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Porphyria cutanea tarda — a case report of severe course of disease in a female with alcohol addiction

Porfiria skórna późna — opis przypadku ciężkiego przebiegu choroby u kobiety uzależnionej od alkoholu

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ABSTRACT

Porphyria cutanea tarda (PCT) belongs to the group of diseases with an increased incidence in the population of alcohol addicted people. Ethanol consumption has an influence on porphiryn metabolism which leads to disturbance in regulation of heme synthesis enzymes as well as direct damage of hepatocytes.

Porphyria is a disease which involves disturbance of hepatic heme synthesis enzymes. In the course of the PCT, porphyrines are accumulated in the skin and excreted with urine. The skin lesions occur during porphyrin disintegration caused by UV light. The clinical presentation of PCT is non-inflammatory blisters, occasionally accompanied by hemorrhage and eschar. Chronic skin damage may result in scarring and changes in pigmentation at the sites of blisters and milia. Other clinical symptoms include: arthritic pain of upper and lower extremities, dizziness, tinnitus, abdominal pain and sudden death.

We present extremely severe case of PCT in female, which was induced by sun exposure, hormone replacement therapy and alcohol intake.

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Key words: alcohol, PCT, porphyria cutanea tarda, hormonal replacement therapy

STRESZCZENIE

Porfiria skórna późna (PCT, *porphyria cutanea tarda*) należy do grupy chorób, których częstość występowania jest zwiększona u osób nadużywających alkoholu. Spożycie etanolu wpływa na metabolizm porfiryn, co prowadzi do zaburzeń regulacji enzymów biorących udział w syntezie hemu oraz bezpośrednio uszkadza hepatocyty. Porfiria jest chorobą związaną z zaburzeniem działania enzymów syntezy hemu w hepatocytach. W przebiegu PCT porfiryny są akumulowane w skórze, a także wydalane z moczem. Zmiany skórne pojawiają się podczas rozpadu porfiryn spowodowanego oddziaływaniem promieniowania UV. Do obrazu klinicznego PCT zalicza się: niezapalne pęcherze z towarzyszącym krwawieniem i strupami, ból stawów kończyn górnych i dolnych, zawroty głowy, szumy uszne, dolegliwości bólowe brzucha oraz nagłą śmierć. Przewlekłe uszkodzenie skóry doprowadza do bliznowacenia oraz zaburzeń pigmentacji. W niniejszej pracy zaprezentowano niezwykle ciężki przypadek PCT indukowany ekspozycją słoneczną, stosowaniem hormonalnej terapii zastępczej oraz nadużywaniem alkoholu.

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Słowa kluczowe: alkohol, PCT, porfiria skórna późna, hormonalna terapia zastępcza

INTRODUCTION

The use of alcoholic beverages has been an integral part of many cultures for thousands of years. As shown by the most recent WHO data, globally, individuals above 15 years of age drink on average 6.2 litres of pure alcohol per year. The highest consumption levels continue to be found in the developed world, in particular in Eastern Europe and Northern Asia [1]. The harmful use of alcohol is a causal factor in more than 200 diseases and injury conditions [1].

The skin lesions seen in ethanol dependant individuals can be an early symptom of alcohol dependence. The most common skin lesions associated with ethanol usage are: icterus, pruritus, hyperpigmentation, telangiectasias, capillary hemangiomas, caput medusa as well as palmar erythema. Furthermore, there are diseases that have been suggestive of alcohol dependence such as: recurrent bacterial skin infections, psoriasis, porphyria cutanea tarda (PCT), skin

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granulomas, neoplasms of nasopharyngeal, liver, pancreas and skin [2].

PTC is a rare and very disfiguring disease which can be induced by ethanol [2]. Influence of ethanol on metabolism of the hepatocytes leads to accumulation of the photosensitive porphyrines in the skin. Authors' main goal is to educate caregivers of the alcohol dependent people about PCT. This is particularly important given the alarming data from the WHO report.

The porphyrias are a collection of enzyme deficiencies which lead to disturbance of heme production. PCT is the most common form of the porphyrias. The incidence of a disease is different in each region of the world. In Argentine and the United States of America it is 1:25000, while in Sweden and Norway it is 1:10000 [3, 4]. It is claimed that Caucasian people are more vulnerable than others [5].

The disease is further divided into two subtypes: acquired and congenital. Type II PCT is inherited in an autosomal dominant mode. The defect leads to a reduction in the activity of uroporphyrinogen decarboxylase in all tissues [6].

First symptoms appear in sporadic form between the 40–70th year of life. It is associated with liver damage which leads to uroporphyrinogen decarboxylase synthesis disturbance. Among factors that have been reported are: alcohol [3, 5, 7], drugs with estrogen-like potency, spironolactone, tamoxifen, highly active antiretroviral therapy and digoxin [3, 5, 7–10]. Autoimmune disorders and viruses such as HCV have also been associated with PCT [7, 11, 12].

The clinical presentation of PCT is non-inflammatory blisters, sometimes accompanied by hemorrhage and eschar. Chronic skin damage may result in scarring and changes in pigmentation at the sites of blisters and milia. There is also an increase in the fragility of the skin, hirsutism and even scleroderma. Other clinical symptoms include arthritic pain of upper and lower extremities, dizziness, tinnitus, abdominal pain and sudden death [13, 14].

CASE DESCRIPTION

A 56-year-old Caucasian female presented to the Clinic of Dermatology in May 2013 with mucosal and skin changes located on hand, face, neck and limbs (Fig. 1, 2). Seven weeks prior to hospitalization inflamed skin lesions were visible on the nasal mucosa and the nasal bridge. Later, hemorrhagic erosions appeared on the chest, limbs and on the dorsal aspect of the hands. These changes were later covered by eschar. Additionally pruritus and oedema of the face and limbs were present. The patient suffered from severe arthritis, dizziness and unilateral tinnitus. Past medical history included hypertension diagnosed 6 years earlier, suspicion of glucose intolerance, hypercholesterolemia. Additionally, the patient had hysterectomy at the age of 43 due to

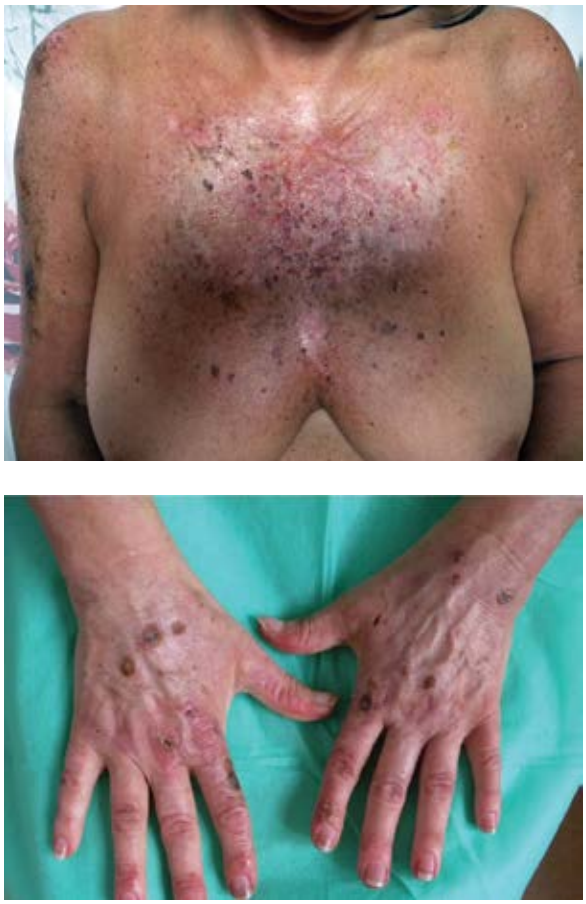

Figure 1. Skin lesions typical of PCT which are present at the beginning of therapy in the Clinic. Necrotic tissues covered by hemorrhagic scabs were observed

fibroids. The preexisting medication included metformin, indapamide, simvastatin, aspirin, pantoprazole, estradiol.

Laboratory tests revealed hypokalemia, hyponatremia, low RBC count (3.35 T/L), macrocytic anemia (Hb: 10,7 g/dL; MCV: 104 fL), decreased hematocrit (31.0 %), hypoalbuminemia (33.4 g/L), decreased APTT, increased fibrinogen, leukocytosis (13.66 G/L) and a slight rise in C Reactive Protein (CRP levels 26.6 mg/dL). The renal, liver and iron studies were normal. Ultrasonographic imaging of the left kidney demonstrated the presence of a single layer of parenchymal fibrosis in hyperechogenic bands, presumably inflammatory changes. Chest X-ray was normal. At this point, all previous medications were discontinued, including the anti-hypertensives.

Before admission to the Clinic, patient was treated as an acute solar urticaria without effect.

Prior to the onset of the symptoms the patient had sun exposure as well as an alcohol abuse episode that lasted for about a week. Contact with the patient was difficult, she was demanding and very irritable. During hospitalization,

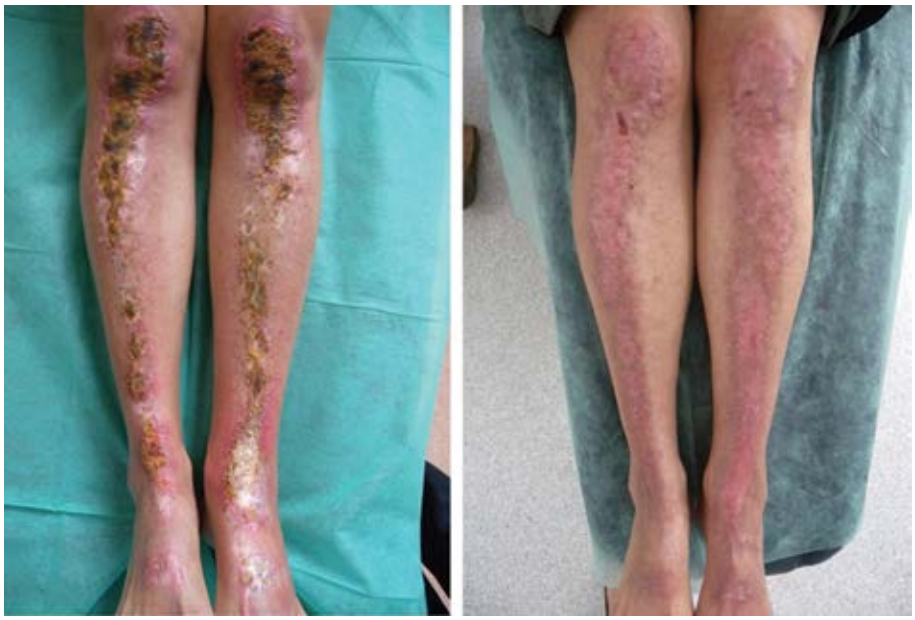

Figure 2. Skin status before as well as after the treatment. Massive necrotic skin lesions covered by scabs. Irreversible scars and hyperpigmentations of the skin in the area of shins

the patient did not agree to psychiatric consultation. The information about patient's alcohol abuse was given by her family. There was no presence of withdrawal symptoms during hospitalization in the Clinic.

Alcohol consumption and estrogens were responsible for enzyme deficiency, UV exposition due to presence of skin lesion.

Diagnosis of PCT was based on the result of clinical examination, histopathological findings as well as a laboratory studies specific to porphyrias [15].

Laboratory studies specific to porphyrias showed increased uroporphyrin, porphyrin and coproporphyrin in the urine. The levels of porphyrin 6-COOH, 5-COOH, Delta-aminolevulinic acid and porphobilinogen were within normal ranges. The porphyrin fluorescent spectrum test of the plasma was normal.

The histopathological examination of the skin showed typical PCT changes [15]. Epidermis was described as smooth and slightly thickened. There was also the evidence of homogenization of the basal epidermis, slight increase in dermal vascularity surrounded by sparse inflammatory infiltration. Immunological studies of the deposits around the vessels showed the presence of IgA, IgM and C3c in the walls of superficial vascular plexuses.

Further diagnostics included exclusion of vasculitis, SLA and scleroderma. The petechial changes on the chest and limbs along with the mucosal erosions led to immunological testing to rule out vasculitis and systemic lupus erythematosus. The results were as follows: Anti-p/Nuclear Hep2 ANA 1:160, PM-Scl positive and anti-p granulocyte, ANCA, cryoglobulins and circulating immune complexes C1q and C3d were negative. Consultation with a laryngologist excluded granulomatous disease. HCV infection was excluded in laboratory tests. Patient was vaccinated against HBV.

There was no history of smoking, usage of causative drugs, except for estrogens.

Treatment with hydroxychloroquine 200 mg daily was started with further reduction of dose to 200 mg twice a week after clinical improvement. After gynecological consultation, the patient was allowed to resume treatment with estradiol. The patient was encouraged to begin the proper therapy. Moreover, avoidance of UV exposure was emphasized. Additional treatment included: cetirizine, hydroxyzine, duloxetine and topical treatment: steroid ointment, mupirocinum 2%, chloramphenicol, octenidine, Cicalfate (Avene Thermal Spring Water, caprylic; mineral oil; zinc oxide; aluminium sucrose octasulfate; aluminium stearate; beeswax; copper sulfate; magnesium stearate). Despite the intensive treatment the heeling of the skin lesions, especially those located on the limbs, was very slow. The patient also received diaminodiphenyl sulfone 500 mg, pentoxifylline 0.1–0.3 g, amoxicillin with clavulanic acid 1.2 GX3 i.v. and vitamin B12 1000 mcg i.m. to intensify the treatment.

After worsening of anemia symptoms, a hematological consultation was conducted. A thorough anemia diagnosis was made and it revealed low cobalamin levels. The hematologist added prednisone 25 mg and folic acid 15 mg daily for the macrocytic anemia.

With the additional treatment there was a normalization of the morphological parameters in the blood count. The cutaneous lesions gradually disappeared, no formation of new lesions was observed (Fig. 2). The treatment with Hydroxychloroquine was finalized after 6 months. Unfortunately, severe scarring was seen after complete wound healing.

DISCUSSION

Our patient report is an example of multiple inducing factors that revealed an acquired form of porphyria cutanea tarda.

Alcohol is metabolized in hepatic microsomal oxidizing system and ethanol consumption has an influence on porphiryn metabolism [16]. It leads to disturbance in the regulation of heme synthesis enzymes as well as direct hepatocyte damage. Those factors can trigger acute or chronic hepatic disease [16]. Disturbances in oxidation-reduction reactions are present in alcohol elimination process. It is acknowledged as a main liver damaging factor [17].

The most common susceptibility factor for PCT is ethanol use. It was revealed in Jalil cohort study in 2010 that in the group of 143 patients alcohol consumption was observed in 87% of cases [5]. Results of the research prepared in Wroclaw, Poland showed that ethanol usage and HCV infection were two main PCT etiological factors [14]. Primarily, it was claimed that fully symptomatic PCT appears only in heavy drinkers. Later, it was revealed that regular consumption of even small amount of alcohol can lead to the manifestation of PCT [18]. Alcohol interacts with heme production enzymes in healthy people and those with biochemical and clinical symptoms of porphyria. After alcohol consumption, in patients with asymptomatic coproporphyrinuria, it can become constitutive while alcohol liver damage will be present. Ethanol is able to convert asymptomatic coproporphyrinuria into fully symptomatic PCT [16].

Alcohol is the most important inducing and aggravating factor of PCT [5, 16]. Alcohol abstinence must be included into patient's treatment plan. It can be a cause of long and turbulent course of the disease as in the above mentioned case. In the study by Jalil, most patients (90%) had 2 or more susceptibility factors [5]. For that reason it is important to ask patients about all probable triggering factors.

Estrogen therapy is the predominant risk factor in women (oral contraception pills and hormone replacement therapy). It has been stated that estrogen therapy may provoke PCT in up to 40% of women with acquired PCT [15]. The estrogens intake was present in 71% of patients researched by Jalil [5]. Our patient was under estrogen therapy due to the previous hysterectomy.

Skin changes that appeared after a week of intensive sun exposure were the main reason why the patient was seeking medical help [2].

There are two standard therapies of PCT: phlebotomy 400–500 mL every 2 weeks until serum ferritin levels fall to 20 ng/mL or a low-dose antimalarial therapy. A drug typically used is hydroxychloroquine — 100 mg twice a week or chloroquine 125 mg twice a week [19]. According to the current guidelines, the patient was treated with anti-malarial drugs. The treatment of PCT additionally consists in avoidance of triggering factors.

In randomized controlled trials, it was proved that hydroxychloroquine is as effective as phlebotomy in the treatment of a group of 48 patients. About 6 months of therapy were needed to receive a good response. There was no significant difference in efficacy between phlebotomy therapy and hydroxychloroquine. Using antimalarial drugs has better compliance among patients, is cheaper and has lower risk of hepatitis and HIV infection [20]. Antimalarial drug therapy was chosen for our patient because of the presence of anemia, good influence on insulin resistance and high compliance of the treatment.

There are some novel methods of treatment of PCT. It is reported that refractory blisters can be successfully treated with pimecrolimus as an adjuvant to hydroxychloroquine [21]. Anemia may preclude phlebotomy. Iron chelating agents as Desferrioxamine and Deferasirox can be used as an alternative to phlebotomy [22, 23]. There was a good result of hydroxychloroquine treatment.

CONCLUSIONS

It is important to consider PCT in differentiation diagnosis of the skin lesions in group of alcohol usage patients. Only early medical intervention can prevent long term treatment and disfiguration.

Diagnosis of PCT should obligate doctor to ask questions about amount of alcohol intake and signs of addiction.

Presence of PCT can be the first symptom of liver damage [18].

Every diagnosed case of PCT should be carefully examined for coexisting risk factors such as cirrhosis hepatis and/or liver cancer [24].

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