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International Journal of Recent Surgical and Medical Sciences

Case Report

Long-term Plasmapheresis for Cholestatic Pruritus

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Received: 16 February 2022

Accepted: 26 April 2022

EPub Ahead of Print: 7 September 2023

Published: 22 December 2023

DOI
10.25259/IJRSMS-2022-2-12

Quick Response Code:

ABSTRACT

Cholestatic pruritus is commonly associated with many hepatobiliary disorders and can be typically controlled with conventional treatment. Therapeutic plasma exchange (TPE) has shown success in improving untreatable cholestatic pruritus with great success. We report on the use of TPE to alleviate debilitating pruritus in one patient with a two-year history of chronic pruritus refractory to conventional treatment. The patient presented with an acute onset of diffuse pruritus that did not fully respond to first or second-line treatments, including bile acid sequestrants. Pruritus significantly affected her quality of life, interfering with daily activity, causing insomnia and weight loss. Due to the severity of her symptoms, biweekly TPE with 5% albumin infusions were initially trialed. Patient found symptoms to be much improved until about the fifth day after each TPE. TPEs were scheduled twice per week alternating with once per week. TPE appeared to be an effective treatment for this patient with chronic cholestatic pruritus. For our patient, TPE seemed to provide relief for about 3-5 days after each TPE.

Keywords: Cholestatic pruritus, Hepatology, Plasmapheresis

INTRODUCTION

Cholestatic pruritus is a common symptom that is associated with many hepatobiliary disorders, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), involving extrahepatic biliary obstruction and/or intrahepatic biliary disruption[1]. The frequency of pruritus varies depending on the underlying condition, but the pathogenesis of cholestatic pruritus is largely unknown[1]. Lysophosphatidic acid, bile salts, opioid receptors, and histamine have all been proposed as critical mediators of pruritus development[2].

Pruritus can have serious implications for a patient's quality of life, and the intensity of symptoms can fluctuate over time. Treatment often begins with managing the underlying disease. Bile acid sequestrant medications, such as cholestyramine, are first-line therapy for moderate to severe pruritus[3]. Rifampicin, naltrexone, and sertraline are common second-line therapies for pruritus[4]. Some patients with severe cholestatic pruritus that are refractory to treatment require liver transplantation[1].

Therapeutic plasma exchange (TPE) removes large-molecular-weight substances from the plasma and replaces them with another fluid, such as 5% albumin[5]. Some uncontrolled case reports of refractory cholestatic pruritus have shown TPE to have great success. In conjunction with antipruritic medication, TPE has been shown to successfully treat severe pruritus, irrespective of the underlying disease[6]. Furthermore, a review of 48 patients using TPE for cholestatic pruritus demonstrated the safety and efficacy of management[6]. Although American guidelines on the use of apheresis in clinical practice acknowledge the benefit TPE has in the management of

pruritus of a hepatobiliary etiology, the evidence is limited[7]. In addition, while response rates are high (around 70–80%), TPE is limited as it does not provide a guaranteed benefit, is relatively expensive, and often requires a central venous catheter or other intravenous device in patients without adequate peripheral access.

METHODS

We performed a retrospective chart review of the patient's medical record. For the chronology, we define week one as the beginning of the patient's pruritus treatment.

CASE REPORT

We present the case of a 65-year-old woman with a two-year history of chronic pruritus refractory to treatment. She first presented to her primary care physician with an acute onset of diffuse pruritus. In week one, the etiology of patient's pruritus was unclear. Allergic etiology was initially a concern; therefore she was given high-dose glucocorticoids with a taper, which provided some relief, but the pruritus shortly returned after discontinuation. She had a follow-up appointment with her primary care physician several weeks later, where she received a second round of high-dose glucocorticoids with a taper. She was referred to dermatology in week 14 where she was treated for presumed scabies using permethrin, which did not improve symptoms. She was also maintained on a moderate dose of glucocorticoids. Due to rising liver enzymes, she was referred to hepatology in week 34. Laboratory and radiologic workup for the etiology of her elevated liver enzymes was initially noncontributory [Table 1], however, an underlying primary cholestatic liver disorder was suspected.

Initial therapeutic recommendations included cholestyramine [Table 2]. Improvement of pruritus was noted after several days of cholestyramine, however, the patient reported decreased energy, postprandial nausea, and refractory pruritus after one week. Ursodiol was then prescribed for cholelithiasis dissolution after endoscopic retrograde cholangiopancreatography (ERCP) demonstrated small stones and sludge, in addition to treatment of a possible underlying primary cholestatic liver disorder, but it failed to improve symptoms. After continued intense pruritus, naltrexone was added to her regimen. After two days, naltrexone improved her pruritus up to 90% with improved sleep. Yet, she continued to report decreased appetite, early satiety, postprandial nausea, decreased exercise tolerance, and a 30-pound weight loss over the prior six months.

It was thought that the patient may have PBC/autoimmune hepatitis (AIH) overlap syndrome, so budesonide was added to her treatment regimen. Liver enzymes initially improved on budesonide, but several weeks later, they presented slightly worse and pruritus remained. Sertraline was then initiated, in addition to continuing cholestyramine, ursodiol, naltrexone and budesonide.

In week 73, the patient's liver enzymes continued to remain elevated despite therapy, as above, therefore, obeticholic acid was added to treat possible refractory PBC. One month later, the patient reported extreme pruritus on her arms, chest and stomach, thought to be due to the obeticholic acid, a well-known side effect, so it was discontinued.

In week 82, the patient's liver enzymes were stable, so she began fenofibrate in addition to her current treatment regimen. Her labs began to improve after starting fenofibrate, but after two months, she still complained of pruritus as well as pain in the right upper quadrant. Since the pruritus was still bothersome with her current medications, multiple changes to her treatment regimen were made. Budesonide was discontinued as there was not great evidence for AIH. Sertraline was discontinued in order to start rifampin due to significant interactions.

In week 106, the patient continued to report significant pruritus and was struggling to sleep at night and could only walk short distances without being fatigued.

After continuing to fail traditional therapy, the patient agreed to a trial of TPE while continuing the other medications. The patient received weekly TPEs over the next five weeks. Each TPE session was a 1-volume plasma exchange via an automated centrifugal apheresis machine that used 5% albumin as the replacement fluid via peripheral venous access. The procedures were tolerated well and she reported an immediate reduction in ocular pruritus. After five treatments of TPE, the patient agreed to continue TPE every other week.

Pruritus relief and sleep improvements continued after each subsequent TPE. The patient was also able to gain weight during this period. However, the patient noted that pruritus severity rebounded after approximately five days post-TPE. Based on these symptoms, TPEs were scheduled twice per week alternating with once per week, and the patient continued to have significant relief from pruritus. She began the evaluation for liver transplantation as definitive treatment for her intractable cholestatic pruritus.

DISCUSSION

History

Cholestatic pruritus is a significant cause of morbidity in patients with chronic liver disease. About 80% of patients with chronic liver diseases, such as PBC and PSC will experience pruritus during the course of their disease[4]. Although the pathogenesis of pruritus is not completely understood, current

Table 1: Diagnostic test results

Date of workup	Type of workup	Results
Laboratory Tests		
Week 24	**Hepatitis A IgG Antibody**	**Positive**
Week 24	Hepatitis A IgM Antibody	Negative
Week 24	Hepatitis B Surface Antigen	Negative
Week 24	Hepatitis B Core Antibody	Negative
Week 24	Hepatitis C Antibody	Negative
Week 34	Mitochondrial Antibody	Negative
Week 34	Immunoglobulin G subclass 4	Negative
Week 73	Mitochondrial (M2) IgG Antibody	Negative
Week 73	**Antinuclear Antibody**	**Positive: speckled pattern**
Week 129	HIV Antibody/Antigen Combo	Negative
Week 129	Mitochondrial Antibody	Negative
Week 129	Smooth Muscle Antibody	Negative
Week 129	**Antinuclear antibody Screen with Titer**	**Positive** **1:80 speckled** **1:80 homogenous**
Week 129	Alpha-1-Antitrypsin Phenotype	M1M1 (normal)
Ultrasound		
Week 9	Showed no overt pathology	
Week 91	Showed no overt pathology	
Week 123	Suggestive of cirrhosis, no mass, non-dilated intrahepatic ducts, 7 mm common bile duct	
Computed Tomography (CT)		
Week 27	Showed no overt pathology	
Magnetic Resonance Cholangiopancreatography (MRCP)		
Week 31	Mildly ectatic common bile duct and left lower lobe airspace disease	
Week 53	Suggestive diffuse hepatocellular dysfunction and no definite biliary ductal abnormalities	
Week 100	Cirrhosis with progressive stigmata of portal venous hypertension resulting from stage IV fibrosis	
Liver Biopsy		
Week 25	Liver with minimal portal inflammation, bile ductular proliferation, and cholestatic rosettes suggestive of stage II–III fibrosis. No findings to suggest PBC or PSC.	
Week 54	Liver with mild portal inflammation, prominent bile ductal reaction and mild cholestasis. Portal, periportal and focal bridging fibrosis suggestive of stage II-III fibrosis. No findings to suggest PBC or PSC.	
Endoscopic Retrograde Cholangiopancreatography (ERCP)		
Week 35	Complete removal of stone fragments within the biliary tree. Mildly dilated common bile duct and normal intrahepatic biliary radicles. Negative for malignancy.	

treatments aim to target potential biochemical culprits[4]. Patients who have refractory pruritus to these treatments may be eligible for TPE and some undergo liver transplantation[1]. We present our patient who was found to have a two-year history of severe pruritus with no prior history of liver disease at symptom onset. The suboptimal response to treatment raised suspicion for a cholestatic origin for her pruritus. The discovery of transaminitis and hyperbilirubinemia without clear etiology prompted referral to hepatology.

Etiology

Interestingly, the patient's liver function tests fell drastically by the time she was seen by her hepatologist in week 24, suggesting the potential efficacy of a treatment she had received previously or spontaneous improvement. Nonetheless, these values remained elevated, and the etiology of her elevated liver enzymes was explored. After numerous laboratory tests, imaging studies, procedures and biopsies [Table 1], the leading diagnosis was antimitochondrial antibody (AMA)-negative PBC given her predominantly cholestatic pattern of liver disease with consistently elevated liver enzymes, hyperbilirubinemia, and prominent pruritus.

Treatment and progression of liver disease

The patient's liver disease was treated with ursodiol, budesonide, obeticholic acid and fenofibrate over the course of approximately two years. The greatest improvement in

Table 2: Medications

Drug taken	Dosage and duration	Patient improvement
High-dose steroids	Unknown dosage: Week 1–18	No relief after taper
Medium-dose steroids	40 mg/day: Week 18–31	No pruritus relief
Permethrin	Unknown dosage: Week 14–17	No pruritus relief
Cholestyramine	4 mg/day: Week 34	No pruritus relief
	4 mg BID: Week 35–38	Temporary pruritus relief but reports decreased energy and nausea with eating
	4 mg BID and uptitrate until improvement: Week 38–47	No pruritus relief
	8 mg BID: Week 47–52	Brief pruritus relief
	8 mg BID: Week 52–92	No pruritus relief
Ursodiol	300 mg BID: Week 38–53	Minimal liver enzyme improvement
	500 BID: Week 53–123	Minimal liver enzyme improvement
Naltrexone	25 mg/day: Week 52–68	90% improvement in pruritus relief with better sleep
	50 mg/day: Week 68–123	No pruritus relief
Vitamin D	1000 mg/day: Week 55–123	N/A
Calcium supplements	1500 mg/day: Week 55–123	N/A
Budesonide	9 mg/day: Week 60–91	Minimal liver enzyme improvement with no pruritus improvement
	9 mg/day with taper: Week 91–94	No pruritus relief
Sertraline	75 mg/day: Week 68–85, Week 92	No pruritus relief
	100 mg/day: Week 80–92	No pruritus relief
Obeticholic Acid	5 mg/day: Week 73–80	Developed severe itching after 4 days
Fenofibrate	145 mg/day: Week 82	Minimal liver enzyme improvement
Rifampin	150 mg BID: Week 93–123	75% improvement in pruritus; better sleep

liver enzymes and bilirubin occurred between the initial diagnosis (week 24) and initial consultation with her hepatologist (week 34). This improvement may be due to high-dose glucocorticoid treatment or spontaneous resolution. Several months of pharmacotherapy did improve liver enzymes for a short period, however this was not sustained as some patients with PBC or other cholestatic disorders can have progressive disease refractory to therapy. Of note, obeticholic acid was discontinued early due to worsening pruritus. This points out the difficulty of balancing treatment for conditions like PBC while trying to manage their resulting symptoms. Unfortunately, she failed these treatments and was diagnosed with cirrhosis via MRI with elastography in week 123.

Treatment and progression of pruritus

The patient's pruritus was treated with prednisone, diphenhydramine, cholestyramine, naltrexone, sertraline and rifampin. Prior to the discovery of her liver disease, prednisone burst and taper was used due to concern for allergic etiology. This seemed to relieve pruritus to an extent, which then returned to baseline after she discontinued her first taper. Moderate-dose prednisone was re-initiated, but pruritus returned and worsened regardless of steroid use, and these were discontinued permanently within six months of initial symptom onset. Her most significant improvement in pruritus was noted with naltrexone, suggesting at least partial μ-opioid receptor activity causing her pruritus, but her response was limited to three months at most[4]. Following persistent pruritus with rifampin therapy, five weekly TPE sessions were scheduled. Symptoms began to improve following the second session but would consistently return five to six days after treatments. TPE every other week was trialed, but weekly sessions were required to control her pruritus. Liver function tests remained at similar levels prior to initiation of TPE, suggesting that pruritus was not dependent on the severity of her liver disease.

What does this case add?

This patient's case highlights important considerations that current literature does not address. First, this case presentation sheds light on the complexity of cholestatic pruritus and emphasizes its unknown pathogenesis. Persistent pruritus following treatment with common first and second-line medications suggest an alternative cause of pruritus in this patient than hypothesized in previous literature[4]. This stresses the need for a personalized approach to the treatment of cholestatic pruritus that may require trial and error. Second is the delicate balance between treating her underlying liver disease and its accompanying symptoms. Pruritus was this patient's most prominent symptom, which limited treatment options. Namely, obeticholic acid, which was used as a

second-line therapy for her presumed AMA-negative PBC, was discontinued due to exacerbation of pruritus, a well-known side effect of this medication. The progressive nature of her disease contributed to her progression to cirrhosis while intractable pruritus contributed to the need for consideration for liver transplantation.

Lastly are considerations surrounding the initiation of TPE for cholestatic pruritus. TPE has been shown to be a relatively safe therapeutic modality, especially if peripheral venous access is used instead of central venous catheter or another invasive device. The treatments for cholestatic pruritus may be effective for most patients, but for the subset of individuals who are refractory to them all, the months or even years of treatment failure may be associated with an extremely low quality of life. A trial of TPE during this time period of exploring pharmacotherapy options may be helpful to these patients. The potential benefit for this subset of individuals is suggested by our patient.

CONCLUSION

TPE may be an effective part of medical management for numerous medical conditions, but there is limited evidence on its effectiveness for cholestasis pruritus. We share our experience of a patient with severe, refractory cholestatic pruritus for whom TPE provided significant relief for 3–5 days after each session.

Acknowledgement

None.

Ethical approval

The research/study complied with the Helsinki Declaration of 1964.

Declaration of patients consent

Patient's consent not required as patient identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Sanson E, Richard LJ, German MN, Rose WN. Long-term Plasmapheresis for Cholestatic Pruritus. Int J Recent Sur Med Sci. 2023;9:122–6. doi: 10.25259/IJRSMS-2022-2-12