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Single Case

Coexisting Primary Sclerosing Cholangitis and Autoimmune Hepatitis: Overlapping Challenges in Diagnosis and Treatment

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Keywords
Primary sclerosing cholangitis · Autoimmune hepatitis · Ulcerative colitis · Overlap syndrome · Vancomycin · Case report

Abstract
Introduction: Hepatobiliary overlap syndromes describe the coinciding presentation of more than one immune-mediated biliary and liver disease in a single patient and present complex challenges in diagnosis and treatment. We report a case of ulcerative colitis with primary sclerosing cholangitis and autoimmune hepatitis overlap syndrome responsive to vancomycin. ***Case Presentation:*** The patient is a 30-year-old female with known ulcerative pancolitis and autoimmune hepatitis. She presented to the emergency department with a constellation of gastrointestinal symptoms, including diffuse lower abdominal pain, bloody diarrhea, and nausea with bilious vomiting. Subsequent imaging revealed the additional diagnosis of primary sclerosing cholangitis, and she was diagnosed with overlap syndrome. Multiple treatment regimens were trialed with minimal improvement. She eventually achieved normalization of both clinical status and biochemical markers after the addition of vancomycin. ***Conclusion:*** Vancomycin is an underutilized therapy; its potential role in primary sclerosing cholangitis and autoimmune hepatitis overlap syndrome has not been previously reported.

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Introduction

Overlap syndrome (OS) is a term used to describe cases where multiple immune-mediated hepatobiliary diseases present concurrently. Autoimmune liver disease is generally categorized by either hepatocellular or cholestatic enzyme predominance. The hepatic subtype, autoimmune hepatitis (AIH), typically presents with elevated aminotransaminases and hypergamma-globulinemia, with characteristic autoantibodies including serum anti-nuclear antibody and anti-smooth muscle antibody. Liver biopsy typically reveals interface hepatitis with a lymphoplasmacytic infiltrate. However, diverse presentations occur, ranging from asymptomatic to chronic/insidious onset, acute hepatitis, cirrhosis, or acute liver failure; additionally, hyperglobulinemia and positive autoantibodies may be absent initially.

The cholestatic subgroup of autoimmune liver disease encompasses both primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). PBC is characterized by elevated serum anti-mitochondrial antibodies (AMA) and cholestatic laboratory findings including a marked alkaline phosphatase elevation. Disease progression is marked by an elevated bilirubin with jaundice, with histology revealing damage to the biliary ducts with portal inflammation and granulomas. PSC has similar cholestatic chemistries and exhibits biliary ductal damage via fibro-obliterative cholangiopathy, which may lead to biliary cirrhosis [1]. Diagnosis requires the exclusion of secondary sclerosing cholangitis, which can mimic PSC. Secondary sclerosing cholangitis can be caused by infectious, immune-mediated, toxic, obstructive, or ischemic injury and includes AIDS-related cholangiopathy and cholangiocarcinoma, among other disorders [1].

PSC is strongly associated with inflammatory bowel disease (IBD), more commonly ulcerative colitis (UC) than Crohn's disease (CD) [1]. It has been hypothesized that PSC evolves in UC patients due to uptake into the enterohepatic circulation of proinflammatory cells from the colon; these agents typically concentrate in the biliary system, where they ultimately cause the biliary ductal damage frequently seen with PSC [2]. Vancomycin may have a therapeutic role in OS treatment given its perceived ability to target this specific pathway. Previous case reports and a few small controlled trials have suggested that vancomycin can be effective in treating patients with UC and PSC [3, 4]. To our knowledge, its role specifically in PSC and AIH overlap has not been previously reported.

Case Report

A 30-year-old female with a complex gastroenterologic past medical history presented to the emergency department with several days of severe diffuse lower abdominal pain radiating to her right flank, bloody diarrhea, and nausea with episodes of bilious vomiting. She had known ulcerative pancolitis (diagnosed 2 years prior to presentation, status post failed biologic therapy with Infliximab and vedolizumab, currently on ustekinumab), and biopsy-proven alcoholic cirrhosis (diagnosed 6 years prior to presentation), in the setting of known coexisting AIH (diagnosed 6 years prior to presentation with significantly elevated liver enzymes, aspartate aminotransferase reaching a maximum of 825 IU/L [normal 10–42] and alanine aminotransferase reaching a maximum of 488 IU/L [normal 6–45], positive anti-nuclear antibody with a titer of 1:80 [normal <1:40] and smooth muscle antibody with a titer of 1:20 [normal <1:20], elevated gamma-globulin to 52 U [normal 0–19], and negative viral serological tests. At the time of diagnosis of AIH, liver biopsy revealed interface hepatitis with lymphoplasmacytic infiltrate in the portal tracts and lobules as well as bridging piecemeal necrosis. The patient had a definitive diagnosis of AIH as per both the 1999 revised original score for AIH [score = 22, indicating definite AIH – note

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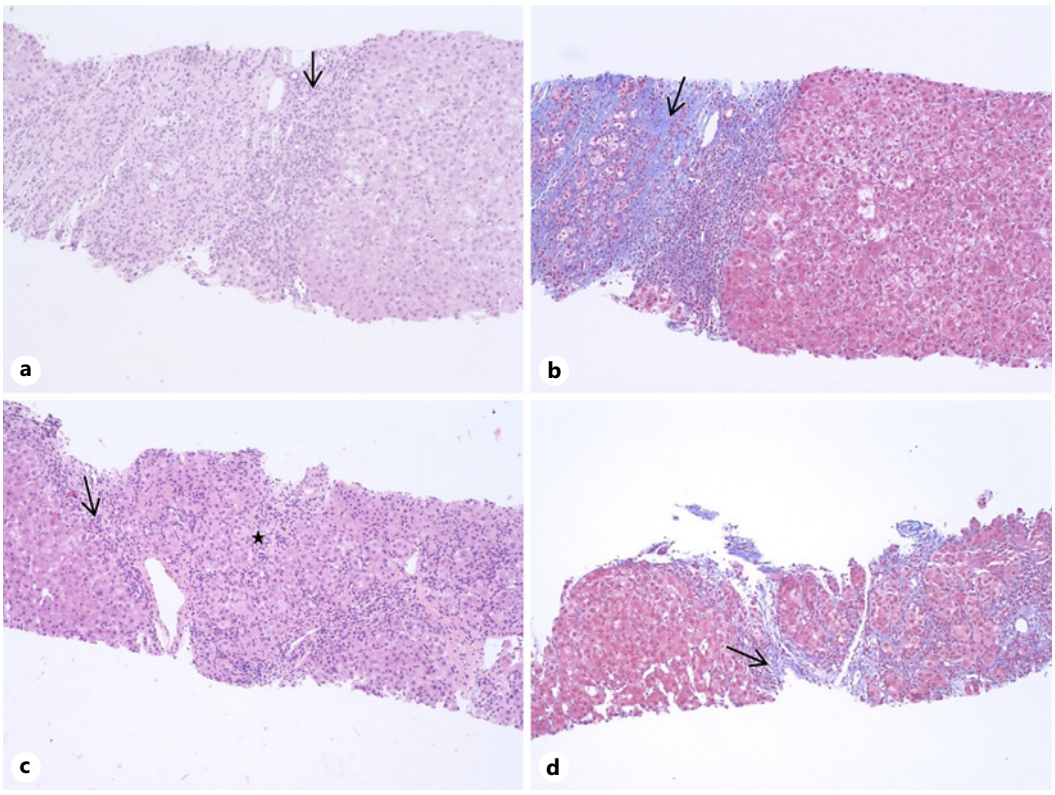

Fig. 1. a–d Liver biopsies demonstrating bridging fibrosis and periportal and lobular lymphoplasmacytic inflammation (×10 magnification). **a** Initial liver biopsy showing periportal lymphoplasmacytic inflammation (arrow; H&E stain). **b** Initial liver biopsy with bridging fibrosis highlighted in blue (grade 3–4, arrow, trichrome stain). **c** Repeat liver biopsy, showing periportal (arrow) and lobular (star) lymphoplasmacytic inflammation (H&E stain). **d** Repeat liver biopsy showing bridging fibrosis highlighted in blue (grade 3–4, arrow, trichrome stain).

that although no early cholestatic changes were found at the time of diagnosis, even if such features had been present on histology, the patient's score would have still been 19, above the threshold to indicate definite AIH] and the 2008 simplified AIH score [score = 8, indicating definite AIH]). She had a remote history of significant alcohol abuse, having quit 7 years earlier when she was diagnosed with cirrhosis secondary to combination of alcohol and AIH (shown in Fig. 1). At the time of her presentation to the emergency department, liver transplant evaluation was pending.

Initial labs were significant for elevated inflammatory markers, with erythrocyte sedimentation rate (ESR) 48 mm/h (normal 0–20), C-reactive protein (CRP) 32.97 mg/L (normal 0–10), and fecal calprotectin 1,131.2 μg/mg (normal 0–49.9). Liver enzymes revealed a slightly elevated , aspartate aminotransferase of 45 IU/L, alanine aminotransferase of 41 IU/L, alkaline phosphatase of 56 IU/L (normal 34–104), albumin of 3.7 g/dL (normal 3.5–5.0), and an elevated total protein of 9.1 g/dL (normal 6.0–8.0). Total bilirubin was 0.7 mg/dL (normal 0.2–1.3), and direct bilirubin was 0.4 mg/dL (normal 0.0–0.3). She also had thrombocytopenia, with a platelet count of 142 × 10^9/L (normal 150–400). Basic metabolic panel and lipase were within normal limits. Stool studies including Clostridium difficile were negative. She was admitted with concern for an acute flare of UC. Further diagnostic testing was pursued: abdominal CT scan showed

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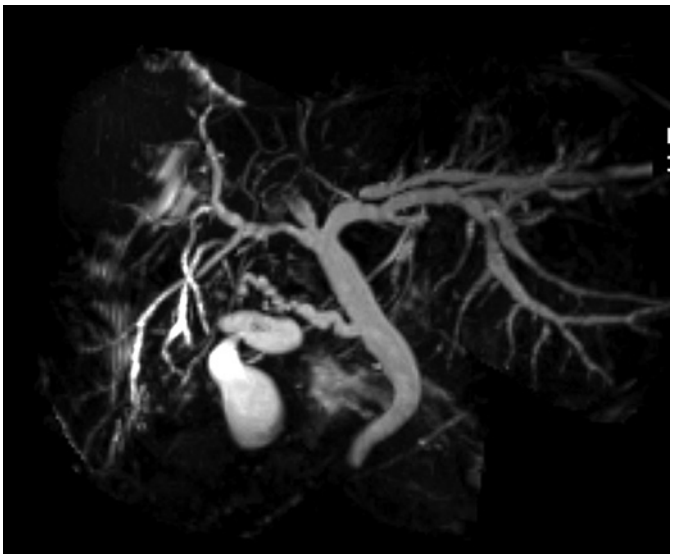

Fig. 2. MRCP showing beading and irregularity of the intrahepatic biliary tree and cystic duct, in keeping with known history of PSC. This image also highlights the dilation of the intrahepatic and extrahepatic biliary system.

mild intrahepatic and extrahepatic biliary ductal dilatation suspicious for PSC and a cirrhotic liver with signs of portal hypertension including splenomegaly. Endoscopy revealed multiple non-bleeding duodenal ulcers and grade II esophageal varices, for which she was started on propranolol 20 mg daily and pantoprazole; non-steroidal anti-inflammatory drugs (NSAIDs) were discontinued. Colonoscopy revealed moderately active UC Mayo score 2, worsened from prior exam. She underwent magnetic resonance cholangiopancreatography (MRCP) which was significant for cirrhotic liver morphology with nodular surface contour and intrahepatic and extrahepatic biliary dilatation with beading and irregularity of the intrahepatic biliary tree and cystic duct, consistent with PSC (shown in Fig. 2).

The constellation of findings supported a diagnosis of PSC-AIH OS; treatment was started with prednisone, azathioprine, and ustekinumab. Although she had partial symptomatic improvement from her UC flare, it was not until 3 weeks after the subsequent addition of vancomycin that she achieved normalization of her biochemical markers (liver enzymes, fecal calprotectin) (shown in Fig. 3), endoscopic improvement of her UC, and full clinical remission.

Discussion

No definitive diagnostic criteria for PSC-AIH OS currently exists. While there are scoring systems to classify the immune hepatopathies individually, the very nature of the coexisting diseases makes these classification systems non-transferrable to OS. Indeed, the International Autoimmune Hepatitis Group (IAIHG) scoring system subtracts points for characteristics indicative of cholestatic disease, as cholestatic characteristics are not typical features of pure AIH [5]. This is problematic for undiagnosed OS patients being assessed with the IAIHG scale. Not only does this scale not have the capacity to diagnose OS, but it also means that OS patients are likely to go undetected for even a baseline AIH diagnosis given that their cholestatic disease characteristics end up lowering their overall diagnostic score.

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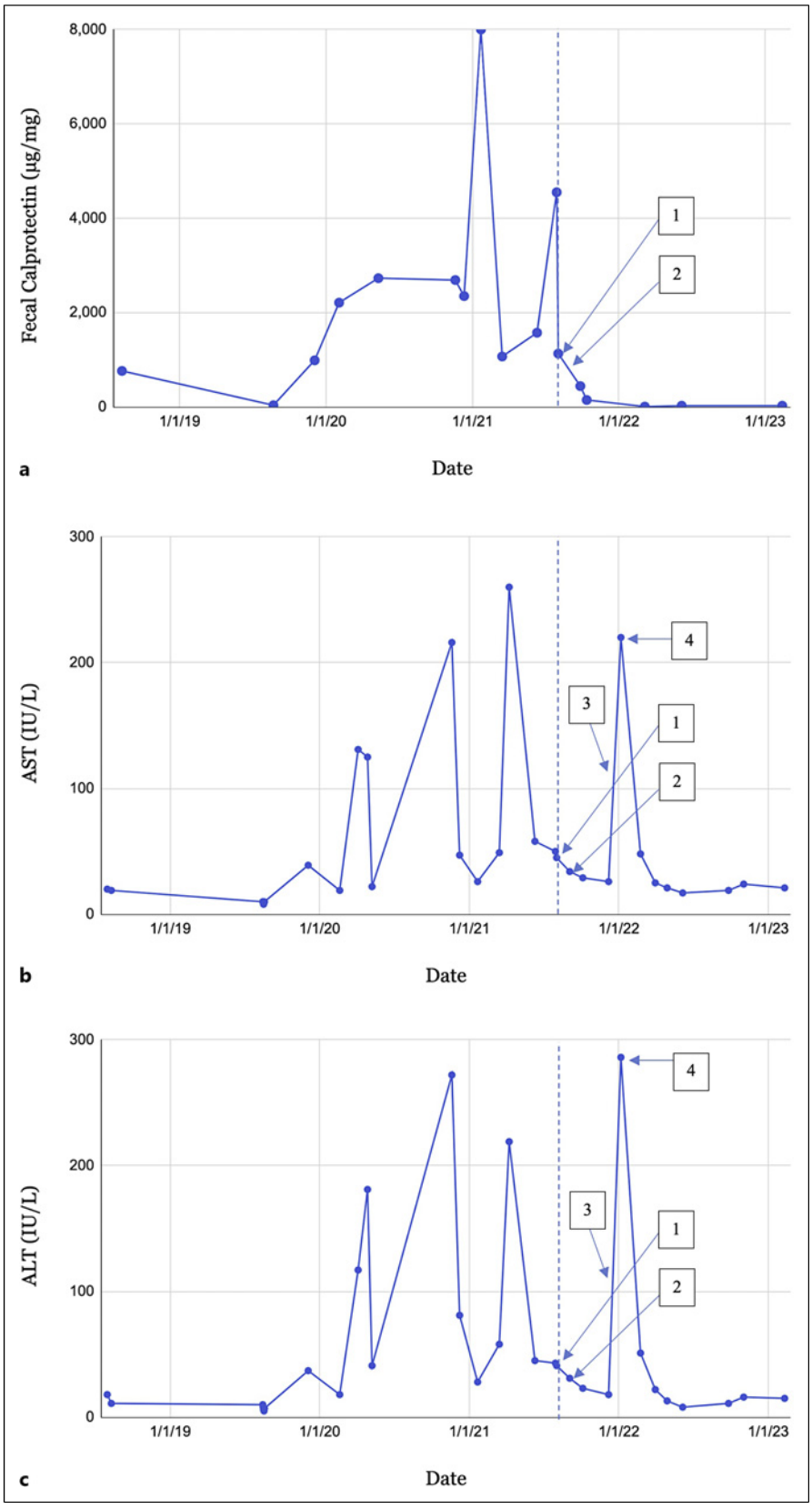

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It is important to note that the 2008 simplified AIH score does not account for cholestatic changes on histology; as such, it may provide a better assessment of AIH in patients with OS. In Muratori et al.'s [6] 2009 letter to the editor, the authors validated the accuracy of the new simplified AIH score in clinical practice, providing data on a study population which included AIH-PBC OS patients. In their study, they were able to demonstrate the efficacy of the 2008 simplified AIH score in the diagnosis of AIH OS in patients with a known diagnosis of PBC. The two scoring systems are clearly not interchangeable, and each ought to be considered based on the specific clinical situation. While the detail of the original scoring system is well suited to diagnose patients with few or atypical features of AIH, the simplified scoring system is well fit to exclude the diagnosis of AIH in patients with other immune manifestations of disease [7].

Despite the challenges of diagnosis, it is important to consider OS when confronted with disease which presents with a clinical or biochemical picture that does not fit the typical classifications of a singular pure hepatobiliary disorder. Data indicate that up to 33% of PSC patients have a concomitant OS [8]. Conversely, studies have revealed an 18% occurrence of PSC overlap in patients with AIH [9]. Further, approximately 70% of PSC patients have co-occurring IBD [10]. With each diagnosis, it is imperative to consider potential coexisting diseases, especially for patients with an atypical presentation or lack of response to standard treatment. Adding to the diagnostic challenge, OS patients frequently present with nonspecific symptoms including fatigue, myalgias, and jaundice. Ultimately, for known AIH patients with IBD symptoms and cholestatic features, evaluation with MRCP may be indicated to evaluate for OS with PSC.

This case report examines one such case of the variant form AIH-PSC OS associated with UC, in which patients have serologic features indicative of AIH with contemporaneous or subsequent findings of the cholangiographic abnormalities characteristic of PSC. While AIH and PSC have been considered to be two distinct diseases, there is some debate as to whether their concomitant discovery in a single patient represents an atypical manifestation of one of the major immune hepatopathies, a separate distinct disease entity, or merely a coincidental co-presentation of two separate diseases. Overlap cases often present in a progressive fashion, with one of the hepatobiliary diseases manifesting prior to presentation of the other. These patients often progress towards cirrhosis and eventual hepatic failure if left untreated. As such, it is crucial to consider OS in patients with AIH who have cholestatic chemistries or who develop resistance to immunosuppression. In fact, what appears to be resistance to immunosuppression may represent a transition from the autoimmune process alone to an OS with a cholestatic component unresponsive to immunosuppressive therapy. A correct diagnosis can impact prognosis: patients diagnosed with AIH-PSC OS have been reported to have worse outcomes than those with AIH-PBC OS or with AIH alone; however, survival of patients with the AIH-PSC variant form has been superior to survival from classical PSC [11, 12].

Once a definitive diagnosis has been established, it is important to select the correct treatment regimen. Treatment for OS is ill-defined but typically includes a combination of anticholestatic ursodeoxycholic acid and immunosuppression with corticosteroids or azathioprine [12]. Ursodeoxycholic acid provides additional protection for PSC patients

Fig. 3. a–c Lab values over time: fecal calprotectin (**a**), aspartate transferase (AST) (**b**), alanine transaminase (ALT) (**c**). Legend: (1) started on prednisone while in the hospital, and 12 days later, started on ustekinumab injections + azathioprine; (2) started on vancomycin given no symptomatic improvement with the previous medications; (3) patient self-discontinued vancomycin without telling provider; (4) patient made appointment with provider as she was not feeling well; was restarted on vancomycin.

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in its reduction of dysplasia risk with UC but does not improve the course of PSC [12]. Given the rarity of OS syndromes, there are currently few trials exploring their treatment; therefore, although these treatment regimens have been shown to induce improvements in labs and histology, long-term clinical efficacy has not been established. If medical therapies fail, patients with late-stage disease typically require liver transplantation. Unfortunately, recurrent disease is significantly higher in transplanted patients with OS compared to either AIH or PSC alone. While only 16% and 18%, respectively, of AIH and PSC patients experience recurrence of the disease process in the transplanted liver, a disheartening 53% of OS patients experience transplant disease recurrence [8]. Thus, there is a pressing need for a therapy to fill this gap.

Vancomycin may be one such auxiliary therapy. As illustrated by Dao et al. [4], vancomycin has been reported to induce remission of UC in some treatment-resistant PSC patients, improving symptoms and resolving abnormalities in liver enzymes and biliary imaging. This finding has been supported by Shah et al. [13], whose cohort study found that in PSC, vancomycin treatment was associated with both clinical and endoscopic remission of UC. While the exact mechanism of action of vancomycin in these patients is unknown, it has been hypothesized that it targets the characteristic variations in the colonic microbiome that can be seen in UC-PSC patients [2–4, 14, 15]. Cox and Cox [2] hypothesized that oral vancomycin, in targeting enteric bacteria, decreases the absorption of inflammatory biliary toxins that contribute to PSC. Shah and colleagues' [16] conceptual framework reported a mechanism of targeted modulation of the gut microbiome to stop disease progression, specifically using vancomycin for PSC with or without co-occurring IBD.

Beyond its clear role in the treatment of PSC, vancomycin also has a potential role to play in OS with PSC patients who have the additional immunocompromised status of co-occurring AIH; in these patients, biologics are more prone to failure. Rahman et al. [14] found that as many as one-third of UC patients undergoing immunosuppressive therapy following liver transplant for PSC developed worsening colonic inflammation; this may explain the increased rate of disease recurrence in OS patients. By adding vancomycin to the medication regimen, recurrence and mortality post-transplant might be significantly reduced.

For PSC patients with UC and co-occurring AIH, the addition of vancomycin has the potential to reduce mortality and disease burden. As supported by the cases described in Damman et al.'s [15] review article, our patient's clinical improvement may be phenomenologically congruent with a direct response to vancomycin's effect in AIH-PSC. Oral vancomycin has been assessed as a possible treatment for PSC and has been shown to be well-tolerated and linked to improved liver chemistries [3, 17]. A large sample-size, randomized, placebo-controlled trial is needed to determine the effect on objective clinical outcomes. Clinicians should be aware of the possible use of vancomycin to treat patients with coexisting PSC +/− AIH and IBD. Further investigation is needed to determine the extent of its therapeutic role.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537798).

Statement of Ethics

The following research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to declare with respect to the research, authorship, and/or publication of this article.

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Author Contributions

H.W. Fiske performed background research and drafted the manuscript. F. Saeed and C. Ward contributed to the conception and design of the work. B. Sinayuk acquired and analyzed the radiology images. V. Ulici acquired and analyzed the pathology images. M. Curry contributed patient data for the article. E. Feller and S.A. Shah critically revised the article. S.A. Shah is the treating physician. All authors provided final approval of the manuscript. H.W. Fiske is the article guarantor and accepts full responsibility for the conduct of the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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