

Beyond the kidney: Nephrologists in the treatment of severe chronic pruritus failing to respond to systemic treatments

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Abstract

We report a case of severe chronic pruritus in a patient with cholestatic liver disease due to a cholangiocarcinoma that did not respond to sequential treatment with bile acid sequestrants, enzyme-inducing agents, opioid antagonists or selective serotonin inhibitors. Since the cause of severe pruritus is the accumulation of some substances in plasma and other tissues, as a result of cholestasis, it has been suggested that the removal of these substances would improve the quality of life of patients. However, the specific nature of the substances and the mechanisms by which they cause itching is still unknown, meaning that there is no targeted therapy or any guidelines available to tackle this situation. Therefore, therapies for chronic pruritus are largely based on clinical experience and anecdotal reports. Considering that Nephrologists are well trained to perform extracorporeal blood purification treatments, we were requested for an experimental therapy with total plasma exchange (TPE), an invasive therapy that has been claimed as effective. However, this report illustrates a case in which TPE displayed a low clinical benefit and prompted us to review the evidence behind the use of extracorporeal devices in cholestatic liver disease.

Introduction

Chronic pruritus, defined as itch persisting for more than 6 weeks, is often associated with poor quality of life [1-3]. The mechanisms underlying chronic pruritus are complex and only partially understood with multiple mediators involved [4-6]. Given the paucity of data from randomized trials, therapeutic choices are largely based on clinical experience and anecdotal reports.

The pathogenesis of pruritus secondary to cholestatic liver disease has been associated with multiple plasma factors such as neurotransmitters (e.g. histamine, serotonin), bile salts, endogenous opioids, progesterone metabolites or lysophosphatidic acid (LPA) [6,7], but there is no correlation with the severity of the underlying disease and liver structure [8]. Thus, the treatment of cholestatic pruritus is currently based on (i) elimination of mediators of pruritus from the enterohepatic circulation with the use of resins or aspiration with a nasogastric tube, (ii) induction of the metabolism of pruritus mediators in the liver with, for example, rifampicin, and (iii) modulation of the central sedation pathway of pruritus with opioid antagonists or with selective inhibitors of serotonin re-uptake [9]. Intractable pruritus is defined by failure on symptoms control despite the sequential regimen with bile acid sequestrants (cholestiramine or clescevelam), enzyme-inducing agents (rifampicin), opioid antagonists (naltrexone) and selective serotonin inhibitors (sertraline) [8]. Currently, correct response to treatment is commonly measured by a visual analogue scale (VAS) or numeric ranged scales (NRS) [10].

In cases with intractable pruritus, an extracorporeal device with adsorbents for removal of protein-bound toxic substances, such as charcoal hemoperfusion, has been claimed as an option [11]. Molecular Adsorbents Recirculation System (MARS) based on albumin dialysis and containing charcoal in the adsorbent circuit has been also used [12]. The simplest extracorporeal approach and one which

has also shown to be effective in reducing the severity of pruritus is plasmapheresis (apheresis procedure that separates and removes the plasma component from a patient) or Therapeutic Plasma Exchange (when plasmapheresis is followed by replacement with fresh frozen plasma infusion). Thus, American Guidelines on the Use of Apheresis in Clinical practice [13] included “pruritus due to hepatobiliary diseases” to the list of disease that would benefit of using plasmapheresis (PE) or Therapeutic Plasma Exchange (TPE). However, the quality of the evidence is scarce (category III) and may be not applicable to all patients (Recommendation 1C).

Nephrologists have broad experience in the management of extracorporeal blood purification treatment including vascular access, anticoagulation, volume management and prescription for solute clearance. Thus, we were requested to perform a TPE by membrane plasma separation in a patient with refractory chronic pruritus secondary to cholestatic cholangiocarcinoma.

Clinical case

A 64-year-old male patient with dyslipidemia and benign prostatic hyperplasia presented a hilar cholangiocarcinoma (Klatskin tumor) that was resected without complications. Few days later after surgery, ascites and hepatic insufficiency appeared. On the tenth day after surgery, mucosal jaundice was observed (Total bilirubin=167 μmol/L), and 14 days after, moderated pruritus was developed (Total

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bilirubin=203 $\mu\text{mol/L}$). Sequential treatment with ursodeoxycholic acid, rifaximin, fenobarbital, naltrexone and topical therapy with calamine and triamcinolone was initiated (Figure 1). The severity of pruritus increased and was graded as 8 using a 10-point numerical rating score (NRS) which lead patient to a moderated anxiety and sleep deprivation (bilirubin=426 $\mu\text{mol/L}$). Since there was no relief of pruritus with the sequential therapy, the use of extracorporeal devices therapy was proposed.

Patient underwent 7 sessions of TPE by membrane plasma separation using a right internal jugular intravenous access. Informed consent was obtained from the patient prior to initiating TPE. All procedures were performed using the PrismafleX Apheresis System with a polypropylene hollow fiber prisma filter (PRISMAFLEX TPE 2000 setTM). In each session, we provided 1 plasma exchange with 2000 mL of 5% albumin and 1000 mL of frozen fresh plasma as replacement fluids. The procedures were performed in 3 consecutive days (at 56, 57, 58 days after admission) and 4 more treatments on alternate days (at 60, 62, 64 and 66 days after hospital admission). During those days, medical treatment for pruritus was continued (Figure 1). Night resting, jaundice, and scratch lesions were assessed daily. Blood tests to monitor bilirubin, histamine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ -glutamyltransferase (GGT), Urea and histamine were analyzed before each TPE (Table 1). There were no incidents during the TPE sessions.

After 7 sessions of TPE, patient improved jaundice and bilirubin decreased to 211 $\mu\text{mol/L}$. Pruritus initially decreased only to a 7 NRS grade, allowing night resting for two days (between 1st and 3rd procedure), but pruritus rebound on the third day despite sustained systemic treatment. After the 7 procedures, the pruritus was as intense as before the initiation of extracorporeal treatment (measured with a grade 8 NRS) and TPE was stopped and jugular venous catheter was removed.

During 8 months follow-up, several infectious complications occurred despite patient did not receive any chemotherapy or immunosuppressive treatment. Two Spontaneous Bacterial Peritonitis (SBP) appeared, one by *Enterococcus faecium* after 71 days after the end of TPE (treated with Teicoplanin) and second by *Pseudomona aeruginosa* after 156 days after the end of TPE. Finally, itching was

ameliorating slowly under sustained medical treatment with bile acid sequestrants, enzyme-inducing agents, opioid antagonists or selective serotonin inhibitors (Figure 1), and 87 days after admission patient pruritus disappeared (Bilirubin=302 $\mu\text{mol/L}$; NRS 0).

Patient died after 260 days of follow-up due to blood infection by *Pseudomona aeruginosa*.

Discussion

This case report illustrates the treatment failure of chronic severe pruritus with TPE in a patient with a cholestatic liver disease. Previously, several reports have suggested their efficacy since 1978, when Geerdink, *et al.* reported the first case of refractory pruritus successfully treated with PE [14]. Eight years later, Cohen, *et al.* [15] published the first series of 5 patients with pruritus secondary to primary biliary cirrhosis (PBC) treated with PE using 1000 ml of normal saline and 5% albumin 3 times per week (maintenance once or twice a week). In those 5 cases, the response was immediate, decreasing the pruritus intensity grade from 3 to 0 or 1 (scored from 0 to 4). Beneficial effect of TPE in cholestatic liver pruritus was claimed after Krawczyk, *et al.* published a series of 17 consecutive patients in which refractory pruritus significantly decreased according to a 10-point NRS and the effect persisted throughout the 90-day follow-up period [16]. Furthermore, the American Society for Aphaeresis included chronic

Table 1. Main analytic findings before and after TPE treatment

Lab Findings	Before TPE (day 56)	After TPE (day 67)
Creatinine ($\mu\text{mol/L}$)	84	58
AST ($\mu\text{kat/L}$)	3.41	4.27
ALT ($\mu\text{kat/L}$)	1.26	1.81
Albumin (g/L)	31	40
Total Bilirubin ($\mu\text{mol/L}$)	352	254
GGT ($\mu\text{kat/L}$)	1.48	0.96
Alkaline phosphatase ($\mu\text{kat/L}$)	2.85	1.49
Phosphate (mmol/L)	1.1	0.77
N-acyl-Histamine ($\mu\text{g/dl}$)	0.06	0.02
Hemoglobin (g/L)	106	102
Reticulocytes ($\times 10^9/\text{L}$)	176	121
Leucocytes ($\times 10^9/\text{L}$)	7.3	6.7
Eosinophils ($\times 10^9/\text{L}$)	0.81	0.1

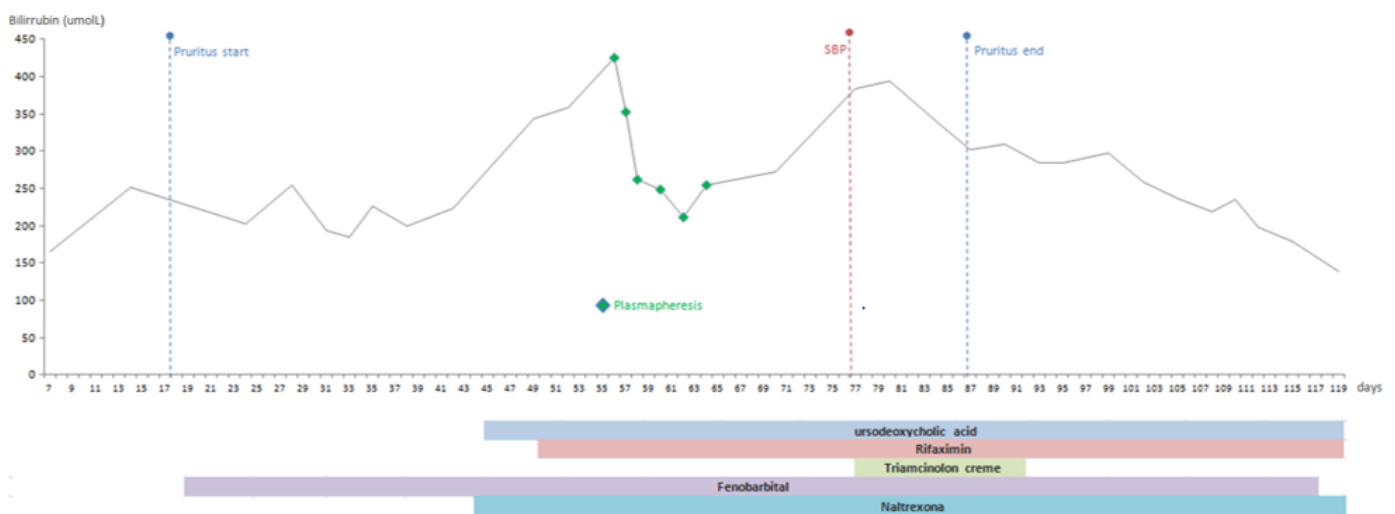


Figure 1. Chronological evolution of Bilirubin levels in the first 100 days after hospital admission. Pruritus starts after 18 days from admission and ends on the 87th day. TPE sessions were performed on days 56, 57, 58, 60, 62, 64 and 66. First SBP episode occurred on day 77

pruritus due to hepatobiliary disease as one of the indications for TPE treatment [13].

Summing up, publications until this date includes 13 reports with 51 patients treated with TPE, associated with an amelioration of pruritus in all but two patients [17]. These two patient's refractoriness to TPE are part of a series of 26 patients with Benign Recurrent Hepatic Cholestasis [18]. In these series, 6 patients out of the total series required plasmapheresis as a treatment for pruritus with two treatment failures. This article does not describe the characteristics of the procedures.

Thus, why the treatment was failed in our patient? The cause of severe pruritus is not well known, neither which is the metabolite to be eliminated. It has been suggested the role of protein-bound toxic substances and it has been proposed the use of charcoal and other adsorbents [8]. Thus, it has been reported clinical response in 9 out of 15 patients (mostly with PBE) treated with Charcoal hemoperfusion with a median of 5 sessions of 4 hours extracorporeal perfusion per week [11]. In patients with no relief of pruritus despite charcoal hemoperfusion, it has been reported that all but one experienced relief from pruritus when Molecular Adsorbents Recirculation System (MARS) was used (based on albumin dialysis and containing charcoal in the adsorbent circuit refractory). There are experiences with 7 hours treatment for two consecutive days with MARS and with 6 hours treatment for 3 consecutive days, presenting good response with long-lasting effect (ranged from 2 to 5 months) [12,19]. Thus, the lack of response could be related to the inefficacy of TPE to remove molecular substances that may be pathogenic. In addition, is the differences observed with our patient related with the dose or the length of the TPE therapy? Most of the cases reported have used albumin 5%, have exchanged between 1 and 1.3 plasma volumes [20,21], and have used maintained PE on a weekly or monthly basis [22]. However, other causes are plausible.

Are the differences observed with our patient related with what is considered an adequate response? Clinical effectiveness has been measured with different questionnaires, not always validated, and it has been considered an adequate response to treatment both the disappearance and the reduction of symptoms to the category of mild. Some other items like night rest or scratching injuries has been evaluated only in some studies [16]. In most cases, the response is described as "early" although it is not always accurately collected. In the series of 3 cases of Chkheidze, *et al.* [17], for example, pruritus was considered mild after 5, 7 and 5 sessions respectively. Furthermore, there is a potential positive publication bias in favor of treatment with PE or TPE.

Other differences could contribute to explain the refractoriness to the treatment in our patient. In most cases the primary cholestatic disease was PBC (37 out of 48 cases of PBC, 1 case secondary to pregnancy, 1 case with Primary Sclerosing Cholangitis, 1 case secondary to drugs and the other 6 cases secondary to Benign Recurrent Hepatic Cholestasis) [17]. In our case, the primary cholestatic disease was a malignant cholangiocarcinoma.

The etiopathogenesis of pruritus is complex, multifactorial and not completely understood. In addition, it is known the big role of the affective component associated with this symptomatology. In fact, the use of placebo treatments has shown effective in daily clinical practice [5], and the symptoms of our patient were self-limiting despite the PE treatment was finished.

At last, the decision to stop the treatment after 7 sessions can be considered hasty since at the end of the treatment the levels of bilirubin in blood were still high. However, no clinical response had been

observed and no article has managed to significantly correlate levels of bilirubin or bile salts with neither the presence nor the intensity of pruritus.

Finally, we must keep in mind that PE has been associated with an increased risk of infections. However, very few adverse effects are described associated with plasmapheresis in the aforementioned series of cases. It should be noted that the most frequently described adverse effect has been mild urticaria (up to 7.7% in the series by Shemin, *et al.* [23] limited with oral medication. In our case, we do not observe any complications related to the TPE treatment since the episodes of SBP occurred, at least, 2 months after the end of treatment. In addition, none of the microorganisms causing infection were encapsulated germs that could be associated with hypogammaglobulinemia secondary to treatment.

Conclusion

In conclusion, extracorporeal devices and TPE are still an experimental therapy in resistant pruritus due to cholestatic liver diseases accepted in current clinical guidelines. However, the quality of the evidence is still low, and its use should be individualized. This clinical case is an example of the need for a randomized clinical trial to further defend the real effectiveness of plasmapheresis for the treatment of chronic refractory pruritus.

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