PORPHYRIA CUTANEA TARDA (PCT), HEMODIALYSIS AND HEPATITIS C: AN OPEN CHALLENGE FOR DIAGNOSIS AND TREATMENT

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INTRODUCTION AND AIMS: Porphyrias are a heterogeneous group of inherited or acquired metabolic disorders, all of which result from partial deficiencies in the activity of enzymes regulating heme biosynthesis (Fig.1).

Porphyria cutanea tarda (PCT), the most common type of porhyria worldwide, manifests itself when hepatic uroporphyrinogen decarboxylase activity is less than 30% of normal, resulting in accumulation of uroporphyrins in the skin and liver. Two forms of PCT are identified: Type I (sporadic) (75%) and Type II (familial) (25%) with total prevalence 1:10.000. PCT has been observed in 1,2-18% of patients with renal failure, undergoing chronic peritoneal dialysis or hemodyalisis [1, 2]. A strong association between PCT and HCV has been reported: among patients with PCT, 50% of HCV RNA positivity and 275-fold increased risk of HCV, but PCT is only 1-5% of HCV population overall [3, 4, 5].

Three possible mechanisms are involved: 1) a decreased or absent activity of uroporphyrinogen decarboxylase, 2) an increase in activity of hepatic 5-aminolevulinic acid synthase (rate-limiting enzyme of heme synthesis), 3) an increase in the rate of tendency of uroporphyrinogen to be oxidized to uroporphomethene (prevalent in sporadic PCT with hepatitis C).

Porphyrins absorb light in the UV range, enter into an excited energy state, energy is released as fluorescence by the formation of singlet oxygen producing tissue damage.

METHODS: We report the case of PCT in HD patient affected with hepatitis C, characterized by the severity of cutaneous signs in which focused treatment is also a conflicting challenge.

RESULTS: A 76-year-old Caucasian man with end-stage renal failure.

At 25: relapsing calcium nephrolithiasis of right kidney.

At 29: appearance of diffuse plaque psoriasis, treated with topical drugs and oral cyclosporine. Ureteropelvic junction stenosis, complicated with acute pyelonephritis requiring unilateral nephrectomy.

At 54: post-transfusion HCV infection.

At 56: episode of anuric acute kidney failure by left uretheral stone with partial rescue of renal function after DJ catheter insertion.

At 73: start of thrice-weekly hemodyalisis after a vascular access setting.

Over the course of one year, he complained of painful skin rash on sun-exposed areas. On examination, he was found to have multiple, tense bullae filled with amber or yellow fluid on dorsal aspect of both hands, face, auricles and scalp, some of which had ruptured causing erosions, photosensitivity, pruritic scarring and milia (small whitish papules). Laboratory investigations: mild anemia (Hb 8,2 g/dL), serum ferritin 152 µg/L transferrin saturation 25%; normal white blood cells, platelets, AST, ALT. GGT , C-reactive protein. Serological tests: HCV-RNA positive (96.956 UI/mL) (genotype 1b); HBV and HIV negative; increased levels of total plasma porphyrin (270 µg/L, nv<4), plasma erythrocyte protoporphyrin (1813 µg/L, nv<800), total urine uroporphyrin (61 µg/24 h, nv<50) and urine coproporphyrin (196 µg/24 h, nv<100). The fluorescence emission spectroscopy of plasma revealed an emission peak at 621 nm, typical for PCT. The sequence analysis identified no mutations on the uroporphyrinogen decarboxylase gene (sporadic PCT). Shear wave elastography revealed no liver fibrosis (F0, METAVIR score) (elasticity value: 4,53 kPa).

Biopsy on skin blister revealed a necrotic-inflammatory bottom, irregular hyperplasia and parakeratosis as initial lichenification. IF: negative. In front of a combined Kt/V >1,4, a residual urine output > 1,0 L/day, erythropoietin treatment (10000 UI/week) and withdrawal/avoidance of iron administration, the lesions had worsened and spread over the past two years. Beyond unsuccessful topical corticosteroids (fluocinonide), repeated phlebotomies were unacceptable in our anemic patient.

CONCLUSIONS: The uncommon concurrence of PTC, HCV-infection and renal failure in the same patient requiring hemodialysis implies a troublesome challenge.

In our patient, apart the strict avoidance of exacerbating factors (sun exposure, alcohol, estrogen), phlebotomy is unsuitable in uremic anemia, antimalarials are contraindicated in psoriasis, HD with high flux membranes remains unable to resolve PCT lesions [6].

Now all-oral direct-acting antivirals (DAA) have changed the HCV treatment landscape. There is limited literature on the efficacy of DAA (boceprevir, ledipasvir, sofosbuvir) in patients with PCT and normal renal function regarding the improvement of skin lesions and reduction of plasma porphyrins, after reaching undetectable viremia (sustained virologic response) [7, 8, 9, 10, 11].

While DAA treatment has not been thoroughly evaluated in the HCV-positive uremic population, these patients should be offered treatment, in consideration of the fact that PCT adds further risk of developing hepatocellular carcinoma.

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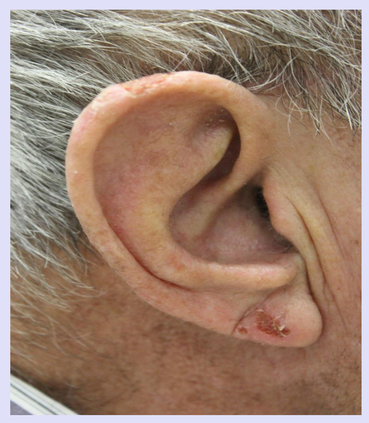
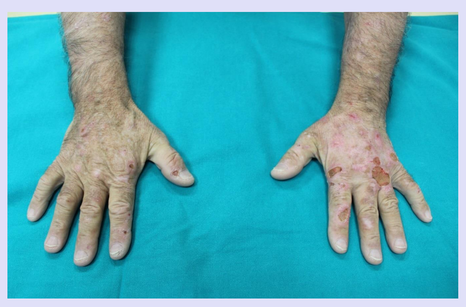




	RESULT	REFERENCE
Haemoglobin	82 g/L	12,0-15,5 g/L
WBC count	5270 x 103/µL	3,90-10.20 x 103µL
Platelet count	155 x 103/µL	150-370 x 103µL/
C-reactive protein	6,1 mg/L	<5,0 mg/L
Transferrin saturation	25%	> 30%
Ferritin	152 ng/mL	11-307 ng/ml
ALT	11 U/L	0-35 U/L
AST	22 U/L	0-35 U/L
GGT	55 U/L	10-45 U/L
Creatinine	9.2 mg/dL	0.5-1,0 mg/dL
BUN	55 mg/dL	10-25 mg/dL
Erythrocyte aminolevulinic acid (ALA) dehydratase	25,91 U/L	25-70 U/L
Plasma porphyrin fluorescent assay	**1 (peak: 621 nm)**	0= NEG,1= POS
Total plasma porphyrin	**270 µg/L**	<4 µg/L
Erythrocyte protoporphyrin	**1813 µg/L**	<800 µg/L
Urine aminolevulinic acid (ALA)	0,88 mg/g creat	<4,5 mg/g creat
Urine coprophorphyrin	**196 µg/g creat**	<100 µg/g creat
Total urine porphyrin	130 µg/24 h	<150 µg/24 h
Urine porphobilinogen	1,01 mg/g creat	<1,7 mg/g creat
Urine uroporphyrin	**61 µg/24 h**	<50 µg/24 h
Total fecal porphyrin	43,83 nmol/g dry weight	<200 nmol/g
HCV-RNA	**96.956 UI/mL (genotype 1b)**	
HBV-DNA	Negative	
HIV-RNA	Negative	

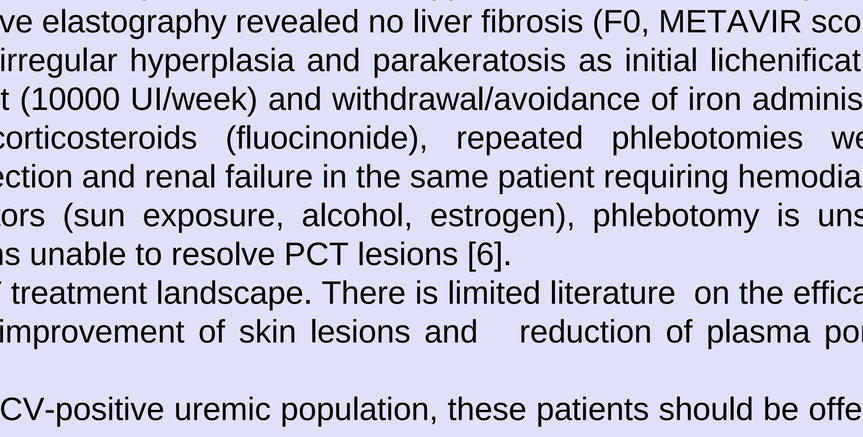
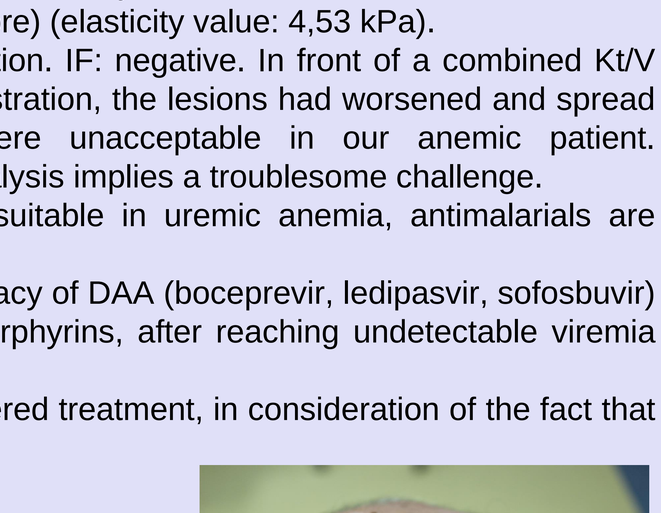
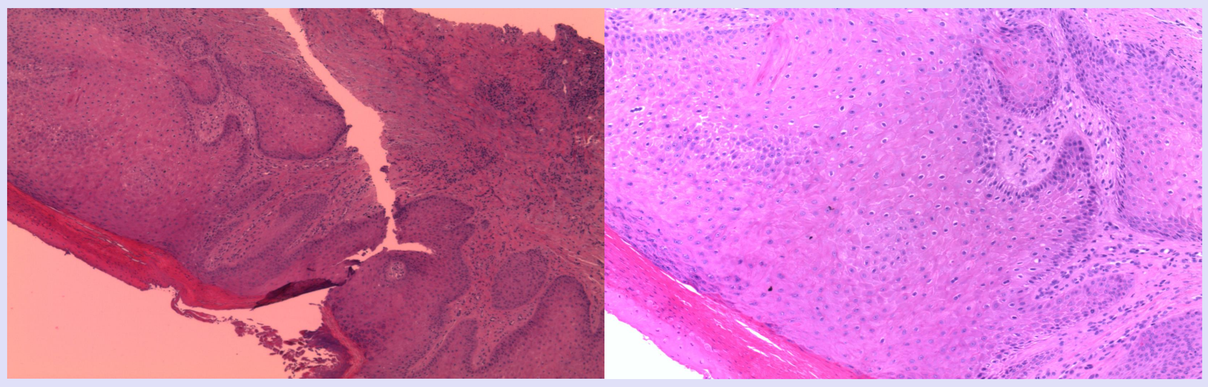


Figure 1: **Haem biosynthetic pathway and porphyrias**
Green boxes=hepatic porphyrias. Red boxes=erythropoietic porphyrias. ALA=5-aminolaevulinic acid. PBG=porphobilinogen. I, III, or IX=type isomers. ALAS=ALA-synthase. ALAD=ALA-dehydratase. PBGD=porphobilinogen deaminase. UROIIIS=uroporphyrinogen III synthase. UROD=uroporphyrinogen decarboxylase. CPO=coproporphyrinogen oxidase. PPOX=protoporphyrinogen oxidase. FECH=ferrochelatase. Fe^{2+}=ferrous iron.

[Source: Puy H, Gouya l, Deybach JC. Porphyrias. Lancet 2010;375(9718):924-37].



Fluorescence emission scan (excitation at 405 nm) of diluted plasma. Maximal fluorescence at 621 nm.



Edge of aspecific ulcer of scalp: straight profile of bottom, covered by necrotic inflammatory debris; no upper limit of blister. Epidermis lining theedge with parakeratosis and irregualar hyperplasia by initial lichenification of tissue (H&E, x10). Detail: epidermis: compact hyper-parakeratosis, minimal spongiosis, impressive irregular acanthosis. Dermis: fibrosis, a few perivascular lymphocytes (H&E, x20).

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