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CLINICAL STUDY

Porphyria cutanea tarda triggered by hepatitis-E virus

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ABSTRACT
Porphyria cutanea tarda (PCT) is the most common chronic porphyria, with approximate prevalence of 1:10,000. PCT is frequently associated with hepatitis C virus (HCV), malignant lymphoma and iron overload. Here, we present a case of PCT onset subsequent to hepatitis E virus infection (HEV), characterised by symptoms including skin fragility, haemorrhagic bullous skin exanthema, and onycholysis. The patient was successfully treated by erythrocytapheresis and hydroxychloroquine. After exclusion of other possible causes of PCT, HEV infection was identified as the likely trigger of the disease in this genetically predisposed individual, representing the first reported instance of such an association. Erythrocytapheresis emerged as a viable alternative to phlebotomy for PCT treatment. This case underscores the significance of considering HEV infection in the aetiology of PCT and highlights erythrocytapheresis as a promising therapeutic approach *(Ref. 8)*. Text in PDF www.elis.sk
KEY WORDS: hepatitis E, porphyria cutanea tarda, erythrocytapheresis, hydroxychloroquine.

Introduction

PCT stands as the most prevalent form of chronic porphyria, affecting roughly 1 in 10,000 individuals. It is caused by a deficiency in uroporphyrinogen III decarboxylase (UROD), an enzyme involved in haem synthesis. PCT manifests in two main types. Type 1 is caused by inhibition of UROD activity by extrinsic or intrinsic factors (e.g., smoking, alcohol, chemicals, viral infection, iron overload), resulting in accumulation of haem precursors and photosensitivity. Type 2 PCT is caused by autosomal dominant inherited mutation in *UROD* gene. (1) The clinical symptoms encompass blisters, skin fragility, bullae, hyperpigmentation of sun-exposed areas of the skin, dark urine, and occasionally, onycholysis. The treatment is aimed at eliminating the triggering factors, photoprotection, phlebotomy/erythrocytapheresis, along with chloroquine administration as necessary.

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Case

A 54-year-old female patient, previously diagnosed with remitting sclerosis multiplex (SM) and not undergoing any specific treatment for SM, experienced symptoms of PCT one year prior to her diagnosis. Notably, she had been diagnosed with DLBCL a year before the onset of PCT symptoms. For DLBCL, she was treated with 4 cycles of R-ESHAP (rituximab, etoposide, solumedrol, cytarabine and cisplatin) + G-CSF lipefilgrastim followed by autologous stem cell transplant (APSCT) three months prior to the onset of PCT symptoms. A subsequent control PET CT scan showed an excellent response to the therapy, showing complete morpho-metabolic remission of the DLBCL six months after APSCT, after which no further specific treatment for DLBCL was administered.

The DLBCL course was complicated by phlegmonous infection affecting the right lower extremity, which was successfully treated with a combination of antibiotics (linezolid+ meropenem) three months prior to the onset of PCT symptoms. Additionally, the patient experienced *Clostridioides difficile* colitis (CDI) which was treated by peroral vancomycin one months prior to the PCT onset.

During the treatment of DLBCL the patient's liver functions were regularly monitored, revealing only a mild elevation of GGT (peaking at 3.74 μkat/l). In March 2022, there was a rapid elevation in liver enzymes, with ALT and AST exceeding 20 times the upper normal limit (UNL). Ultrasonography ruled out biliary tree obstruction or any diffuse or solid liver lesions. Subsequent serum analysis confirmed hepatitis-E infection (HEV RNA: 1,197,500 UI/ml), following the exclusion of other potential causes of elevated liver enzymes, including hepatitis B, A or C, malignancy, drug-induced liver injury, or alcohol abuse. Remarkably, both IgM and IgA anti-HEV antibodies were consistently negative

in multiple tests, presumably due to impaired humoral immune response in the aftermath of recent APSCT.

The patient commenced supportive and symptomatic treatment for hepatitis E (silymarin at 210 mg/day and ademetionine at 1,000 mg/day). After four weeks, a spontaneous regression of both liver transaminases and viraemia was observed (ALT returning to normal limits, AST falling below 3 times the UNL, HEV RNA <500 UI/ml). The While the overall clinical status of the patient improved, persisting complains included dark urine and newly emergent symptoms of skin fragility with haemorrhagic bullous skin exanthema on the dorsal forearms, fingers, and onycholysis. Blood analysis revealed mild elevation of liver transaminases (ALT below three times UNL, AST below two times UNL), along with increased ferritin (<2,500 ug/l) and iron levels (43.1 μmol/l). Notably, HEV viraemia tested negative. The clinical presentation suggested the diagnosis of PCT, which was confirmed by elevation of total porphyrins content (>4800 ug/l) in the 24-hour urine analysis. High-performance liquid chromatography (HPLC) revealed increased 24-hour urine levels of uroporphyrin and heptacarboxyporphyrin, while aminolaevulinic acid and porphobilinogen in urine were negative. Genetic testing was performed to explore potential genetic predispositions, revealing a negative result for haemochromatosis upon *HFE* mutations analysis. However, further analysis revealed heterozygosity for the *UROD* c.616C>T gene mutation, indicating a potential risk factor for PCT development (1).

The patient received guidance on strict photoprotection and due to unavailability of chloroquine in the Czech Republic, a regimen of low-dose hydroxychloroquine (200 mg twice weekly) was initiated. However, the therapeutic response was limited. Subsequently, a single erythrocytapheresis was performed, resulting in partial regression of skin lesions. Owing to the decrease in haemoglobin levels to 109 g/l, further erythrocytapheresis sessions were not pursued. Instead, the patient continued on hydroxychloroquine at 200 mg twice weekly. Notably, clinical remission and substantial metabolic regression of PCT was achieved six months after treatment initiation. Serologically, HEV remained in sustained remission, with no signs of DLBCL relapse observed to date.

Discussion

Several factors could have influenced the PCT development in this case.

Firstly, the presence of *UROD* gene mutation predisposes patient to PCT, especially when combined with other triggering factors.

Secondly, while conflicting reports have been published regarding the association between PCT and malignant lymphoma or its treatments, including autologous and allogenic bone marrow transplants and PCT (2–5), the time gap between the patient's last chemotherapy/APSCT and the onset of PCT, coupled with substantial regression or even remission of the lymphoma suggests an unlikely (yet possible) association in this instance.

Thirdly, iron overload has been also implicated as a possible trigger for PCT. Although our patient exhibited elevated serum iron, transferrin and ferritin levels, there was no history of blood transfusion, iron supplementation or hemochromatosis, suggesting an alternative mechanism for iron overload.

Lastly, the diagnosis of hepatitis E prior to the onset of PCT symptoms raises intriguing questions about the relationship between HEV infection and PCT.

While the link between HCV infection, iron overload and PCT is documented (6), the mechanism by which HEV interacts with iron metabolism remains poorly understood (7, 8).

Despite these gaps in knowledge, given the absence of other elucidating factors, we consider HEV infection a plausible trigger for PCT in this case.

Furthermore, we highlight onycholysis as a relatively uncommon presentation of PCT and underscore the efficacy of erythrocytapheresis as an alternative to phlebotomy in the setting of haematologic malignancies.

Conclusion

This case marks the first reported instance of hepatitis E potentially triggering PCT, presenting with the uncommon symptom of onycholysis in a genetically predisposed individual. Additionally, we highlight erythrocytapheresis as a viable alternative to phlebotomy in the management of PCT. Further research is warranted to elucidate the exact mechanism by which hepatitis E impacts iron metabolism or haem synthesis.

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