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Case Report

Primary Sclerosing Cholangitis Pruritus Treated with Plasmapheresis

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ABSTRACT

Evidence regarding the efficacy of plasmapheresis for pruritus due to hepatobiliary disease is sparse. The mechanism of pruritus in this context is poorly understood. Some candidates for the offending agents are bile salts and histamine. Primary sclerosing cholangitis is one such disease and appears to have an autoimmune component. The rationale for plasmapheresis for patients who are refractory to medical therapy has some plausibility because the nonspecific nature of plasmapheresis may significantly decrease one or more of the offending substances in the patient's plasma. We share our experience of a patient with pruritus due to primary sclerosing cholangitis who benefited from plasmapheresis.

Keywords: Plasmapheresis, Primary sclerosing cholangitis, Pruritus

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, progressive inflammatory condition that causes scarring within the bile ducts that carry bile from the liver to the small intestine. The inflammation seen in PSC is thought to be autoimmune in nature, as some patients with this condition are found to have elevated self-antibody titers, indicating an overactive immune system targeting the bile ducts.[1] Certain HLA genetic profiles confer a higher risk of developing the disorder and eventual scarring as well.[2]

The result of this scarring is the formation of fibrotic strictures of medium and large ducts in the biliary tree. This leads to complications of cholestasis due to the inability of the bile to flow through to the intestines and ultimately hepatic failure without intervention. Other symptoms of PSC include pruritus, fatigue, abdominal tenderness, and yellowing of the skin and eyes reflective of the liver's insufficient functioning over time.

In terms of histopathology, PSC is characterized by concentric laminations around intrahepatic bile ducts known as "onion skin" fibrosis. PSC is also a premalignant disease, as many as 20% of patients with the condition develop cholangiocarcinoma.[2] This carcinogenesis is thought to be induced by both inflammatory mediators and the toxicity contributed by bile back up.

Epidemiologically, males are twice as likely to develop PSC than females, most individuals are diagnosed between 30 and 40 years of age, and the disease is interestingly seen predominantly in nonsmokers. Both incidence and prevalence of PSC are higher in North American and Northern Europe compared with the rest of the world.[1]

Individuals are considered for a diagnosis of PSC with liver tests that demonstrate a pattern of cholestatic abnormality. The diagnosis is typically confirmed via cholangiography showing the

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structuring and circumferential dilation of the bile ducts that is characteristic of the disease.[2]

PSC has no definitive cure and is largely managed with immunosuppressive therapies, though some patients are able to receive a liver transplant. Additionally, plasmapheresis has been shown to improve pruritic symptoms of PSC in isolated cases. While the exact etiology of the pruritus seen in PSC patients is not known, scarce case reports indicate that plasmapheresis may be able to remove the pruritogenic material from the circulation helping to reduce the itchiness that these patients experience.[3] We discuss in this case report one patient who experienced some benefit from such a treatment course.

CASE PRESENTATION

A 26-year-old male patient presented with persistent pruritus, jaundice, intermittent fever, and abdominal pain. He was started on diphenhydramine, doxepin, tramadol, cholestyramine, rifampin, and ursodiol to alleviate his symptoms, but they continued to worsen. His medical history was significant for primary sclerosing cholangitis (PSC) diagnosed 5 years earlier. Magnetic resonance cholangiopancreatography (MRCP) showed characteristic moderate to severe intrahepatic biliary ductal dilation with irregular strictures most notably in the left hepatic lobe and associated strictures in the common bile duct.

His HLA phenotype was positive for B8 but not DR3. Anti-nuclear antibody testing showed a nucleolar pattern and an anti-nuclear antibody (ANA) titer of 40. Tests for mitochondrial antibodies, rheumatoid factor, smooth muscle antibodies, and tissue transglutaminase antibodies were negative.

He had end-stage liver disease with associated ulcerative colitis and was seen regularly at the gastroenterology and hepatology clinic for the management of both conditions. He was on the liver transplant list with the possibility of a living donor liver transplant. At presentation, he reported that he was not sleeping well at night despite taking zolpidem.

Physical examination revealed icteric sclerae with jaundiced skin and scattered excoriations without rash. His liver function test results were elevated (total bilirubin: 3.5 mg/dL, alkaline phosphatase [ALP]: 559 μ/L, gamma glutamyl transferase (GGT): 807 μ/L). His hematology parameters (red blood cells, white blood cells, and platelets) were within normal limits. Due to the persistent pruritus and elevated liver function parameters, the transfusion medicine service was consulted to perform therapeutic plasma exchange (TPE), once to twice weekly for 4 weeks via peripheral venous access. The TPEs were 1-volume plasma exchanges that were performed using centrifugal plasmapheresis with 5% albumin as the replacement fluid.

After the first two TPEs, the patient reported no significant reduction in itching. However, he noticed substantially reduced itching and improved sleep after the third TPE. His total bilirubin levels immediately before the TPE series was 2.5 to 4 mg/dL. During and immediately after the series, the total bilirubin was 1.7 to 3 mg/dL. Due to challenges with obtaining peripheral venous access, TPE was discontinued after seven procedures per the patient's preference.

Subsequently, his itching and poor sleep symptoms worsened back to his pre-TPE baseline. Similarly, his total bilirubin progressively increased to the 3 to 4 mg/dL range. Throughout his course of TPE and subsequently, he never stopped the medications that he began before TPE. He eventually received a right lobe living donor liver transplant ~9 months after cessation of TPE. After the transplant, he did well and reported no related symptoms of pruritus.

DISCUSSION

PSC is thought to have both genetic and environmental components to its development. Many patients diagnosed with PSC also have a concurrent diagnosis inflammatory in nature, with inflammatory bowel disease being a particularly common additional diagnosis. PSC is also thought to be autoimmune in nature, as some patients present with elevated levels of antineutrophilic cytoplasmic antibodies, antinuclear antibodies, and anticardiolipin antibodies.[1] Additionally, it appears that individuals with the HLA B8 and HLA DR3 genetic profiles confer a higher risk of developing PSC.[1] Both are relevant to our patient, as he had antinuclear antibodies and HLA B8.

The mechanism by which the damage to bile ducts seen in PSC and other cholestatic diseases leads to pruritus has not been definitively clarified. However, current treatment recommendations that include plasmapheresis are grounded in the suggested mechanism that bile salts that accumulate in the hardened and narrow bile ducts seen in PSC act as pruritogens that directly contribute to the sensation of itchiness. The activation and degranulation of mast cells induced by bile salts provides an additional possible contributor to this presentation.[4] Outside of the direct actions of built up bile salts, the activation of μ-opioid receptors caused by elevated endogenous opioid levels that have been seen in cholestatic patients could also be a factor in this symptom development. This concept is supported by the antipruritic effects seen in cholestatic patients with the administration of μ-opioid antagonists.

Removing potential pruritogens from the circulation serves as the biological rational for attempting courses of

TPE.[2] Plasmapheresis is a continuous process that involves removing a relatively small volume of whole blood from the patient, using a centrifuge to separate the whole blood into its component parts by density, removing the plasma into a waste bag, and simultaneously replacing the volume with a replacement fluid such as 5% albumin. A typical 1-volume plasma exchange replaces ~63% of the patient's plasma.

The evidence underlying the use of therapeutic plasma exchange (TPE) for cholestatic pruritus due to PSC relies heavily on sparse case reports documenting improved symptom management in patients where this therapy is used. Some patients reported long lasting improvement of their pruritic symptoms with periodic TPE therapy, while others reported only mild improvement for a brief amount of time before therapy discontinuation.[2] A comprehensive review of the literature is beyond our scope, but as one indication of the evidence, 10 of 13 (77%) reported cases of patients with chronic pruritus due to hepatobiliary disorders responded to TPE.[3]

One case report of a patient with intense pruritus in primary sclerosing cholangitis had long symptomatic remissions of pruritus after plasmapheresis.[5] The authors speculate that the successful therapy may be related to the removal of immune complexes, as there was no lasting effect on the patient's liver function tests.[5] This is relevant to our patient, as he reported significant benefit from TPE during the series that stopped after the TPEs were stopped due to difficulties with obtaining venous access in accordance with patient preferences.

One limitation is measuring the effect of TPE. In our patient, the magnitude of benefit from TPE is difficult to measure objectively and precisely. On the one hand, he reported improvements in pruritus and sleep from after the third TPE to the end of the TPE series. But on the other hand, one could argue that the benefit was not great enough for him to want to continue TPEs beyond the initial 7. Moreover, no laboratory analytes are unambiguous markers that correlate with pruritus. His total bilirubin values decreased from 2.5–4 mg/dL immediately pre-TPE to 1.7–3 mg/dL during TPE and immediately post-TPE. Of note, he did not have any bile acid values during this time. Finally, he continued the same medications during the TPE series, and these could have confounded the effect of TPE. However, there were so significant changes to his medications around the time of the TPE series, so one could argue that the addition of TPE was the only change and that it was the imputable cause of the clinical benefit.

Conflict of interest

None declared.

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