CASE REPORT

Refractory pruritus in primary biliary cirrhosis

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Dr Nuno Cercas Pinheiro,
ncercaspinheiro@gmail.com**SUMMARY**

Pruritus is a major symptom of primary biliary cirrhosis, cholestatic autoimmune disease which affects mostly middle-age women. Often, it can be severe and refractory to multiple treatments, and mostly affecting the patient's health-related quality of life. Intense pruritus can be itself an indication to liver transplantation, in extreme cases leading to suicide. Its physiopathology has not yet been fully elucidated, but recent studies added the elevation of autotaxin and lysophosphatidic acid to the group of classic mechanisms already linked to cholestatic pruritus. In this case report we illustrate how ultraviolet B phototherapy appears to successfully control severe pruritus and contribute to the healing of pruritic skin lesions caused by intense scratching. There is limited medical literature concerning this therapeutic approach on cholestatic pruritus, but we hope that further randomised controlled trials will successfully establish it as an effective treatment in the near future.

BACKGROUND

This case report illustrates how pruritus in cholestatic liver diseases such as primary biliary cirrhosis (PBC) can be severe, continuous and refractory to multiple therapeutic interventions, deeply affecting health-related quality of life (HQoL). It also shows how ultraviolet B (UVB) phototherapy can play a role in the management of cholestatic pruritus, improving not only the symptom but also contributing to the healing of scratch lesions.

CASE PRESENTATION

A 50-year-old woman, without any relevant medical history, presented 15 years ago with asthenia and persistent elevated values of the γ -glutamyl transpeptidase which was noticed in a routine blood analysis, this led her to have a hepatology consultation. Further evaluation was performed which revealed normal abdominal ultrasound and the presence of the antimitochondrial antibodies (AMA-E₂) in the serum. Liver biopsy was performed, revealing histology compatible with PBC, CHILD A, MELD 10 and the patient initiated ursodeoxycholic acid (UDAC) 250 mg 2id and cholestiramine 4 g thrice daily. After 2 years she developed moderate pruritus, graded 5 (in the visual analogue scale (VAS), ranging between 0 and 10), located at legs, variable through the day, aggravating at night, which led to an increase in cholestiramine dose to 4 g four times a day. The clinical picture aggravated 5 years ago, leading to the addition of the rifampicin 150 mg once daily, later escalated to 600 mg once daily, to the therapeutic scheme. After a period of stabilisation pruritus grew in intensity in the last 2 years,

spreading to her upper limbs and torso. Now it was classified 10 on VAS, and associated with extensive scratch lesions in her lower limbs and torso (figures 1 and 2). The patient also developed moderate anxiety and mild depression, without suicidal ideation. Her HQoL was affected in many items, such as sleep deprivation, lack of energy, lack of concentration and impaired productivity at work. Her body image was also affected due to the development of extensive pruritic skin lesions, mainly located at the lower limbs. The worsening of pruritus led to the inclusion of the naltrexone 12,5 mg once daily, which the patient did not tolerate due to severe side effects, and sertraline 100 mg once daily to the therapeutic scheme, suspending rifampicin, without satisfactory response.

TREATMENT

The patient initiated UVB phototherapy three times a week, a total of 37 sessions, with a wavelength of 311 nm and a cumulative dose of 6240 J/cm², plus the pharmacological scheme previously initiated (figures 3 and 4). UVB exposure time increased through the sessions, ranging from 1 to 15 min.

OUTCOME AND FOLLOW-UP

After 1 month of treatment she referred great improvement in pruritus, classifying it 5 on VAS. On the third month of treatment important healing of scratch lesions was observed, as well as amelioration of HQoL items. Nowadays the patient classifies pruritus 2 on VAS, and markedly improvement on skin lesions has been observed (figures 5 and 6). There was also a positive evolution on depressive symptoms and reduction of anxiety, as well as

Figure 1 Scratch lesions before ultraviolet B phototherapy.

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Figure 2 Detailed view of scratch lesion before treatment.

better productivity at work. The patient maintains therapeutic pharmacological scheme of UDAC 250 mg twice daily, cholestiramine 4 g four times a day and rifampicin 300 mg once daily, complementing it with regular sessions of UVB phototherapy and regular trips to sunny destinations. The patient maintains regular follow-up in hepatology consultations, with regular blood analysis and abdominal ultrasounds.

DISCUSSION

Pruritus is a well known and major symptom associated with PBC, chronic cholestatic autoimmune disease that affects mostly middle-aged women.¹ It can be often quite severe, deeply impacting a patient's quality of life. Intense and uncontrolled pruritus is associated with depressive and anxiety symptoms, leading in extreme cases to suicide.²⁻⁵ Refractory and uncontrolled pruritus can be itself an indication for liver transplantation, even if severe liver failure has not yet been established.^{6,7}

Its physiopathology has not yet been fully understood. Classic theories involve increased activation of the serotonin and opioid neurotransmission and elevation of substance P. Accumulation of

Figure 3 Scratch lesions during ultraviolet B phototherapy.

Figure 4 Scratch lesions during ultraviolet B phototherapy.

unknown pruritogens due to cholestasis would be the direct responsible or the trigger of pruritus.^{1,6-12} Curiously pruritus does not appear in all cholestatic patients, and when it does it might fluctuate during the natural history of the disease. In addition to this, in the late stage of cholestasis, when liver ceases its function completely and maximum levels of bile acids in serum are achieved, pruritus seems to vanish.^{1,6-12} Recently the enzyme autotaxin (ATX) and its final product lysophosphatidic acid (LPA) have been implied in pruritus physiopathology.^{13,14} These substances appear to be elevated in cholestatic patient's serum, and their plasma levels seem to correlate with pruritus intensity. In addition to this, the intradermal injection of LPA in the mice-induced dose-dependent scratch response.¹³

Refractory cholestatic pruritus remains an important therapeutic challenge, perhaps due to the multiplicity of mechanisms that seem to underlie it. Pharmacological options consist of several drugs administrated alone or, more often, in association. The first step on pruritus pharmacological ladder is the use of non-absorbable resins such as cholestiramine, responsible for binding pruritogens in the gut preventing their reabsorption through enterohepatic circulation.^{6,7} Next step will be the administration of the rifampicin, an enzymatic inducer, leading to accelerated liver metabolism of pruritogens.^{6,7} Up ahead on

Figure 5 Scratch lesions after ultraviolet B phototherapy.

Figure 6 Detailed view of scratch lesion after treatment.

the pharmacological ladder comes the use of naltrexone, an opioid antagonist which will slow down the upregulated opioid tone that seems to be associated with cholestasis.^{6 7} Naltrexone can be difficult to tolerate since it can be responsible for severe opioid withdrawal syndrome,^{6 7} which our patient experienced leading to its discontinuation. Last but not the least there is sertraline, a selective serotonin reuptake inhibitor that has demonstrated its antipruritic effect which is independent of its widely accepted antidepressive properties.^{6 7} Hydroxyzine, an antihistamine, is also frequently used as a sedative, improving the often disturbed sleep of chronic cholestatic patients with severe pruritus.^{6 7} Experimental approaches to pruritus control include the use of MARS and PROMETHEUS, extracorporeal circulation techniques allowing temporary substitution of the liver function, associated with modest results.^{6 7} When everything else fails, refractory pruritus itself can be an indication to liver transplantation.^{6 7} The implication of ATX and LPA in pruritus physiopathology opens the door for the appearance of more focused and specific pharmacologic interventions.^{13 14}

UVB phototherapy has sporadically been described in literature as an effective way of managing cholestatic pruritus. In 1980 one paper reported this fact in 5 of 6 patients with PBC,¹⁵ in 1987 another paper addressed improvement in one patient with PBC,¹⁶ and in 1994 phototherapy was described as effective on treating pruritus in a 7-year-old child with cholestasis.¹⁷ More recently, an observational study of 2012 described important improvement in pruritus with UVB phototherapy in 10 of 13 patients with cholestatic disease, 4 of them with PBC.¹⁸

UVB phototherapy is a validated therapy in treating pruritus associated with chronic renal failure, systemic mastocytosis, cutaneous T-cell lymphoma or atopic dermatitis.^{18–20} UVB phototherapy has been proved a secure and effective therapeutic approach in the field of dermatology. The case reports and observational studies available in medical literature concerning cholestatic pruritus, although few in number, associate UVB phototherapy with consistent and great improve in pruritus intensity, measured with VAS, without influencing serum parameters of cholestasis.^{15–18} However, perhaps due to the paucity of data available, UVB phototherapy has not yet been integrated in any guidelines regarding treatment of the cholestatic pruritus.

This therapeutic approach consists of using ultraviolet lamps emitting light at the UVB spectrum (290–320 nm). This wave

length enters the epidermis at the level of dermoepidermal junction. Epidermis is believed to be the place where itch receptors can be found.¹⁹ It has been recently hypothesised that UVB phototherapy might decrease itch perception due to its interaction with itch receptors at dermoepidermal junction.¹⁸ On the other hand, it may alter or inactivate pruritogens that accumulate on skin.¹⁸ Despite its effects at epidermis level, the fact that UVB phototherapy increases urinary excretion of bile acids cannot be ignored, an effect well known in the use of this therapy on neonatal hyperbilirrubinemias.^{18 19}

The risk of skin cancer is taken in account when using this therapy. The dose of radiation is established for each patient, and it is stopped at the minimal sign of erythema.^{18–20} All patients should wear protective goggles and genital shields in male participants.^{18–20} Sun exposure is avoided during the treatment.^{16–18} Sunblock application should be respected after each radiation.^{18–20} The history of skin cancer, *lupus erythematosus* or *xeroderma pigmentosum* contra indicates the UVB phototherapy.^{18–20} The use of photosensitising medication such as tetracyclines or quinolones must be avoided.^{18–20} In our case there was no sign of erythema or skin cancer during the period of the UVB treatment.

In the present case we observed drastic reduction of pruritus evaluated by VAS (score was improved from 10 to 2), without alteration of serum cholestatic parameters. In addition to this, pruritic skin lesions caused by scratching experienced great improvement as the pictures can state. The reduction in scratching reflex, caused by the improvement in pruritus, might contribute to this improvement.

However, this work consists only of a case report and thus only observational conclusions can be drawn, and as so spontaneous relief of pruritus cannot be excluded. In addition to this, despite the great improvement in pruritus achieved only after the beginning of phototherapy sessions, one cannot exclude the concomitant contribution of pharmacotherapy, which the patient maintained during the sessions, to the final result. On the other hand, a late effect of traditional pruritus pharmacotherapy could theoretically be itself the cause of such amelioration, although not commonly seen in the daily practice. Finally, self-cessation of pruritus independent of therapy could also be plausible.

In order to establish UVB phototherapy as a reliable and effective therapeutic approach it must be submitted to double blind randomised clinical trials. Meanwhile, it appears to be a useful treatment for refractory pruritus in cholestasis, conjugated with other well established therapies. Furthermore, better understanding of pruritus physiopathology is needed in order to develop more effective treatments to this symptom, often disturbing, sometimes lethal.

Learning points

- ▶ Pruritus is one of the most frequent and disabling symptoms of primary biliary cirrhosis.
- ▶ Pruritus can affect the patient's quality of life and self-image.
- ▶ New perspectives on pruritus physiopathology include activation of the autotaxin and lysophosphatidic acid.
- ▶ Ultraviolet B phototherapy appears to be an effective and safe therapy for some of the patients.

Competing interests None.

Patient consent Obtained.

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