Porphyria cutanea tarda associated with alcohol abuse: three case reports

Zengqi Tang[1], Jianchi Ma[1], Liangchun Wang[1], and Zhenrui Shi[1]

[1]Sun Yat-Sen Memorial Hospital

July 9, 2022

Abstract

We present three Chinese male patients with similar complaints of recurrent episodes of vesicles, blisters, erosion/ulcers predominantly on sun-exposed areas. They were diagnosed as having porphyria cutanea tarda after a clinical investigation. Of note, all patients had a history of alcohol abuse with or without apparent liver function damage.

Porphyria cutanea tarda associated with alcohol abuse: three case reports

Zengqi Tang[1], Jianchi Ma[1], Liangchun Wang[1] and Zhenrui Shi[1]

1.Department of Dermatology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, China

*Corresponding author:

Zhenrui Shi, MD, PhD

Address: 107 Yanjiang Rd W, Guangzhou, China 510120

E-mail: zrshi1989@outlook.com

Telephone: +86-20-8133 2289

Conflict of interests: The authors have no conflict of interest to declare.

Funding: This article has no funding source.

Text word count:1520

Number of references: 15

Tables:0

Figures:3

Abbreviations

ALA, aminolevulinate synthase ;ALT, alanine aminotransferase;AST, aspartate aminotransferase ;DIF, direct immunofluorescence; EBA,epidermolysis bullosa acquisita; FEP, free erythrocyte protoporphyrin; GGT, gamma-glutamyl transferase; HCC, Hepatocellular carcinoma; HIV,human immunodeficiency virus; PAS staining ,periodic acid-schiff stain;PCT, porphyria cutanea tarda; UROD, uroporphyrinogen decarboxylase;

Abstract

Background

Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide and is often initially diagnosed when cutaneous manifestations arise. In patients with PCT, there is a significant association with liver disease that can be triggered by genetic and environmental factors,

Case presentation

We present three Chinese male patients aged between 50 to 60 years old, with similar complaints of recurrent episodes of vesicles, blisters, erosion/ulcers predominantly on sun-exposed areas. They were diagnosed as having PCT after a clinical investigation. Of note, all patients had a history of alcohol abuse with or without apparent liver function damage. Treatment includes hydroxychloroquine and alcohol discontinuation. Patients showed marked improvement in skin lesions with no relapse.

Conclusions

PCT is rare and easy to be misdiagnosed because the skin signs could be indistinct at the beginning. The authors would like to raise awareness of alcohol intake an important susceptibility factor and possibly, diagnostic clues for PCT.

Keywords

Case report; Porphyria cutanea tarda (PCT); Alcohol abuse

Introduction

Porphyria cutanea tarda (PCT) is the most frequent type of porphyria and resulted from a catalytic deficiency of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in heme biosynthesis [1]. Accumulation of photosensitive byproducts, namely uroporphyrinogen, leads to the fragility and blistering of sun-exposed skin in PCT patients. The common age of presentation is fifth to sixth decade and it occurs slightly more commonly in males. Three different types of PCT are currently distinguished: an acquired variant accounting for 80% of PCT cases, also referred to as sporadic or type I PCT, in which the enzymatic deficiency is limited to the liver; an autosomal dominantly inherited form, also known as familial or type II PCT, in which a decrease of enzymatic activity is found in all tissues; type III PCT is similar to type II concerning familial occurrence, but their erythrocyte UROD activity is normal [2]. Patients with type I PCT is closely associated with liver diseases triggered by genetic and environmental factors, such as alcohol abuse, iron overload, hemochromatosis, and hepatitis C virus infection [3]. We herein present 3 PCT cases with a history of alcohol abuse. Of considerable interest, the 3 patient showed complete remission after cessation or reduction of alcohol consumption during our follow-up that emphasize the importance of environmental factors in PCT development.

Case presentation

Case 1

A 63-year-old man presented recurrent blisters on his face, neck, hands and forearms for 3 month. He was previously diagnosed as pemphigoid but responded poorly to topical steroids. Associated symptoms included pruritus and increased skin fragility. He denied a personal or family history of liver disease, hepatitis and iron abnormalities. The patient had consumed alcohol for more than 10 years with a daily amount of 150-300 ml (alcohol by volume, ABV >40%) .

Physical examination revealed multiple tense blisters, superficial erosions with crusting and scars distributed on the face, neck, forearms, dorsum of the hands and feet (Figure 1A-C). His laboratory results were as follows: aspartate aminotransferase (AST) 30 U/L (0–50), alanine aminotransferase 55 U/L (0–50) , gamma-glutamyl transferase (GGT) 147 U/L (0–55), transferrin saturation (TS) 65%. Tests of hepatitis C, hepatitis B and HIV tests were negative. Wood's lamp examination of his urine demonstrated coral-colored fluorescence (Figure 1D). Skin biopsy found a superficial ulcer, dilated capillaries of the dermal papillae, perivascular extravasation of red blood cells, infiltration of mixed inflammatory cells in the dermis and a

negative immunofluorescence staining (Figure 1E). Periodic Acid-Schiff (PAS) staining showed deposition of purple-red material around the dermal vessel and the dermal-epidermal junction (Figure 1F).

The patient was diagnosed with PCT and treated with glycyrrhizin during hospitalization, and his skin lesions were greatly regressed. He was counseled on cessation of alcohol consumption and manipulation of photoprotection. No medication was prescribed after discharge from hospital. The patient was followed-up for 4 years and maintained complete remission.

Case 2

A 66-year-old man consulted our dermatology clinic with a chief complaint of itchy blisters on his face and forearms for 6 months. He was previously diagnosed with chronic actinic dermatitis but merely improved by avoiding sun exposure and administration of antihistamines. His medical and family history was not significant. The patient had a daily intake of 100-200ml of brandy (AVB 35-60%) for over 8 years. Physical examination revealed slight ulcers and hyperpigmentation over his face and the dorsal surface of his hands (Figure 2A-B). Laboratory findings showed mildly elevated liver enzymes: AST 111 U/L, ALT 79 U/L, GGT 163 U/L, transferrin saturation 75%. Hepatitis screen tests were negative. Urine porphyrin is positive under the Wood's lamp (Figure 2C). Skin biopsy showed changes of superficial ulcers and crusts, epidermal spongiosis with inflammatory cell infiltrate in dermis. PAS staining showed amorphous hyaline material around the walls of capillaries. Therefore, he was diagnosed as PCT and commenced on oral glycyrrhizin and hydroxychloroquine (HCQ, 200 mg per week). We instructed him to stop drinking and avoid sun exposure. His skin lesions were significantly improved and serum levels of liver enzymes returned to normal. The patient was followed up for 2 years and maintained a satisfactory remission.

Case 3

A 55-year-old man presented to our dermatology clinic because of blisters on the scalp, face and hand for 6 months. His medical history and family history were both unremarkable. The patient had consumed 200-300 ml of wine every day for 15 years . Physical examination revealed grey-yellowish skin, several bean-sized blood blisters, superficial ulcers and atrophic scars on the scalp ,face, and dorsal of his hands (Figure 3). Conjunctival icterus was noted. Liver function test showed elevated liver enzyme levels: ALT 378 U/L, AST 542 U/L, GGT 254 U/L. Urine porphyrin was positively tested by Wood's lamp. Therefore, he was diagnosed with PCT and commenced on oral glycyrrhizin and HCQ (200 mg per week). He was also advised to stop alcohol consumption. He did not completely abstain from alcohol, but the daily drinking volume was greatly reduced to one-third of the original amount. His lesion was gradually resolved without relapse during a one-year follow-up.

Discussion

Clinically overt PCT is due to hepatic accumulation of uroporphyrin, which consequently circulate in the plasma and capillaries, get activated on exposure to sun light, results in immune-mediated reaction, release of free radicals, and damage of the lower dermis and basement membranes [2]. Characteristics of PCT skin lesions include increased photosensitivity, skin fragility, painful vesicles/bullae and erosions/crusts on sun-exposed sites such as face, dorsum of hands and forearms. Crusting of lesions take weeks to heal, resulting in atrophic scars with milia formation. Post-inflammatory hyperpigmentation, scarring alopecia, hypertrichosis, and sclerodermoid changes are also observed.

The diagnosis of PCT depends on a detailed history, characteristic symptoms, and laboratory tests. High level of urine and serum uroporphyrin and heptacarboxyl porphyrin is important for diagnosis. In our cases, we did not measure urine level of porphyrins but instead adopted qualitative examination of porphyrins using Wood's lamp as previously reported [4]. All three patients were tested positive by Wood's light, suggesting that Wood's light is a convenient and useful test for clinical screening of PCT. Histological examination of involved skin is not required to confirm the diagnosis of any cutaneous porphyria, but it help to exclude other entities in the differential diagnosis, including epidermolysis bullosa acquisita (EBA), drug-induced pseudoporphyria, and phototoxic drug eruptions.

There are multiple environmental triggers of PCT including alcohol abuse, smoke, estrogens therapy, hepatitis and liver disease[5]. Other factors, including HIV infection[6], systemic lupus erythematosus [7]and end-stage renal disease on hemodialysis [8] are also associated with the development of PCT. Heavy alcohol use of >40 g per day has been considered an important susceptibility factor and was reported in about 60 to 90% of PCT cases[9], although only about 2% of subjects with chronic heavy alcohol were reported to have PCT [2]. Mechanisms of PCT development triggered by alcohol are unclear. It was suggested that alcohol increased iron absorption and resulted in iron accumulation in liver that subsequently stimulated the production of hepaticδ-aminolevulinate synthase (ALA) and free radicals[10]. The three patients in our report were heavy drinkers of alcohol. Notably, patient 1 achieved complete remission of skin lesions purely by cessation of drinking, suggestive of cessation of alcohol as a general treatment for PCT. A recent study showed that patients with PCT had high mortality, which was attributed to gastrointestinal diseases and cancers of gut, liver/gallbladder, and lungs [11]. Further studies are warranted to investigate how lifestyles such as alcohol consumption affect the long-term complications and mortality of PCT.

Hereditary hemochromatosis (HH) is defined as an inherited iron overload disorder characterized by excessive absorption of iron. High frequency of hereditary hemochromatosis gene mutations including C282Y and H63D, occurs in patients with PCT [12]. Ideally, patients with PCT should be offered genetic test to uncover possible HH. Serum level of ransferrin saturation were raised in two of our cases, suggestive of overloaded iron and potential association with high risk of C282Y homozygotes [13]. However, the two patients demonstrated good response to therapy, thus gene test was not performed.

PCT can be treated efficiently by phlebotomy or a low dose regimen of either HCQ or chloroquine[14]. Patients showed equal improvement as comparing those received 200 mg chloroquine per week to those with 450 ml phlebotomy per 2 weeks, whereas the former group showed better compliance. The mechanism of action of HCQ or chloroquine remains unclear. The most accepted concept is that the drugs act as mobilizers of porphyrins and transform hepatocyte porphyrins into water-soluble complexes that are subsequently excreted in urine [15]. It is suitable for patients who have anemia, blood vessel disorders or are unwilling to have multiple phlebotomies. To be noted, excessive dosage might cause worsening of the photosensitivity and elevation of porphyrin. The suggested dose is 100 mg HCQ or 125 mg chloroquine twice a week. In our cases, HCQ of 200 mg per week showed great efficacy on control of skin lesions.

Conclusion

PCT is rare and easily misdiagnosed because of atypical skin lesions at early stage. Alcohol abuse could be a valuable for clue for disease diagnosis and a less-harmful and easy accessible treatment for PCT.

Declarations

Ethics Approval and consent to participate: Not applicable.

Consent for Publication :Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Authors' contributions:Z Tang, J Ma collected the patients'information, L Wang and Z Shi drafted the manuscript. All authors read and approved the final manuscript.

Reference

1. Bulat V, Lugovic L, Situm M, Buljan M , Bradic L. Porphyria cutanea tarda as the most common porphyria. Acta Dermatovenerol Croat 2007;15:254-63.

2. Singal AK. Porphyria cutanea tarda: Recent update. Mol Genet Metab 2019;128:271-81.

3. Frank J , Poblete-Gutierrez P. Porphyria cutanea tarda–when skin meets liver. Best Pract Res Clin Gastroenterol 2010;24:735-45.

4. Mondal AK, Kumar P , Gharami RC. A baby with photosensitivity and red teeth. Indian Dermatol Online J 2013;4:260-1.

5. Ryan Caballes F, Sendi H , Bonkovsky HL. Hepatitis C, porphyria cutanea tarda and liver iron: an update. Liver Int 2012;32:880-93.

6. Pagnotta PA, Melito VA, Lavandera JV, Parera VE, Rossetti MV, Zuccoli JR et al. Role of ABCB1 and glutathione S-transferase gene variants in the association of porphyria cutanea tarda and human immunodeficiency virus infection. Biomed Rep 2021;14:22.

7. Gibson GE , McEvoy MT. Coexistence of lupus erythematosus and porphyria cutanea tarda in fifteen patients. J Am Acad Dermatol 1998;38:569-73.

8. Seubert S, Seubert A, Rumpf KW , Kiffe H. A porphyria cutanea tarda-like distribution pattern of porphyrins in plasma, hemodialysate, hemofiltrate, and urine of patients on chronic hemodialysis. J Invest Dermatol 1985;85:107-9.

9. Elder GH. Alcohol intake and porphyria cutanea tarda. Clin Dermatol 1999;17:431-6.

10. Albano E. Alcohol, oxidative stress and free radical damage. Proc Nutr Soc 2006;65:278-90.

11. Christiansen AL, Brock A, Bygum A, Rasmussen LM , Jepsen P. Increased mortality in patients with porphyria cutanea tarda-A nationwide cohort study. J Am Acad Dermatol 2020;83:817-23.

12. Vieira FM, Nakhle MC, Abrantes-Lemos CP, Cancado EL , Reis VM. Precipitating factors of porphyria cutanea tarda in Brazil with emphasis on hemochromatosis gene (HFE) mutations. Study of 60 patients. An Bras Dermatol 2013;88:530-40.

13. Kowdley KV, Brown KE, Ahn J , Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol 2019;114:1202-18.

14. Singal AK, Kormos-Hallberg C, Lee C, Sadagoparamanujam VM, Grady JJ, Freeman DH, Jr. et al. Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. Clin Gastroenterol Hepatol 2012;10:1402-9.

15. Kowertz MJ. The therapeutic effect of chloroquine. Hepatic recovery in porphyria cutanea tarda. JAMA 1973;223:515-9.

Figures and legend

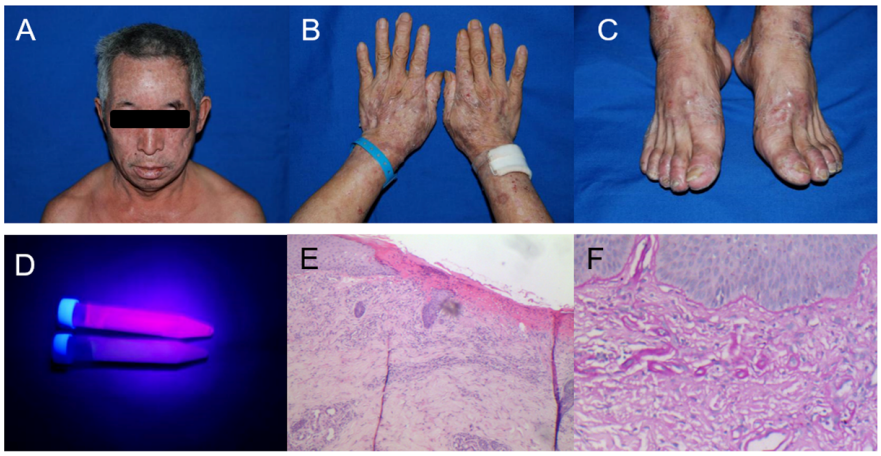

Figure 1. (A-C) Multiple tense blisters, superficial erosions with crusting and scars distributed on the face, neck, forearms, dorsum of the hands and feet. (D) Urine from patient 1 appears pink to red under Wood's lamp with ultraviolet light. (E) Histopathological manifestation revealed crust and diffuse infiltration of

histiocytes, eosinophilia and neutrophils in the dermis (magnification 10×). (F) Acid-fast staining showed cyclic blue-violet dispositions around the blood vessels (magnification 40×).

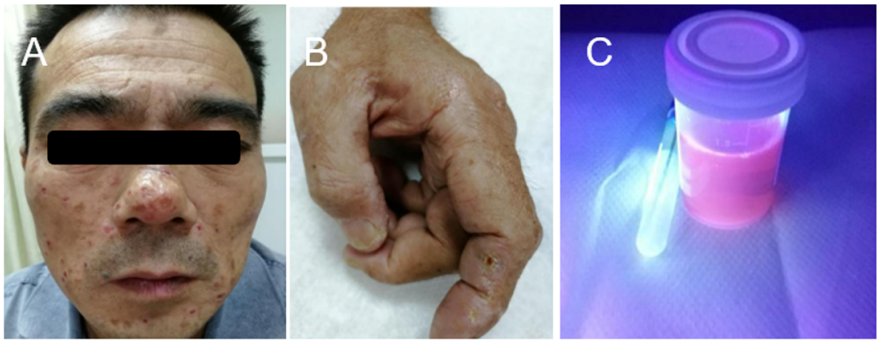

Figure 2. (A-B) Clinical photograph of lesions in case 2.(C) Urine from patient 2 appeared pink to red under Wood's lamp with ultraviolet light.

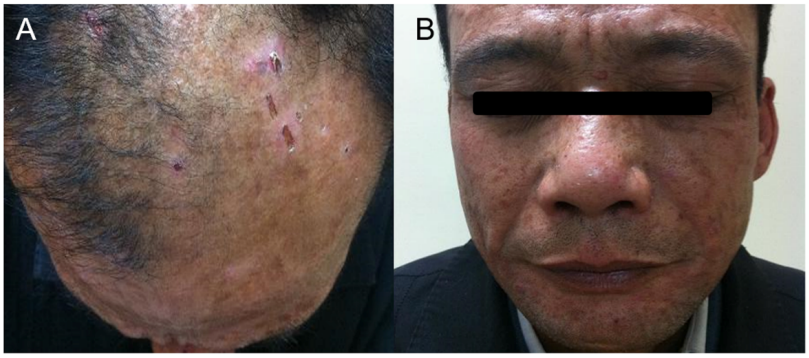

Figure 3. Clinical photograph of lesions in case 3, showing blood blisters, shallow ulcers and atrophic scars on the scalp (A) and face (B).