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Porphyria Cutanea Tarda – a Case Report

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Abstract

Porphyria cutanea tarda is a metabolic disorder that results from a reduced enzymatic activity of uroporphyrinogen decarboxylase. It is the commonest chronic porphyria. Two types of this disease have been reported up to now: acquired (Type 1, 80%) and inherited (Type 2, 20%) an autosomal dominant pattern with low clinical penetrance. Both types are associated with haemochromatosis, alcohol abuse, estrogens, iron overload, hepatitis C virus infection, and halogenated aromatic hydrocarbons causing deficiency of the uroporphyrinogen decarboxylase enzyme in the liver.
In this case report we described a 23-year-old woman with increased hair growth on the face and neck, who visited an outpatient dermatology clinic for laser hair removal due to excessive hair growth on the face and neck during the last eight years (Figures 1, 2). Four laser treatments were carried out with incomplete effects. After the fourth laser hair removal treatment, a small sore on the tip of the nose was observed. The patient used oral contraceptive pills during the past 8 months. No additional medications were taken. The diagnosis of porphyria cutanea tarda was confirmed by specific biochemical analyses, since increased excretion of uroporphyrin and coproporphyrin were detected. After discontinuation of drospirenone and ethinyl estradiol (YazÒ tablets) a gradual clinical and laboratory improvement was noticed suggesting a causative role of this drug. There are many published reports discussing and describing estrogens as contraceptive agents, hormone supplements for postmenopausal replacement therapy in females, and adjunctive hormonal therapy in males with prostatic carcinoma, being the probable trigger of porphyria cutanea tarda. However, the mechanisms by which estrogens exert their effects on disease expression have not yet been fully clarified. Conclusion: this case report points to the importance of hypertrichosis as the first manifestation of porphyria cutanea tarda, since it may be a long lasting sign before the onset of other clinical symptoms of the disese.

Key words

Porphyrias; Estrogens + adverse effects; Hypertrichosis; Hair Removal; Antimalarials

Porphyrias are a group of clinically and genetically heterogeneous metabolic disorders that result from either an inherited or an acquired dysfunction of enzymes crucial for heme biosynthesis (1). Porphyria cutanea tarda (PCT) is the most common type of porphyria worldwide and its prevalence is estimated to be 1:10.000 with an equal sex ratio. Age of onset is usually around the ages of 30-40, not before puberty (2). There are at least two clinically similar forms that can currently be distinguished, both associated with decreased activity of uroporphyrinogen decarboxylase (UROD) enzyme in the liver: acquired-sporadic form (PCT type 1, 80%), and hereditary PCT (type 2, 20%), also referred to as familial form (3, 4). A high degree of molecular heterogeneity has been documented in familial PCT, since more than 105 different mutations in the UROD gene (mapped to chromosomal region 1p34) have been identified in patients with type 2 PCT (5). However, the rising incidence of PCT in females is probably due to

widespread use of estrogens in oral contraceptives as well as in other hormone supplements (6).

The disease was first recognized in the 1930s, by Waldenström, who identified a group of patients with excessive porphyrins in urine, skin lesions on sun exposed areas and a late ("tarda") onset in adulthood, so he named the disease "porphyria cutanea tarda" (7). The disease is characterized by skin photosensitivity with blistering on sun-exposed areas, skin fragility, hyperpigmentation or hypopigmentation and hypertrichosis (8).

Case report

We present a 23-year-old female patient who visited an outpatient dermatology clinic for laser hair removal due to excessive hair growth on the face and neck during the last eight years (Figures 1, 2). Four laser treatments were carried out with incomplete effects, and during the fifth visit, a sore was observed on the tip of the nose. After additional examination, the patient explained that she developed repeated blisters on the face and hands which healed spontaneously leaving scars at the age of 7 and 19, usually after prolonged sun exposure (Figures 3, 4). At the age of 15, she noticed excessive hair growth on the face and neck and darker urine. The patient was using combined oral contraceptives containing drospirenone and ethinyl estradiol (Yaz$^{©}$) during the last eight months before hospitalization. Also, during the last two years before admission to our clinic, the patient was observed by a gastroenterologist due to occasional dull pain in the upper abdomen and triple elevated serum transaminaze levels, higher urine and serum copper and ferritin levels. Abdominal

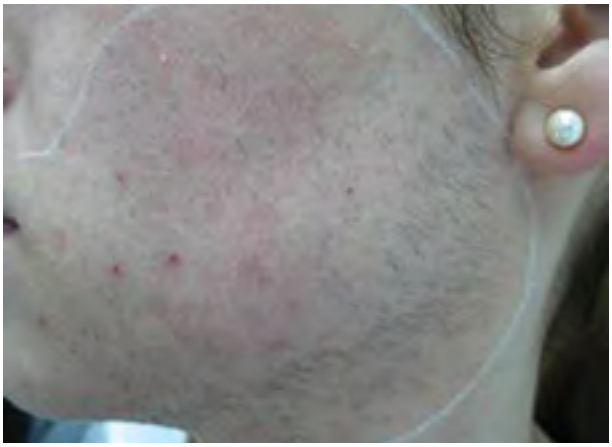

Figure 1. Hypertrichosis of the malar regions

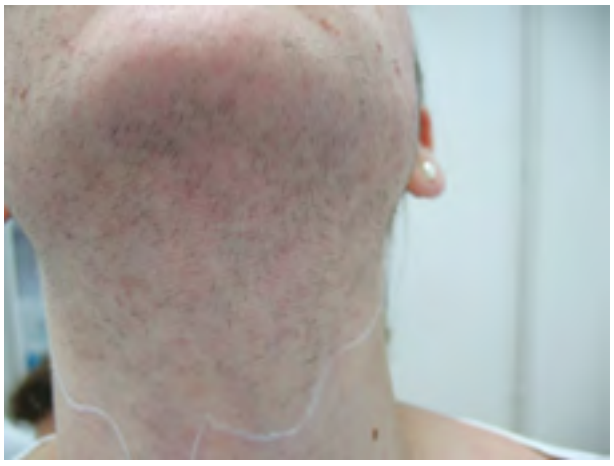

Figure 2. Hypertrichosis on the neck

ultrasound was within normal limits, except for two gallbladder concrements. There was no prior history of exposure to other drugs, alcohol, or viral hepatitis, and no evidence of porphyria or hypertrichosis in family members.

The laboratory analysis showed increased serum levels of aspartate aminotransferase (AST) 162 U/l (n.v. 0-34), alanine aminotransferase (ALT) 210 U/l (n.v. 7-49), and ferritin 470 mg/l (n.v. 20-280), as well as 24-urine copper 0.122 mg/24h (n.v. <0.05 mg/l). Urinary porphyrin excretion analysis revealed markedly elevated levels of total porphyrins up to 9023 μg/24 h (n.v. < 150). Full blood cell count, serum biochemistry studies, urea and creatinine, iron kinetics, ELISA- tests for hepatitis B surface antigen (HbsAg), anti-hepatitis C virus (HCV) antibodies, anti-human immunodeficiency virus-1 (HIV-1) and anti-HIV-2 antibodies, antimitochondrial, anti-smooth muscle and antinuclear antibodies, as well as abdominal ultrasound were negative or within normal limits. Direct immunofluorescence examination of the skin biopsy sample revealed deposition of fibrinogen at the dermo-epidermal junction and around blood vessels.

Histopathological examination of the skin lesion biopsy specimen from the hand showed typical early leasions in porphyria cutanea tarda (Figure 5), while histopathological examination of the liver biopsy revealed infiltration and mild periportal inflammation which was predominantly mononuclear. Also, iron deposits were present in periportal macrophage areas as well as in smaller groups of periportal hepatocytes (Figure 6).

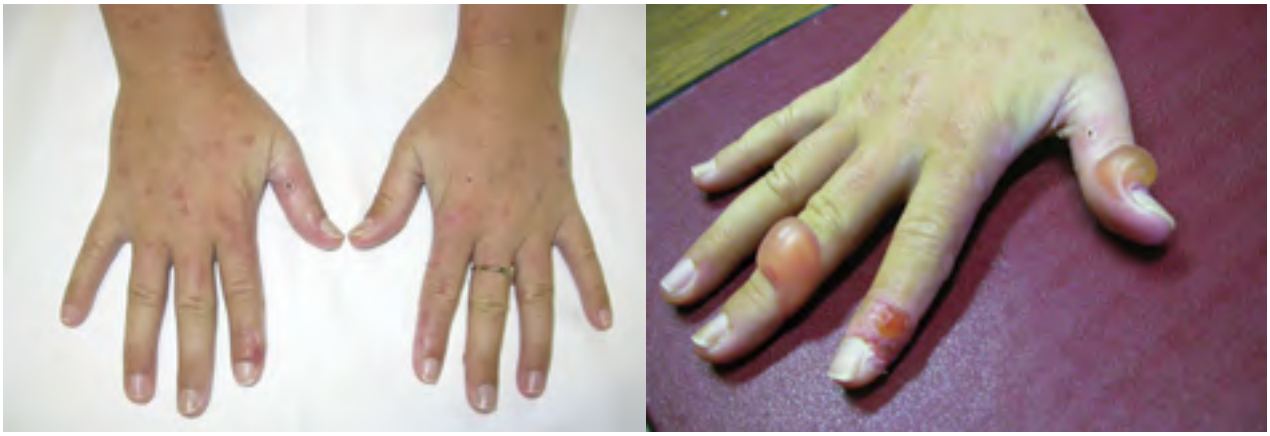

Figure 3. and Figure 4. Tense bullae on the dorsal side of the middle finger and thumb; erosion on the first finger

Clinical, histological, and laboratory findings were consistent with the diagnosis of PTC. Oral contraceptives were discontinued and treatment with hydroxichloroquine (200 mg 2x per week) and periodic phlebotomy of 300-500 ml with a consultation of a hematologist were initiated. Clinical improvement was apparent after four weeks, evidenced by the absence of new lesions. Four months later, the patient presented with a lighter urine color and reduction of uroporphyrin and coproporphyrin levels. After 3 years of follow up at our department there are no clinical or laboratory signs of PTC. Results of repeated laboratory tests are listed in Table 1.

Discussion

Porphyria cutanea tarda is the most common type of porphyria. It belongs to the group of chronic porphyrias and has four different forms: PCT,

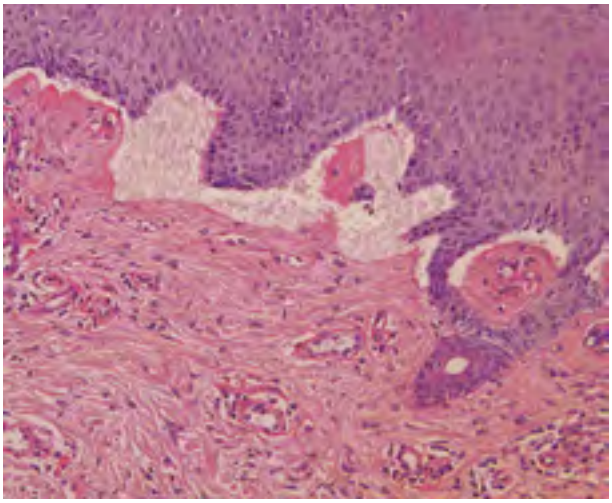

Figure 5. Separation of the epidermis from the dermis in a one segment with a lobular proliferation of capillaries in PAS positive upper dermis (PASx50)

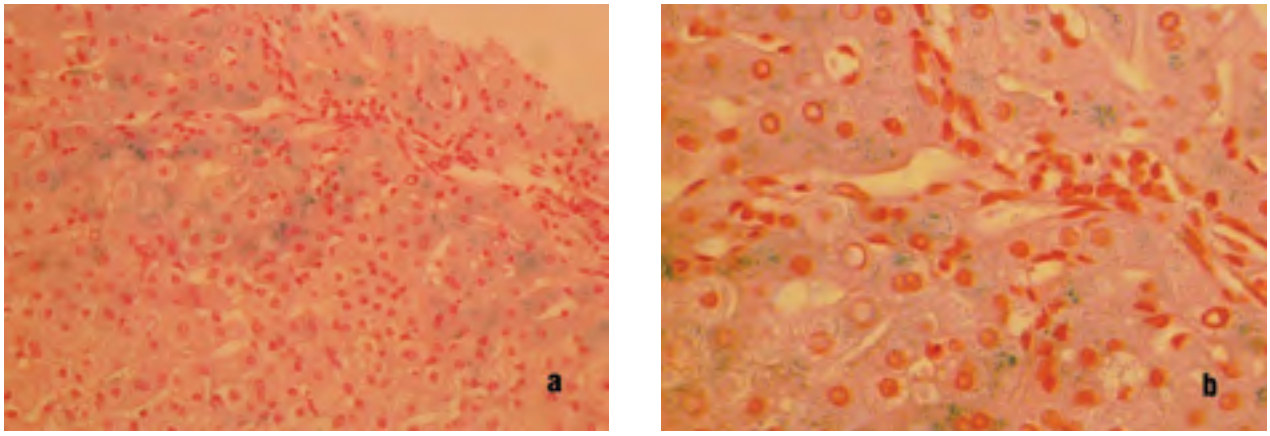

Figure 6. Iron deposits within macrophages and in small groups of periportal localized hepatocytes: a) Perl's iron stain x200; b) Perl's iron stain x400

Table 1. Laboratory test results during the follow-up

Follow-up period	Iron µmol/l (n.v. 9-31)	TIBC µmol/l (n.v. 48-80)	UIBC µmol/l (n.v. 48-80)	Ferritin µg/l (n.v. <280)	ALT U/l (n.v. 7-49)	AST U/l (n.v. 0- 34)	E x1012/L (n.v. 3.80-5.80)	Hgb g/L (n.v. 115-165)	URPOR µmol/24h (n.v <1.2)	COPOR µmol/24h (n.v <0.18)
After 3 months	18.1	54.5	36.4	55.9	42	33	4.49	161	8.8	0.5
After 6 months	6.9	75.1	68.2	7.1	27	33	3.94	118	0	0.1
After 9 months	12.1	60	47.9	6.8	29	33	4.50	120	0	0
After 12 months	12.5	ND	ND	9.4	35	36	4.86	134	0	0
After 24 months	18.7	53	34.2	33.3	16	20	4.63	137	ND	ND
After 36 months	9.6	ND	ND	5.1	18	23	4.33	117	0	0.08

TIBC - total iron bind capacity; UIBC - unsaturated iron bind capacity; ALT - alanine aminotransferase; AST - aspartate aminotransferase; E - eosinophils; Hgb - haemoglobin; URPOR - uroporphyrin; COPOR - coproporphyrin; n.v. - normal values; n – normally; ND - not done

hepatoerythropoietic porphyria (HEP), erythropoietic protoporphyria (EPP) and congenital erythropoietic porphyria (CEP) (4). PTC belongs to the group of cutaneous and chronic hepatic porphyrias (2).

This metabolic disorder results from a decreased catalytic activity of uroporphyrinogen decarboxylase (UROD) which is the fifth enzyme in heme biosynthesis (7, 9). In type 1 PCT, UROD deficiency is restricted to the liver. Opposite to this, in type 2 PCT, decreased levels of residual UROD activity, by approximately 50%, are found in all tissues, including red blood cells and skin fibroblasts (1b,1f).

Approximately 80% of all cases of porphyria cutanea tarda are acquired (4, 10, 11, 12), and type 2 PCT is known as familial (4, 13). However, not every PTC patient with positive family history will necessarily suffer from type 2 PTC, because the penetrance of this autosomal dominant form is less then 10%. Thus, type 3 PCT with normal erythrocyte UROD activities and familial occurrence has been suggested (2, 6). Biochemically, PTC is characterized by eleveted levels of porphyrins, principally by hepatic accumulation of uroporphyrin, oxidized substrate of UROD, which circulates in plazma and urine. When clinically manifested, the residual UROD activity in PTC is 25% of the normal level or less (6). The half-normal enzyme activity in patients with the type 2 PTC represents a significant predisposing factor, but is insufficient by itself to cause symptoms of PCT. Other genetic and environmental factors contribute to susceptibility in both types 1 and 2 PCT. Low level enzyme activity is caused by iron-dependent oxidation of uroporphyrinogen to uroporphomethene, which acts as a competitive inhibitor of UROD in the liver (2, 6). Thus, iron overload acts as a causative factor and as a therapeutic target. Serum iron and ferritin levels are elevated or in the upper normal range, but in clinically overt PCT, iron overload in the liver is present in basically all patients, like in our patient, while elevation of plasma iron is found only in up to one-half of affected individuals (2).

Numerous agents and conditions are known to contribute to the development of PTC: excess hepatic iron such as haemochromatosis - causing

polymorphisms in cytochromes (CYP1A2) and transferrin receptor 1 gene (TFRC) mutations, commonly present in patients with types 1 and 2 PCT; hepatitis C and HIV infections, as well as excessive alcohol intake; all the aforementioned may increase intestinal iron absorption by decreasing hepcidin production in hepatocytes; exposure to estrogens in women, and in men receiving adjunctive estrogen therapy in the treatment of prostate carcinoma; hexachlorbenzene and hemodialysis in patients with renal failure (4). The increased hepatic iron and oxidative stress leads to the formation of the enzyme inhibitor and oxidation of porphyrinogens to porphyrins (4). Histopathological examination of the liver biopsy revealed iron deposition in our patient.

Chronic porphyrias are characterized by the development of mild-to-severe chronic cutaneous lesions, usually after sun exposure. Uroporphyrin is responsible for the skin photosensitivity in the affected individuals. Other signs include skin fragility as well as blistering, erosions, crusts, milia and scar formation on sun-exposed areas on the trunk and extremities. Additionally, hyperpigmentation, hypertrichosis, sclerodermoid plaques, scarring alopecia and onycholysis may be observed (14). Generally, histopathologic skin examination does not contribute to confirming the presumptive diagnosis (2), but in our patient it pointed to the early lesions in porphyria cutanea tarda.

The diagnosis of PCT can be confirmed by specific biochemical analyses, since an increased excretion of uroporphyrin and coproporphyrin can be detected, like in our patient (2, 6). Measurement of erythrocyte UROD activity, as a screening technique to distinguish type 1 and type 2 PCT, apparently is not very reliable, because some patients with type 2 PCT may reveal residual UROD activities which may overlap with the lowest values found in patients with type 1 PCT (2). Additional molecular genetic analysis may be helpful not only in individuals with erythrocyte UROD activity in an intermediate range, but is also recommended for setting the diagnosis in patients with no family history, since they may have predisposing UROD mutations (3). Unfortunately, this genetic analysis was not available in our patient.

Classic PCT should be distinguished from epidermolysis bullosa acquisita, polymorphous light eruption, phototoxic and bullous drug eruptions (by measuring urinary and stool porphyrins), as well as other types of cutaneous porphyrias that manifest with blistering: variegate porphyria (acute course), hereditary coproporphyria (increased coproporphirins in urine and feces), mild variants of HEP (onset in early childhood), CEP (fluorescent erythrocytes), EPP (porphyrins increased in fesec but not in urine) and pseudoporphyria cutanea tarda (2, 4). The latter is associated with the use of specific drugs: non-steroidal antiinflammatory drugs (e.g. naproxen, nabumetone, and ketoprofen), furosemide, antibiotics (e.g. tetracyclines and nalidixic acid) and retinoids (6).

In our case, we considered oral contraceptive pills to be the causative agent responsible for exacerbation of clinically asymptomatic PTC, especially after clinical improvement that started after they were discontinued. The mechanism by which estrogens induce PTC is still unknown and the onset of PTC ranges from two months to seven years after initiation of estrogen therapy (15). This latency period was consistent with a delay in onset of symptoms which lasted about 8 months in our patient. Hypertrichosis was the leading symptom during the last eight years in our patient and the reason for laser hair removal treatment. Also, hypertrichosis was an indication for introduction of oral contraceptives, consequently leading to exacerbation and clinical manifestations of PCT. Hypertrichosis may be the first diagnostic sign of PTC (16, 17). Kapoor et al. described a female patient with hepatitis C infection and hypertrichosis that persisted for 29 years before other clinical manifestations of PCT developed (17). Facial hypertrichosis usually develops gradually and it is more apparent in females. The thickness, color and density of these hairs vary from person to person. These are particularly prominent along the temples and the cheeks, but may occasionally involve the trunk and extremities, and may continue to grow. Hypertrichosis may also be a symptom of PTC in women and young children. Some Turkish reports of hexachlorbenzene poisoning described children as “monkey-children”. The mechanism of this phenomenon is unknown; it is believed that the surface receptors of growth factors for hair bulb keratinocytes are activated by the dual action of light and porphyrins (18).

Effective treatments for PTC include: sun

avoidance, use of sunscreens and elimination of the underlying cause like alcohol abuse, discontinuation of estrogen therapy (19), or treatment of hepatitis C with interferon-alpha (20). However, venesection 300 - 500 ml every two weeks, and low dose antimalarial agents are usually required. Venesection leads to resolution of blisters within 2-3 months, and normalization of porphyrin concentrations within 13 months. At that point, treatment is usually discontinued. Antimalarial agents (chloroquine or hydroxychloroquine twice weekly) are safe, cheap, convenient and effective in the treatment of PTC, resolving blistering and skin fragility within 6 months and normalizing urinary porphyrin excretion after 6-15 months (21-27). Our patient responded well to the treatment. However, it has recently been shown that the genetic background of PCT patients, particularly the presence of common hemochromatosis gene mutations, C282Y and H63D, may predict the outcome of chloroquine treatment: PCT patients homozygous for C282Y seemed to retain high serum iron, ferritin, and transferring level and failed to respond to chloroquine therapy (28). Hypertrichosis usually resolves slowly compared to other clinical manifestations (24). Long-term follow-up is necessary for all patients with PTC.

Conclusion

This case highlights the importance of a detailed clinical history for all patients with signs of hypertrichosis (not hirsutism) undergoing laser hair removal. They should be routinely tested for porphyria, since hypertrichosis, often the reason for female patients to visit dermatologist may be the initial symptom of porphyria cutanea tarda.

Abbreviations

PCT - porphyria cutanea tarda
UROD - uroporphyrinogen decarboxylase
AST - aspartate aminotransferase
ALT - alanine aminotransferase
ELISA - enzyme-linked immunosorbent assay
HbsAg - hepatitis B surface antigen
HCV - hepatitis C virus
HIV - human immunodeficiency virus
TIBC - total iron bind capacity
UIBC - unsaturated iron bind capacity
E - eosinophils
Hgb - haemoglobin
URPOR - uroporhyrin
COPOR - coproporphyrin
HEP - hepatoerythropoietic porphyria
EPP - erythropoietic protoporphyria
CEP - congenital erythropoietic porphyria
CYP - cytochrome P
TFRC - transferring receptor 1 gene

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Porfirija kutanea tarda - prikaz slučaja

Sažetak

Uvod: Porfirija kutanea tarda (PCT) metabolički je poremećaj koji nastaje kao rezultat smanjene aktivnosti uroporfirinogen dekarboksilaze. Opisuju se dva tipa PCT: stečeni, tzv. izolovani ili tip I, koji se javlja češće, kod oko 80% svih obolelih i nasledni, familijarni ili tip II koji se nasleđuje dominantno ali sa malom penetracijom inkriminisanog gena. Oba tipa se javljaju povezano sa određenim, tzv. faktorima rizika ili deklanširajućim faktorima, kao što su: alkohol, estrogeni, prezasićenost gvožđem, infekcija virusom hepatitisa C, izloženost halogenim aromatičnim ugljovodonicima koji svi uzrokuju smanjenje enzima uroporfirinogen dekarboksilaze (UROD) u jetri. U PCT je utvrđen visok nivo molekularne heterogenosti s obzirom da je kod pacijenata sa PCT tip II do danas utvrđeno više od 105 različitih mutacija gena odgovornog za sintezu UROD enzima (gen mapiran na hromozomskoj regiji 1p34). Ipak, rastuća incidencija PCT kod žena se pripisuje upotrebi estrogena kako u obliku tableta za kontracepciju tako i u okviru suplementarne hormonske terapije.

Prikaz slučaja: U radu je prikazan slučaj osobe ženskog pola, stare 23 godine, kod koje su zbog hirzutizma na licu i vratu koji je bio prisutan u poslednjih osam godina, sprovedena četiri tretmana aleksandritnim laserom. Posle četiri tretmana, manifestovala se ranica na vrhu nosa. Nakon detaljno uzete anamneze, pacijentkinja je navela da su joj se na koži lica u periodu 7–19. godine povremeno javljali vodeni plikčići, i to na koži lica i šaka. Promene su se javljale naočito u vezi s povećanom i produženom ekspozicijom suncu, a spontano su nestajale ostavljajući blage ožiljke. U 15. godini života primetila je povećanu kosmatost na licu i na vratu, kao i tamnu boju mokraće. Poslednje dve godine pre nego što je došla na pregled kod nas, pacijentkinja se javila gastroenterologu zbog povremenih tupih bolova u predelu gornjeg abdomena koji su bili praćeni trostrukim povećenjem serumskih transaminaza, povećanim nivoom bakra u urinu i serumu i povećanim nivoom feritina u serumu. Ultrasonografski pregled gornjeg abdomena je otkrio samo dva konkrementa u žučnoj kesici. Anamneza u smislu uzimanja drugih lekova, potrošnje alkohola ili preležanog virusnog hepatitisa bila je negativna. Porodična anamneza, u smislu prisustva porfirije i povećane kosmatosti (hipertrihoze) kod srodnika, bila je negativna. Laboratorijski nalazi koji su odstupali od uobičajenih fizioloških vrednosti bili su: povišena vrednost asparataminotransferaze i alanin-aminotransferaze, feritina u serumu; povišene vrednosti bakra u 24-časovnom urinu; 60 puta povećan nivo porfirina i nivo koproporfirina u 24-časovnom urinu. Histopatološki pregled bioptiranog uzorka obolele kože sa nadlanice odgovarao je ranim lezijama kod PCT, a histopatološki pregled bioptiranog uzorka jetre je pored

blagog periportalnog zapaljenskog mononuklearnog infiltrata otkrio depozite gvožđa u periportalnom makrofagnom prostoru kao i u malim grupama periportalno lokalizovanih hepatocita. Pacijentkinja je bila na terapiji oralnim kontraceptivima tokom poslednjih 8 meseci. Nije bilo upotrebe drugih lekova. Nakon isključivanja drospirenona i etinilestradiola (Yaz tbl.), primećeno je postepeno kliničko i laboratorijsko poboljšanje koje je ukazivalo na kauzalnu ulogu leka.
Dijagnoza PCT postavljena je na osnovu kliničkog, laboratorijskog i histopatološkog pregleda.
Lečenje je započeto ukidanjem oralnog kontraceptiva i niskim dozama antimalarika hidroksihlorokvina (200 mg 2 x nedeljno) i periodičnim flebotomijama (300–500 ml u početku uz konsultaciju hematologa). Kliničko poboljšanje bilo je evidentno 4 nedelje nakon započinjanja lečenja i manifestovalo se sledećim: prestanak pojave novih lezija; svetlija boja mokraće; smanjenje uroporfirina i koproporfirina u 24-časovnom urinu. Sve vreme tokom naredne tri godine, kada je pacijentkinja redovno klinički i laboratorijski kontrolisana, nije bilo recidiva tj. pojava novih promena na koži i laboratorijskih odstupanja.
Diskusija: Treba naglasiti da negativna porodična anamneza ne isključuje postojanje tipa II PCT, s obzirom na nisku penetrantnost mutacije PCT gena u ovom autozomno-dominantno nasledom obliku bolesti. Tako su pojedini autori definisali tip III PCT u kome oboleli imaju normalan nivo UROD enzimske aktivnosti u eritrocitima a imaju istovremeno obolele srodnike u porodici. Biohemijski PCT karakterišu povišene vrednosti porfirina (u serumu i urinu) i to prvenstveno zbog povećane akumulacije uroporfirina u jetri. Uroporfirini predstavljaju supstrat na čiju oksidaciju utiče UROD enzim, a koji u PCT cirkuliše u povećanim količinama u plazmi i urinu. Kod klinički manifestne PCT, aktivnost UROD enzima mora biti manja od 25% (po nekima manja i od 20%) od normalne aktivnosti, stoga 50% enzimska aktivnost koja je prisutna kod oboleleih od tipa II PCT može predstavljati samo predisponirajući faktor, ali je nedovoljno niska da bi izazvala simptome PCT. Stoga je neophodno prisustvo drugih genetskih i spoljašnjih faktora koji bi doprineli povećanoj prijemčivosti jedne osobe za obolevanje kako od tipa I tako i od tipa II PCT. Treba znati da je nizak nivo enzimske aktivnosti UROD enzima (manje od 25% od normalnih vrednosti) u klinički manifestnoj PCT, posledica oksidacije uroporfirinogena u uroporfomeren koji deluje kao kompetitivni inhibitor UROD enzimu u jetri. Ovaj enzimski proces je zavisan od gvožđa. Serumski nivo gvožđa i feritina je povećan, ali može biti i na gornjoj granici normalih vrednosti. Bitno je da PCT postaje klinički manifestna samo ukoliko postoji povećana aklumulacija gvožđa u jetri. Za razliku od jetre, nivo gvoža u serumu može biti povećan kod samo 50% obolelih. Iako se određivanje nivoa UROD aktivnosti u eritrocitima smatra tehnikom skrininga za diferencijaciju tipa I od tipa II PCT, ova metoda nije dovoljno pouzdana zato što pojedini pacijenti sa tipom II mogu imati smanjenu UROD aktivnost koja se preklapa sa najmanjom vrednosti (intermedijerni nivo) UROD aktivnosti kod osoba sa tipom I PCT. Zbog toga je potrebno dodatno molekularno genetsko ispitivanje. Ovo ispitivanje nije indikovano samo kod onih osoba koje imaju intermedijerni nivo UROD aktivnosti u eritrocitima. Ovo ispitivanje treba sprovoditi i u cilju postavljanja egzaktne dijagnoze kod pacijenata koji nemaju obolele srodnike, a imaju mutacije na UROD genu. Nažalost, mi nismo bili u mogućnosti da sprovedemo genetsko ispitivanje.Postoji mnogo radova u kojima se navodi da estrogeni mogu biti okidači kod PCT. Ipak, mehanizam kojim estrogeni utiču na ispoljavanje bolesti nisu u potpunosti razjašnjeni. Iako dietilstilbestrol i estrogen izazivaju povećanu sintezu aminolevulonske kiseline u jetri, kojom se ne može objasniti ekskrecija porfirina karakteristična za PCT. Štaviše, većina pacijenata koja uzima estrogene ne pokazuje klinička niti biohemijska odstupanja karakteristična za PCT.
Zaključak: Ovim radom želimo da naglasimo značaj hipertrihoze, kao prve manifestacije PCT jer to može biti prvi i jedini klinički znak, koji tokom dugog vremenskog perioda prethodi pojavi drugih kliničkih znakova i simptoma.

Ključne reči

Porfirije; Estrogeni + neželjena dejstva; Hipertrihoza; Uklanjanje malja; Antimalarici