant HSV hepatitis that developed in a patient with Crohn's disease after being treated with a TNF- α inhibitor, adalimumab.

Case Description

A 20-year-old African American female, with a medical history of diabetes mellitus and hyperlipidemia, was diagnosed with Crohn's ileitis in 2015. She was initiated on dual therapy with adalimumab (40 mg subcutaneously, every 2 weeks) and 6-Mercaptopurine (6-MP; 50 mg/day orally) and demonstrated marked clinical improvement. She did not experience any significant flare-up events for nearly 2 years despite nonadherence with 6-MP after 1 year of therapy.

In September 2017, she presented to the hospital with worsening abdominal pain of 3 weeks duration and increased frequency of nonbloody loose stools for 3 days. Her vital signs on presentation were stable. Laboratory evaluation showed C-reactive protein (CRP) that was elevated to 15 mg/L. The remainder of her labs were unremarkable. Computerized tomography (CT) of the abdomen and pelvis revealed active

inflammation of the terminal ileum, with a 2.6 \times 2.3 cm mesenteric abscess. She was started on empiric broad-spectrum antibiotic coverage with intravenous metronidazole and ceftriaxone. The abscess was not amenable to image-guided percutaneous drainage due to its deep-seated location. Intravenous methylprednisolone was added after 2 days. During the 5 days of hospital stay, she expressed marked clinical improvement and was discharged on a 2-week course of tapering prednisone (initiated at 40 mg/day) plus 4 weeks of oral antibiotics (ciprofloxacin and metronidazole). Subsequent doses of adalimumab were held. She was scheduled for an outpatient follow-up in 2 weeks for possible repeat colonoscopy and to discuss surgical options once acute inflammation subsided with steroids and antibiotics.

However, the patient presented again to the emergency department 11 days after discharge with generalized cramping abdominal pain along with fever and chills. On examination, she was tachycardic (heart rate 130–140 beats/min) and febrile (39.4°C). White blood cell (WBC) count was elevated at 11.81 k/dL. Repeat CT scan of the abdomen showed a decrease in the size of the mesenteric abscess. She was switched back to intravenous antibiotics (metronidazole and ceftriaxone), and 2 days later she underwent ileocecal resection with ileocolic anastomosis. Intraoperative findings were significant for abscess formation from perforation at the base of the mesentery along the terminal ileum. The histologic sections showed chronic active colitis with transmural inflammation and abscess formation.

She tolerated the surgery well; however, on postoperative day (POD) 3, she developed dark, coffee-ground emesis. Laboratory workup at that time revealed hemoglobin 10.6 g/dL, WBC count 4.99 k/dL (further dropped to 3.24 k/dL on POD 4), and marked decrease in platelet count to 7K/ μ L (209K/ μ L at admission). The coagulation profile showed



elevated prothrombin time/international normalized ratio (89.4seconds / 12.0), activated partial thromboplastin time (> 223seconds), fibrin degradation products (>160µg/mL) and lactic dehydrogenase (7680 U/L); and low fibrinogen level (101 mg/dL). The overall picture was consistent with disseminated intravascular coagulopathy (DIC). Liver function tests showed marked elevation in transaminases (aspartate transaminase 9800 U/L, alanine transaminase 3119 U/L), alkaline phosphatase 89 U/L, and total bilirubin 1.2 mg/dL. There was no history of acetaminophen ingestion. There were no known drug allergies and no known personal or family history of autoimmune liver disease. Serologies for hepatitis B surface antigen, HIV 1/2 and rapid plasma reagin test were negative. Liver biopsy was contemplated, but could not be performed due to significant coagulopathy.

Over the ensuing 72 hours, she started to bleed from mucosal surfaces (including rectum, vagina, nasal cavity, gastrointestinal tract). Her hospital course was further complicated by acute kidney injury with a rise in creatinine to 3.93 mg/dL (baseline 0.8 mg/dL). Despite aggressive management in the intensive care unit including intubation, pressors and transfusion of fresh frozen plasma, cryoprecipitate, platelets, and packed red blood cells, the patient succumbed to her illness on POD 7.

An informed consent for full body autopsy was obtained from the next of kin. At autopsy, the liver was grossly mottled. The histological sections demonstrated confluent massive necrosis with minimal inflammation (Figure 1). Nuclei of the hepatocytes showed extensive ground-glass change. Immunohistochemistry (IHC) for HSV showed strong and diffuse positivity (Figure 2), confirming the diagnosis of fulminant HSV hepatitis. Focal necrosis with patchy HSV-IHC positivity was also observed in the spleen (Figure 3). Serological testing for HSV was not performed ante-mortem.

Discussion

The estimated seroprevalence of HSV-1 and HSV-2 in the United States is approximately 50% and 15%, respectively.¹⁵ There are, however, no reported data on HSV seroprevalence specifically in IBD patients.⁸ Conventional IBD treatment modalities such as systemic steroids and antimetabolites (such as azathioprine) are known to cause increased risk of HSV reactivation.^{3,4,8} The data surrounding the risk of HSV hepatitis associated with the use of TNF-α inhibitors are very sparse.

TNF-α inhibitors such as infliximab, adalimumab, and certolizumab pegol are disease-modifying agents that have significantly improved the quality of life in IBD patients.¹⁶ Adalimumab is an IgG1-type anti-TNF-α human monoclonal antibody that is administered subcutaneously.^{16,17} It was approved for the treatment of moderate to severe Crohn's disease by the Food and Drug Administration (FDA) in 2007.¹⁷ The most significant side effects of TNF-α inhibitors are related to development of opportunistic infections,

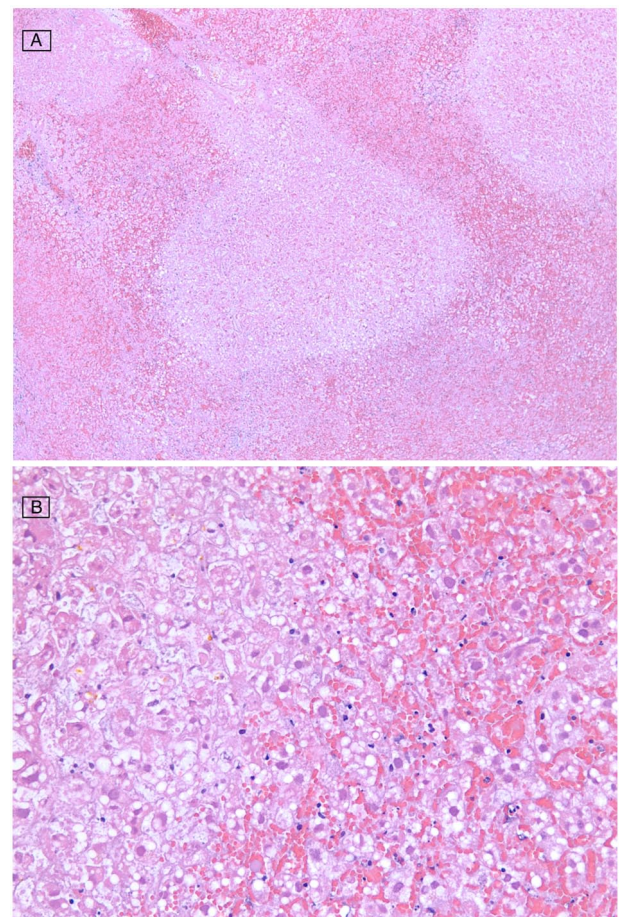


Figure 1. Postmortem histological section from liver showing confluent massive necrosis with minimal inflammation (A). At higher power, large ground-glass nuclei are seen (B).

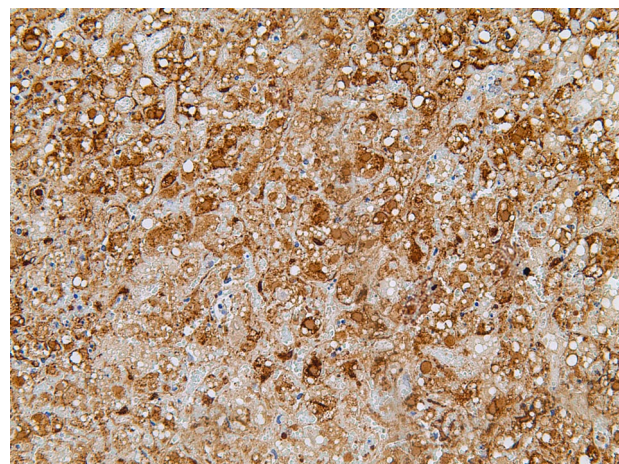


Figure 2. Strong and diffusely positive immunohistochemical staining for HSV in liver.

malignancies, injection/infusion reactions, and appearance of autoimmunity.¹⁶ Serious infections occur at an estimated rate of 6.7 events per 100 patient years in Crohn's disease patients receiving treatment with TNF-α inhibitors.¹⁷

The first case of disseminated (cutaneous) HSV-1 infection following treatment with TNF-α inhibitor (infliximab)

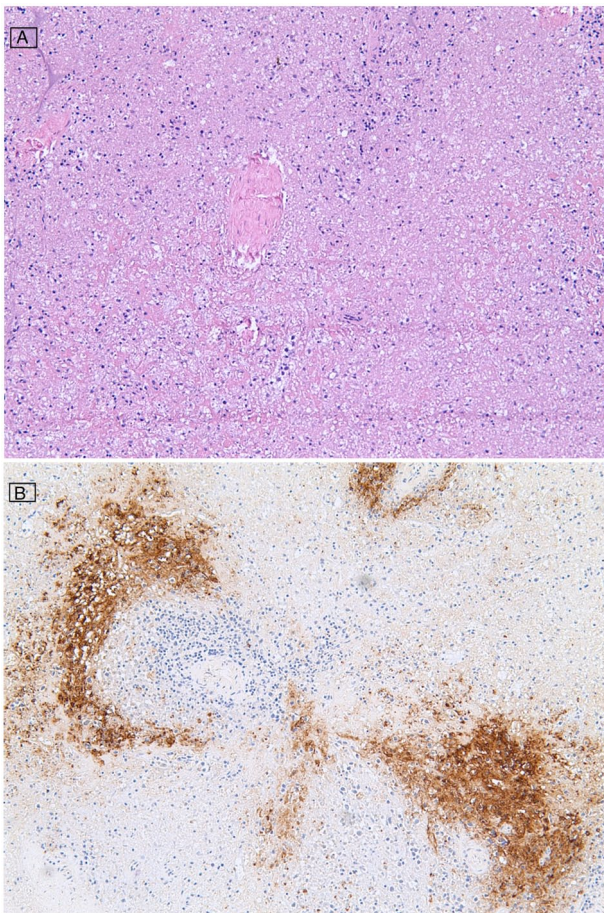


Figure 3. Focal necrosis (A), with patchy HSV-immunohistochemical positivity (B) in the spleen.

was reported in 2008.¹⁸ However, there are limited data on the effect of TNF- α inhibitors on the incidence of tissue-invasive HSV infections.⁸ To the best of our knowledge, to date, there are only two reported cases of IBD treated by TNF- α inhibitors (infliximab and adalimumab) with subsequent development of HSV hepatitis.^{3,13} We hereby describe another such extremely rare case of fulminant HSV hepatitis that developed in a patient with Crohn's disease after receiving treatment with a TNF- α inhibitor, adalimumab for 2 years. Our patient developed hepatitis around 30 days after the last dose of adalimumab. This is consistent with adalimumab's potential role in the development of HSV hepatitis, given that adalimumab has half-life ($t_{1/2}$) of 10 to 20 days.

HSV hepatitis is an uncommon cause of fulminant hepatic failure, which typically presents with nonspecific clinical features such as fever, anorexia, nausea, vomiting, and abdominal pain.^{3,4} As was seen in our patient, the typical mucocutaneous lesions of HSV may not be identified in approximately half of the cases.^{3,4,7} The laboratory workup usually shows leukopenia, thrombocytopenia, coagulopathy, and anicteric hepatitis.^{3,4,7,19} Acute renal failure is seen in more than half of the cases.⁷ DIC, as observed in our patient, is also commonly reported in HSV hepatitis.^{4,19} Encephalopathy is usually a late presentation.¹⁹

In the absence of characteristic clinical findings, the ante-mortem diagnosis of HSV hepatitis is essentially based on liver biopsy. Liver biopsy, although considered a gold standard for diagnosing HSV hepatitis,^{3,6,8,14,19,20} is often times not performed due to the presence of significant coagulopathy associated with the disease.^{6,19,20} Histological sections demonstrate extensive necrosis with adjacent congestion and minimal inflammatory infiltrates. Due to extensive necrosis or ballooning degeneration, the characteristic cytopathic changes associated with HSV infection (including viral inclusions) may not be appreciated. HSV-IHC stain can be used for confirmation in such cases.^{6,19} Viral serology is nonspecific for diagnosing HSV infections.^{6–8,19,20} HSV DNA polymerase chain reaction testing can, however, be a useful diagnostic tool.^{3,6,8,19,20} HSV hepatitis is associated with high mortality, which is often rapid, in up to 90% of the cases.^{3–7,20} Timely institution of acyclovir has been shown to reduce the progression to mortality and the need to transplant from 88% to 51%.⁷ It is therefore suggested that empiric therapy with intravenous acyclovir should be initiated while awaiting confirmation of the diagnosis, for a better chance of a favorable outcome.^{3,4,7,14}

Despite being potentially treatable,⁷ the nonspecific clinical presentation commonly precludes a timely diagnosis leading to rapid decline to fulminant liver failure.^{5,7,20} As in our patient, HSV hepatitis is diagnosed on autopsy in more than 50% of the cases.⁷ A worse prognosis has been reported in immunocompromised older males with coagulopathy or encephalopathy. The degree of elevation of aminotransferases has also been linked with progression of disease.⁷

Conclusion

HSV hepatitis is a rapidly fatal, yet potentially treatable cause of fulminant hepatitis seen mostly in immunocompromised patients. Conventional treatment modalities for IBD, such as steroids and azathioprine, have been known to cause HSV hepatitis. There are, however, only 2 published case reports describing an association between TNF- α inhibitor use and development of HSV hepatitis in IBD patients. Nonspecific clinical presentation of HSV hepatitis warrants a high degree of clinical suspicion to establish a timely diagnosis. Suggestive clinical findings (none of which is pathognomonic) include fever, anicteric hepatitis, acute renal failure, coagulopathy, leukopenia, and thrombocytopenia. Characteristic mucocutaneous lesions of HSV infection, which might be an important clue, may not always be present. Treatment should be started based on clinical suspicion, as the condition is often associated with rapid clinical decline and death. Liver biopsy should be performed whenever possible. Characteristic inclusions, although pathognomonic, may not always be appreciated due to associated necrosis. In such cases, IHC stain for HSV may help clinch the diagnosis. Empiric treatment with parenteral acyclovir may significantly reduce the mortality rate in cases with acute hepatic failure.

Author Contributions

All authors contributed in the write-up and editing of the article.

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REFERENCES

- Schiødt FV, Davern TJ, Shakil AO, McGuire B, Samuel G, Lee WM. Viral hepatitis-related acute liver failure. *Am J Gastroenterol*. 2003;98:448–453.
- Flewett TH, Parker RG, Philip WM. Acute hepatitis due to herpes simplex virus in an adult. *J Clin Pathol*. 1969;22:60–66.
- Haag LM, Hofmann J, Kredel LI, et al. Herpes simplex virus sepsis in a young woman with Crohn's disease. *J Crohns Colitis*. 2015;9:1169–1173.
- Kaufman B, Gandhi SA, Louie E, Rizzi R, Illei P. Herpes simplex virus hepatitis: case report and review. *Clin Infect Dis*. 1997;24:334–338.
- Shlien RD, Meyers S, Lee JA, Dische R, Janowitz HD. Fulminant herpes simplex hepatitis in a patient with ulcerative colitis. *Gut*. 1988;29:257–261.
- Ergle K, Caruso L, Burt M, Desai B, Patel R. Herpes simplex virus (HSV) in the differential for fulminant hepatic failure. *Case Reports in Clinical Medicine*. 2015;4:63–68.
- Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl*. 2007;13:1428–1434.
- Phadke VK, Friedman-Moraco RJ, Quigley BC, Farris AB, Norvell JP. Concomitant herpes simplex virus colitis and hepatitis in a man with ulcerative colitis: case report and review of the literature. *Medicine (Baltimore)*. 2016;95:e5082.
- Wolfsen HC, Bolen JW, Bowen JL, Fenster LF. Fulminant herpes hepatitis mimicking hepatic abscesses. *J Clin Gastroenterol*. 1993;16:61–64.
- Seksik P, Gozlan J, Guitton C, Galula G, Maury E, Offenstadt G. Fatal herpetic hepatitis in adult following short corticotherapy: a case report. *Intensive Care Med*. 1999;25:415–417.
- Bissig KD, Zimmermann A, Bernasch D, Furrer H, Dufour JF. Herpes simplex virus hepatitis 4 years after liver transplantation. *J Gastroenterol*. 2003;38:1005–1008.
- Levitsky J, Duddempudi AT, Lakeman FD, et al. Detection and diagnosis of herpes simplex virus infection in adults with acute liver failure. *Liver Transpl*. 2008;14:1498–1504.
- Golds G, Worobetz L. Fulminant hepatic failure in a patient with Crohn's disease on infliximab possibly related to reactivation of herpes simplex virus 2 infection. *Case Reports Hepatol*. 2016;2016:2132056.
- Natu A, Iuppa G, Packer CD. Herpes simplex virus hepatitis: a presentation of multi-institutional cases to promote early diagnosis and management of the disease. *Case Rep Hepatol*. 2017;2017:3180984.
- Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999–2010. *J Infect Dis*. 2014;209:325–333.
- Triantafyllidis JK, Merikas E, Georgopoulos F. Current and emerging drugs for the treatment of inflammatory bowel disease. *Drug Des Devel Ther*. 2011;5:185–210.
- Randall CW, Vizcete JA, Martinez N, et al. From historical perspectives to modern therapy: a review of current and future biological treatments for Crohn's disease. *Therap Adv Gastroenterol*. 2015;8:143–159.
- Justice EA, Khan SY, Logan S, Jobanputra P. Disseminated cutaneous herpes simplex virus-1 in a woman with rheumatoid arthritis receiving infliximab: a case report. *J Med Case Rep*. 2008;2:282.
- Poley RA, Snowdon JF, Howes DW. Herpes Simplex virus hepatitis in an immunocompetent adult: a fatal outcome due to liver failure. *Case Rep Crit Care*. 2011;2011:138341.
- Riediger C, Sauer P, Matevossian E, Muller MW, Buchler P, Friess H. Herpes simplex virus sepsis and acute liver failure. *Clin Transplant*. 2009;23:37–41.