The co-infection of Hepatitis C- and HIV associated with high risk of porphyria cutanea tarda: A case report and review of the literature

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ABSTRACT:

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Porphyria Cutanea Tarda (PCT) is caused by a deficiency of Uroporphyrinogen Decarboxylase (UROD). There are risk factors that promote the destruction of liver cells such as alcohol, estrogen, HIV, and hepatitis C virus. In PCT, the high levels of uroporphyrin in blood and urine are detected. In this case report, the male patient had a history of infection with hepatitis C and HIV simultaneously. His chief complaints were erythematous papules, blisters, and scars in the back of his hands. Laboratory tests revealed high levels of uroporphyrin in blood and urine. Histopathological examination showed subepidermal separation with festooning of dermal papillae. In conclusion, the presence of blisters and scars located on sun-exposed areas in the patient with history of hepatitis C and HIV infection should alert the physicians to be aware of PCT as one of the differential diagnosis.

Key words: Porphyria cutanea tarda, Hepatitis C virus, Human immunodeficiency virus

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Introduction

Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide and its prevalence is estimated to be between 1:10 000 to 1:70 000. The male-female ratio is approximately equal[1]. PCT is due to either a genetic or acquired deficiency of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme pathway. The condition can be divided according to its characteristics into four types. The sporadic form (Type 1), also named "acquired", is characterized by a decreased hepatic activity of UROD while the disease is active. The hereditary form (Type 2) is an autosomal dominant disease with genetic mutations of the UROD gene and is associated with family history. The toxic form of PCT (Type 3) is characterized by its sporadic nature. The hepatoerythropoietic form (Type 4) is caused by a homozygotic defect of UROD. However, all types of PCT have very similar clinical courses[2].

The acquired (type 1) PCT usually manifests with cutaneous signs caused by deposits of uroporphyrin and partially decarboxylated porphyrins. These porphyrin depositions cannot absorb the energy and cause damage the skin[3]. The clinical findings include photosensitivity, blisters, erosions, and milia on the sun-exposed areas of the body. In addition, hypertrichosis, hyper-hypopigmentation, sclerodermoid plaques, and scarring alopecia may also be observed[4].

The risk factors for liver damage that can induce PCT includes normal or increased amounts of hepatic iron (e.g. in hereditary hemochromatosis), HIV infection, hepatitis B or C infection, alcohol abuse, estrogen use, smoking, chlorinated polycyclic aromatic hydrocarbons, and hemodialysis.

Here we present a case of a patient diagnosed with type 1 PCT with cutaneous lesion and multiple risk factors including of HIV/AIDS, and hepatitis C infection.

Case report

A 44-year-old man presented with bullae, redness of the skin, and burning sensation at both dorsa of the hands for approximately 11 weeks. He denied any recent trauma or insect bite on the affected areas. His medical history includes being diagnosed with coinfection of HIV and hepatitis C virus (HCV) 8 years ago. He has been treated with oral HARRT therapy (the once-daily triple regimen of nevirapine 400 mg, lamivudine 300 mg and tenofovia 300 mg).

At first hospital visit, his vital signs, heart, lung and abdominal examination were within normal ranges. No hepatosplenomegaly was present. The skin examination (Figure 1A–B) revealed multiple eroded erythematous papules and some bullae with hypo- and hyper-pigmented

macules and patches over the dorsal aspect of both hands, particularly the sun-exposed areas. There was no skin lesion on the rest of his body, including the non-sun-exposed areas. Neither hypertrichosis nor peripheral lymphadenopathy was detected.

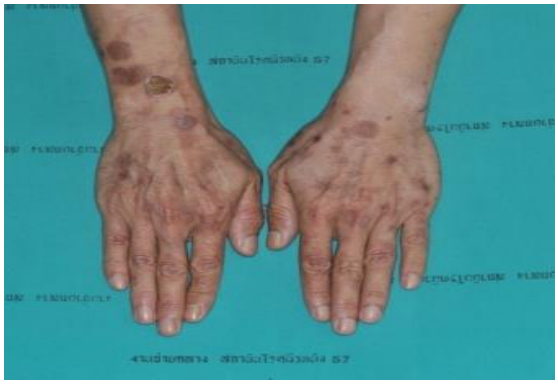

Figure 1A Skin examination: multiple erythematous papules, some bullae and hypo- and hyper-pigmented macules and patches over the dorsal aspect of both hands

Regarding his laboratory test, complete blood count was normal, with hemoglobin level of 16.5 g/dL. However, liver function showed the increased levels of aspartate aminotransferase and alanine aminotransferase of 73 and 104 IU/L respectively (normal range of both enzymes are 0-40 U/L). The increased levels of GGT (gamma glutamyl transpeptidase) to 554 U/L and alkaline phosphatase 126 U/L were also appreciated. The iron panel revealed a low serum iron of 43 mcg/dL, low transferrin of 123 mg/dL, low TIBC of 151 mcg/dL, transferrin saturation of 28%, and elevated ferritin of 989.2 ng/mL. In addition to the positive urine fluorescence test with Wood's lamp, his urine uroporphyrin 958.4 µg/day (0-50µg/day) and serum porphyrins 42.0mcq/L (1.0-5.6 mcq/L) were also elevated.

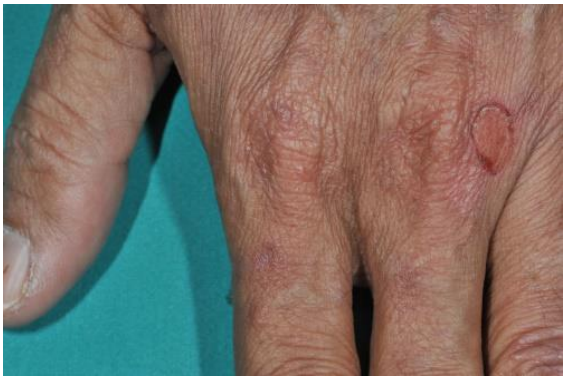

Figure 1B Solitary, well-defined, eroded, erythematous patch on dorsum of hand

His recent status of HIV/AIDS and hepatitis C co-infection was monitored by the following tests. Positive HIV by Western blot test with absolute CD4 count of 459 cells/µL and absolute CD8 count of 158 cells/µL. Anti HCV antibody was reactive. There are several differential diagnoses for his clinical manifestation but, given the characteristic cutaneous lesions and abnormal serum and urine porphyrin levels, PCT is at the top of the list. Other lab tests including, ANA, anti BMZ IgG and IgM antibody, indirect immunofluorescence for circulating anti-intercellular IgG antibody and

anti-basement membrane zone antibody were all negative. Unfortunately, a genetic mutation of UROD was not performed in this case. Due to the classic cutaneous lesion, positive associated risk factors, and abnormality of the above laboratory tests, therefore, the diagnosis of PCT was confirmed. His clinical setting is most likely to be classified as the sporadic form of PCT (type 1).

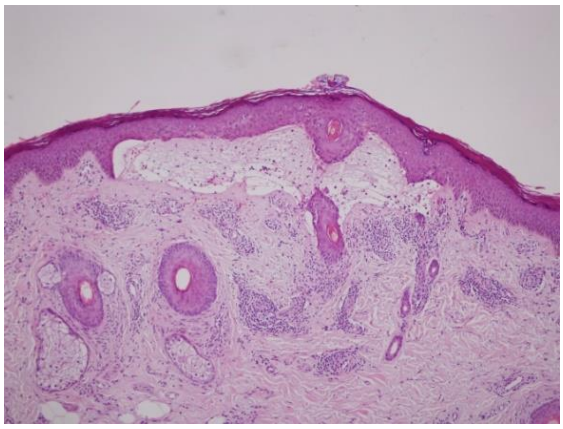

Figure 2A Histological features. Subepidermal blister of acral skin with minimal dermal inflammatory infiltrate. Festooning of the dermal papillae is seen

Histopathological study from his left index was also consistent with the diagnosis of PCT. The skin specimen showed a sub-epidermal blister with festooning dermal papillae and minimal inflammatory perivascular lymphocytic and eosinophilic infiltration in the dermis (Figure 2A). On PAS-diastase stain, the PAS positive basement membrane zone was observed at the floor of the blister as well as in the walls of upper dermal capillaries. Direct immunofluorescence revealed positive C3, IgA and IgM at blood vessel walls and fibrinogen. IgG was positive at dermoepidermal junction (Figure 2B).

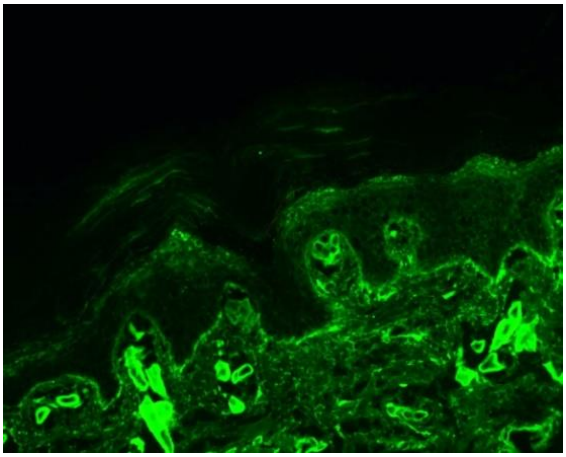

Figure 2B DIF show positive C3, IgA and IgM at blood vessel walls and fibrinogen. IgG was positive at dermoepidermal junction

Discussion

The skin lesion of PCT results from decreased activity of hepatic uroporphyrinogen decarboxylase (UROD). Porphyrins were deposited in various tissues over the body. In the skin, porphyrins are excited by sunlight and the energy was initiated by photochemical reactions so it can cause skin damage.

Porphyria cutanea tarda is usually suspected on clinical grounds and the diagnosis is

confirmed by the characteristic urinary porphyrin excretion profile. Although the dermatological manifestations of PCT and variegate porphyria are similar, our patient informed no suggestive symptoms of porphyia in family or past history of periodic neurological and gastrointestinal attacks which might present in some cases of a rare-typed variegate porphyria. Therefore, we exclude variegate porphyria (VP) from the list of the clinical differential diagnoses. However, determination of the wavelength of the fluorescence peak of plasma porphyrins and molecular genetic testing to identify associated-gene mutation are useful in differentiating PCT from VP. The plasma in VP contains porphyrin covalently bound to protein with a fluorescence emission maximum at 624–626 nm.[5] while PCT gives different fluorescence emission peak at 618-622 nm[6]. There is an increased prevalence of mutations in the C282Y hemochromatosis (HFE) gene in individuals with familial PCT whereas many different enzyme protoporphyrinogen oxidase gene (PPOX) mutations have been identified in different families with VP.

The association of PCT to HIV infection and HARRT therapy is well recognized[7], although not completely understood. It is believed that HIV might interfere with the porphyrin metabolism and the function are the cytochrome P450. Celesia BM et al. reported the onset of porphyria cutanea tarda in HIV-infected patients after initiation of tipranavir/ritonavir. After withdrawal of these drugs with proper photoprotection, remission was observed[8]

Both physician and public should be alert to the association between hepatitis C virus (HCV), HIV and PCT and beware of hepatocellular carcinoma transformation in this health problem[9,10]. It is believed that chronic HCV infection impair porphyrin metabolism through a reduction of glutathione in hepatocytes causing the accumulation of oxidized uroporphyrins which in turn exerts an inhibitory effect on *UROD*[11]. Gisbert et al found that the prevalence of PCT among HCV-infected patients has been reported at 1–5%[12]. HIV and HCV co-infection appears to be significantly associated with elevated serum porphyrins. Because both infections share the same mode of transmission, so the patient with HIV infection presented with cutaneous manifestation of PCT should be promptly investigated for hepatitis serology profile. There were several publications on PCT with HIV and HCV co- infection as were summarized in Table 1

Well-documented evidence as shown in Table 1 highlights the higher risk of PCT development in a person with HIV and HCV co-infection than an individual infected by HIV or HCV alone.

Table 1 Review publications on HIV and HCV infections as risk factors in porphyria cutanea tarda

Author (ref.)	Country	Methodology	Participant	Gene mutation	Type of PCT	Result
Quansah et al,[1]	USA	Case report	n=1, male. Alcohol and heroin abuse, CMV retinitis	Genetic mutation of UROD: -ve	Type 1	Strong correlation between HCV and PCT
Nagy et al, [2]	Hungary	Descriptive study	n=50,	C282Y and H63D Hemochromatosis (HFE) gene mutations: +ve	Type 1	Presence of *HEF* gene mutation and HCV infection are the risk factors for PCT
Bernardes et al,[3]	Brazil	Case report	n=3,male , on HAART therapy	-none	Type 1	HIV is a risk factor for PCT
O'Connor et al,[7]	Canada	Case report	n=2, male, drug and alcohol abuse with opportunistic infection	None	Type 1	HIV and HCV co - infection is a risk factor for PCT
Celesia et al,[8]	Italy	Case report	n=6 on tipranavir/ritonavir	None	Type1	Protease inhibitor (tipranavir/ritonavir) is a risk factor for PCT
Egger et al, [9]	USA	Observational study	n=39, male and female alcohol, smoking estrogen use	C282Y and H63D Hemochromatosis (HFE) gene mutations: +ve	Type 1 and 2	Multifactors i.e. alcohol, smoking, HCV, estrogen, HFE mutation (C282Y, 63D), are the risk factors for PCT.
Murphy et at,[10]	USA	Case report	n=6, HIV -ve	None	Type 1	HBV, HCV infection are the risk factors for PCT.
Lacour et al,[11]	France	Descriptive study,prevalence of hepatitis C virus antibodies	n=13,	None	Type 1	HCV is a risk factor for PCT
Gisbert et al,[12]	Spain	Systemic review and meta-analysis Study of the prevalence of hepatitis C virus in PCT cases	n=2,167	None	Type1 and Type 2	HCV and genetic and/or environmental factors are the risk factors for PCT

Treatment of PCT consists of iron depletion, elimination of porphyrins and avoidance of trigger factors (i.e. alcohol abuse, estrogen intake and sunlight exposure). The following treatments are mainly recommended, namely phlebotomy and weekly-low-dose of chloroquine by which complete remission can be expected in 6 to 9 months.

Conclusion

On the one hand, a diagnosis of PCT, especially in a young patient, should alert a physician to promptly investigate for the underlying HIV and HCV infection. On the other hand, blistering on the skin in a HIV and/or HCV infected individual with photosensitivity should remind a physician of PCT as one of the differential diagnoses. Abnormal porphyrin profile that is commonly found in these infections may contribute to the clinical manifestations of PCT. Both HIV and HCV have been isolated from the blister in infected patients with PCT and their transmission is also considered as a potential health risk, therefore, skin lesions of PCT can be an important warning sign of infectious risk from these patients.

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