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Paraneoplastic porphyria cutanea tarda associated with cholangiocarcinoma: Case report

Kolanjiokarsinomda paraneoplastik sendrom olarak görülen kutanöz porfiri tarda vakası

Mehmet SÖKMEN[1], Hüseyin DEMİRSOY[1], Özdal ERSOY[1], Gonca GÖKYİĞİT[2], Nihat AKBAYIR[1], Çetin KARACA[1], Kamil ÖZDİL[1], Beşir KESİCİ[1], Can CALIŞKAN[3], Banu YILMAZ[4]

Departments of [1]Gastroenterology, [2]Dermatology, [3]Radiology and [4]Pathology, Şişli Etfal Education and Research Hospital, İstanbul

The porphyrias are a group of disorders of the heme biosynthesis pathway that present with acute neurovisceral symptoms, skin lesions or both. Porphyria cutanea tarda, presenting as a non-acute form, is the most common type of porphyria that encompasses a group of related disorders, all of which arise from deficient activity of the heme synthetic enzyme, uroporphyrinogen decarboxylase, in the liver. In the literature, concomitant presentation of porphyria with hepatocellular carcinoma is common; however, no case of porphyria cutanea tarda associated with cholangiocarcinoma has been seen. Here, we present a case of porphyria cutanea tarda seen in the course of cholangiocarcinoma, which can be attributed to a paraneoplastic syndrome. Our case is of interest because of its rarity. We also give a brief review of the literature regarding porphyria and cholangiocarcinoma.

Key words: Paraneoplastic syndromes, porphyria, cholangiocarcinoma

Porfiriler akut nöroviseral semptomlar ve/veya cilt lezyonları ile karşımıza çıkan, hem biyosentezindeki bozukluklardır. Kutanöz porfiri tarda ise akut formda karşımıza çıkmayan ve en sık karşılaşılan porfiri türüdür. Tüm formlarında, heme sentezinde kullanılan üroporfirinojen dekarboksilaz enziminin karaciğerdeki aktivitesinde eksiklik vardır. Literatürde hepatoselüler kanser ile porfiri birlikteliğine sık rastlansa da kolanjiokarsinom ile birlikteliği bildirilmemiştir. Bu sebeple vakamız nadir görülen bir vaka olmakla birlikte, yazımızda porfiriler ve kolanjiokarsinom da kısaca özetlenmiştir.

Anahtar kelimeler: Paraneoplastik sendrom, porfiri, kolonjiokarsinom

INTRODUCTION

The porphyrias are a group of disorders of the heme biosynthesis pathway that present with acute neurovisceral symptoms, skin lesions or both. They occur as a result of the accumulation of porphyrins and their precursors in the tissues, which are produced in excess amounts due to lack or deficiency of enzymes that are essential for heme biosynthesis. They are simply classified as acute and non-acute forms. Porphyria cutanea tarda (PCT), presenting as a non-acute form, is the most common type of porphyria that encompasses a group of related disorders, all of which arise from deficient activity of the heme synthetic enzyme, uroporphyrinogen decarboxylase (URO-D), in the liver. The most common photocutaneous manifestations of PCT are due to increased mechanical fragility of the skin after sunlight exposure; erosions and blistering cause painful indolent sores that eventuate in milia, dyspigmentation, and scarring. Excretion of porphyrins in both urine and stool is also characteristically increased.

The disease generally starts during the middle ages. The mechanism of the enzyme deficiency has not yet been completely understood; however, the disease is thought to be most probably acquired. There is also a possibility of genetic tendency, but in most of the patients (80%), there is no mutation in the gene related with URO-D. PCT may accompany various malignancies; the most commonly associated malignancies are known to be primary liver cancers (1-5). In the literature, concomitant presentation of porphyria with hepatocellular carcinoma (HCC) is common; however, no case of PCT

Address for correspondence: Özdal ERSOY
Department of Gastroenterology, Şişli Etfal Education and Research Hospital, İstanbul, Turkey
Phone: +90 212 231 22 09 /1439
E-mail: ozdalersoy@gmail.com

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associated with cholangiocarcinoma was seen previously. Herein, we present a case of PCT seen in the course of cholangiocarcinoma, which can be reported as a rare occurrence.

CASE REPORT

A 75-year-old male patient admitted to the hospital with jaundice, discoloration of the stool, darkening of urine, fatigue, and wound-type skin lesions on his face, arms and legs. His past medical history was nonsignificant apart from subtotal gastrectomy operation performed 30 years ago.

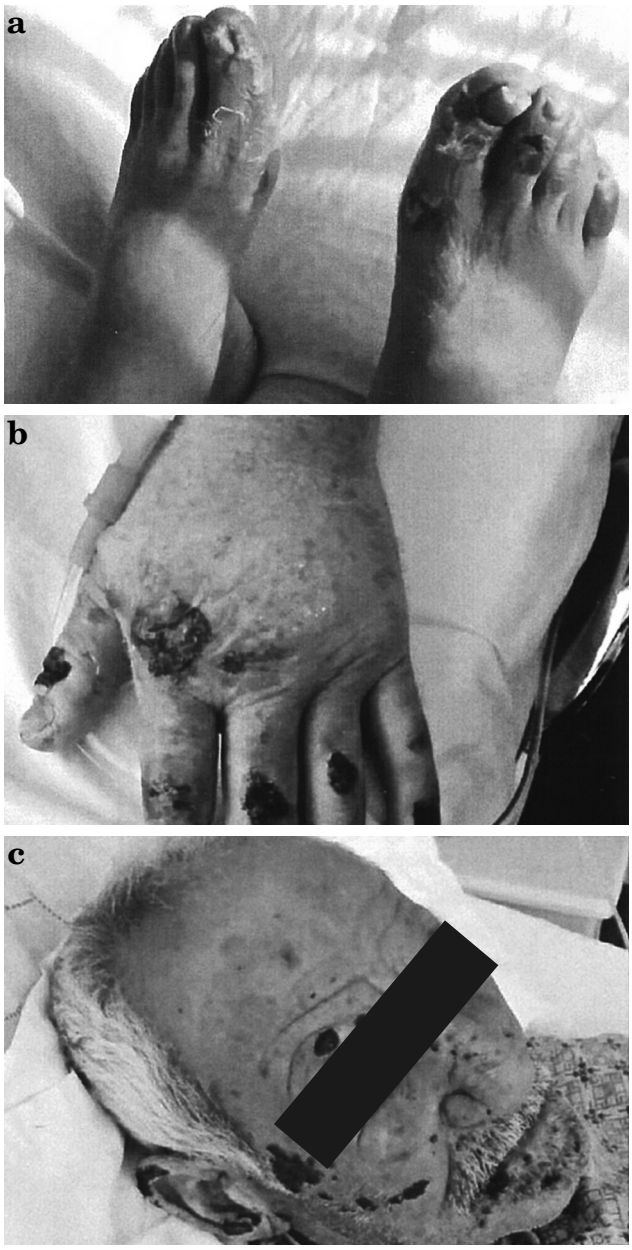


Figure 1. Different types of skin lesions – erosions, blisters, crusted erosions- on feet **a)**, hand **b)** and face **c)** of the patient

On physical examination, jaundice was prominent on the skin and the scleras. He had bullous, purplish-colored skin erosions of 1-1.5 cm in diameter on the dorsal aspects of the hands, forearms, feet and face; some of these lesions showed spontaneous drainage, while other erosions and blisters were necrotic and crusted (Figure 1a-c). Abdominal examination revealed a median operation incision scar, and a non-tender liver with smooth margins was palpable 4 cm below the costal margin. Examinations of the other systems were found to be normal.

Initial laboratory values were as follows: Hb: 11 g/dl, MCV: 62 fL, MCH: 22 pg, ESR 16 mm/1 hour, AST: 157 U/L, ALT: 218 U/L, GGT: 1212 U/L, ALP: 1006 U/L, LDH: 223 U/L, total bilirubin: 14.69 mg/dl, direct bilirubin: 10.93 mg/dl, total protein: 6.6 g/dl, and albumin: 4.3 g/dl; other biochemistry values were within normal limits. HbsAg was negative, anti-HCV was negative, AFP: 4.8 U/ml, CEA: 14.52 U/ml, CA 19-9: > 1000 U/ml, and CA 12-5: 58 U/ml. Uroporphyrin I was 59.1 µg/d in 24-h urine and coproporphyrin I and III were 301.7 µg/d and 547.0 µg/d, respectively (normal range for all: 25 µg/day).

Abdominal ultrasonographic (USG) examination revealed dilatation of intrahepatic bile ducts and a solid mass with a diameter of 4 cm near the hilus in the left lobe of the liver and adjacent to the common bile duct (Figure 2). Similar findings were determined in magnetic resonance cholangiopancreatography (MRCP) examination, but the pancreas was found to be normal. In percutaneous transhe-

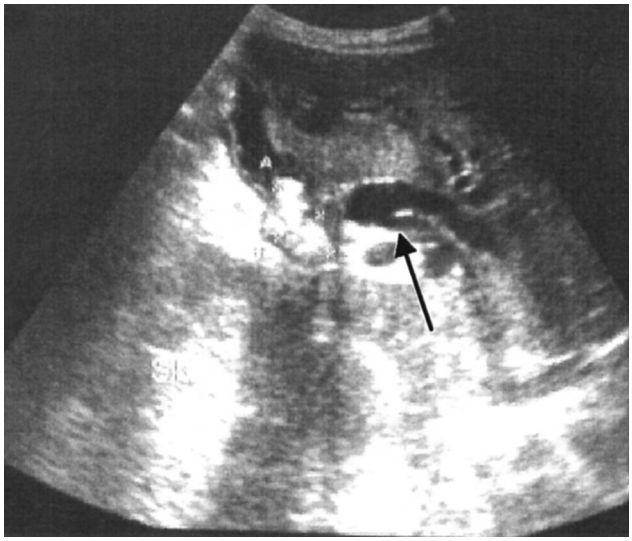


Figure 2. Abdominal ultrasonographic examination demonstrating intrahepatic mass *(arrow)*

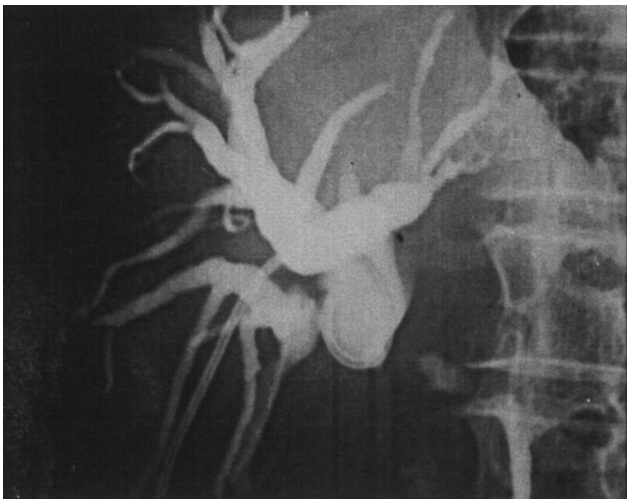


Figure 3. Dilatation of intrahepatic bile ducts shown on percutaneous transhepatic cholangiogram (PCT)

patic cholangiogram (PTC), right and left intrahepatic bile ducts and the proximal part of the main hepatic bile duct were seen as markedly dilated; therefore, the common bile duct could not be demonstrated and a sudden interruption at the hilar region was seen (Figure 3). A malignant biliary obstruction was considered. USG-guided core biopsy of this lesion was performed, and cholangiocarcinoma was diagnosed histopathologically (Figure 4a-b). During PTC, in order to establish the diagnosis of cholangiocarcinoma, a 6 cm long 8 F self-extendable Nitinol (6X8) stent was also inserted into the common bile duct percutaneously during the same session to remove the obstruction at the hilar region (Figure 6a-b). Following stent placement, total bilirubin levels rapidly decreased from 16 mg/dl to 3 mg/dl and cholestatic enzymes also markedly decreased. Diagnosis of PCT was established with the characteristic skin lesions and the increased amount of porphyrin derivatives (uroporphyrin I, coproporphyrin I and III) in 24-h urine. The skin biopsy was also consistent with the diagnosis of porphyria (Figure 5).

Symptomatic and palliative treatment was applied to the patient. One month after the placement of the common bile duct stent and the specific chemotherapy regimen was started by the oncology department, the patient showed improvement and jaundice and skin lesions had disappeared.

To our knowledge, we report the first case in the literature of porphyria cutaneous tarda occurring in a patient with cholangiocarcinoma, which may be a rarely seen entity.

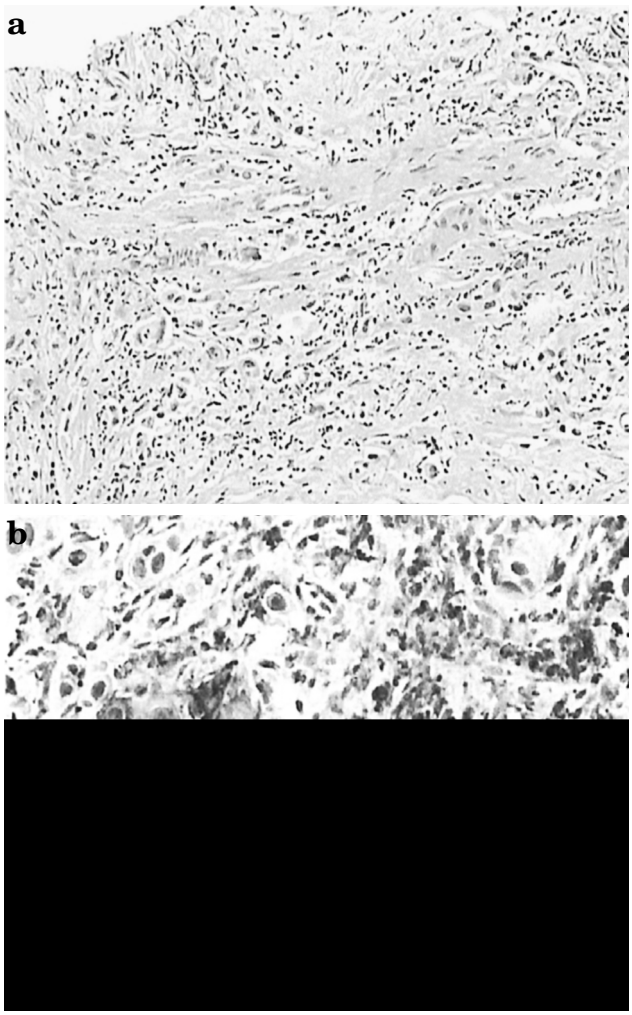


Figure 4. Histopathological examination of the liver lesion (20x10, H&E staining). **a)** trabecular and tubular structures formed by atypical epithelial cells, **b)** CEA positivity in tumor cells

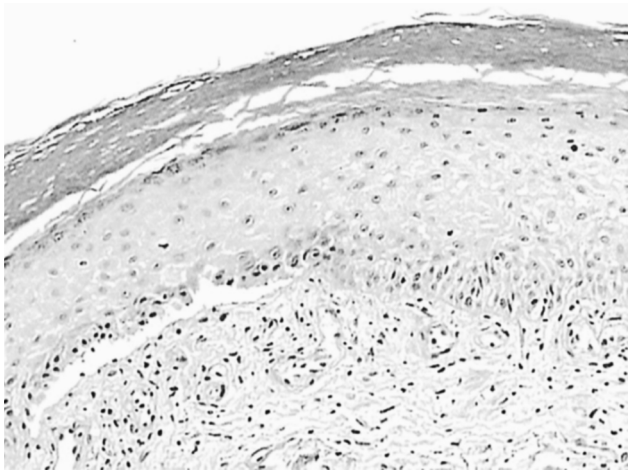


Figure 5. Skin biopsy showing subepidermal separation (dermoepidermal junction cleavage) with minimal dermal inflammatory infiltrate and presence of thickened upper dermal capillary vasculature at papillary dermis, H&E, x100

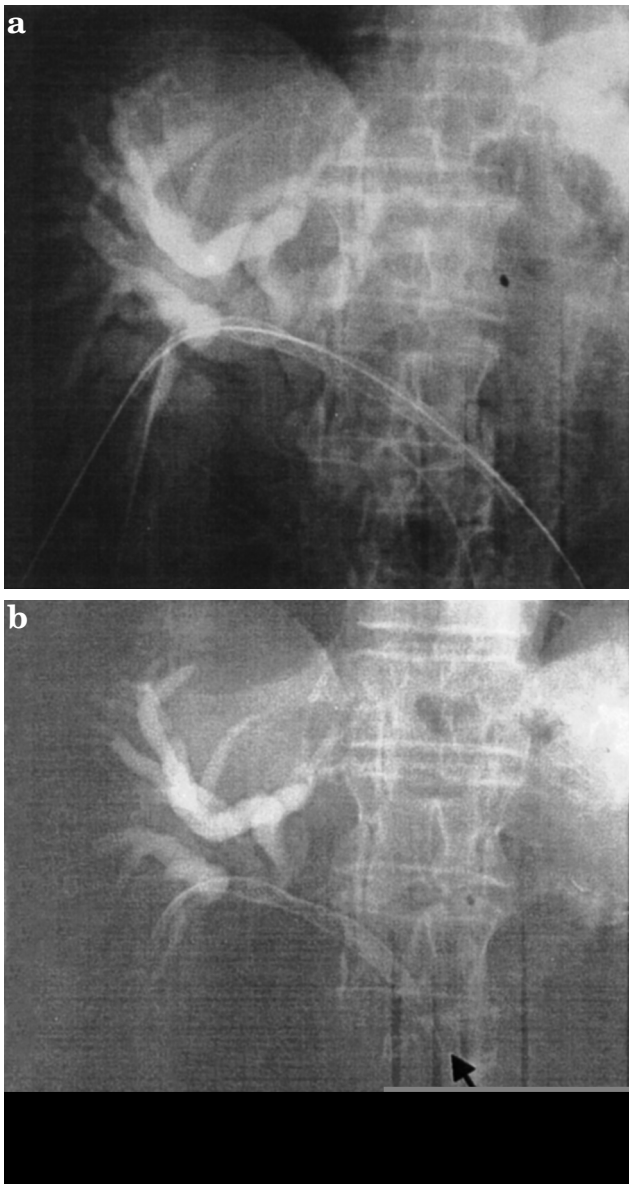


Figure 6. a-b) Insertion of the percutaneous stent into the choledochus

DISCUSSION

Cholangiocarcinoma, which is the second most common primary liver tumor, accounts for 7-25% of primary liver tumors. Extrahepatic type tumors (87-92%) may be classified as proximal and distal tumors. Proximal tumors are also referred to as hilar cholangiocarcinoma, Klatskin tumor or perihilar tumor, whereas intrahepatic type tumors (8-13%) are peripheral tumors and may also be referred to as small duct or intraparenchymal tumors. Intrahepatic types may be subclassified as mass producing, periductal infiltrative and intraductal growth types (6-8).

In the non-cirrhotic liver, peripheral tumors are usually seen, whereas in the liver with chronic biliary disease, proximal and distal tumors are more common. However, our case represents an example of a perihilar type tumor of a proximal extrahepatic cholangiocarcinoma, although the patient had a non-cirrhotic liver.

Paraneoplastic syndromes related with cancer are common. They may be seen in approximately 1/7 cancer patients. Paraneoplastic syndromes may affect various organs. Even though the exact pathogenesis of the paraneoplastic syndrome is still not known, it is most likely due to auto-immune mechanisms. Paraneoplastic syndromes can be seen in HCC (10, 11). To our knowledge, there is no case of cholangiocarcinoma in the literature presenting a paraneoplastic syndrome during its course.

Paraneoplastic syndromes may be the first symptoms of malignancy or may occur in later stages during the course of disease. In our case initially, the signs of the paraneoplastic syndrome (diagnosed as PCT) that appeared clinically were bullous skin lesions on face, hands and feet. Jaundice, the symptom of the underlying primary disease (diagnosed as cholangiocarcinoma), was added to the clinical picture afterwards.

While many paraneoplastic syndromes have an independent course apart from the associated tumor, in some cases, successful treatment of the underlying disease may treat the paraneoplastic syndrome as well (12). After removal of the causal factors of PCT, symptoms of this paraneoplastic syndrome may be managed (1, 2). Similarly, in our case, after insertion of the stent into the bile duct and application of the specific chemotherapy regimen, the skin lesions of PCT also disappeared.

After observing the skin lesions over the organs exposed to daylight, such as hands, feet and face, which are the characteristic features of PCT, uroporphyrin derivatives in 24-h urine were measured to establish the diagnosis. Apparently high levels of uroporphyrin I and III in the urine as well as the increased levels of coproporphyrin I and III supported the diagnosis of PCT.

In appropriate cases, total resection of the tumor can be done safely and long-term survival is achieved (6, 15, 16). Age, general condition of the patient and concomitant diseases are the main factors that may impede surgical therapy. Advanced age and presence of peripheral and central type

lesions in our patient precluded our performing any surgical therapy, and therefore palliative therapy was preferred. After the insertion of an intrahepatic stent, chemotherapy (gemcitabine 1 g/m^2 once a week, for 7 weeks) was started by the oncology clinic. One month after stent insertion and chemotherapy had been administered, the patient showed improvement, and skin lesions and jaundice had disappeared. The patient was followed thereafter by the oncology department and was free of skin symptoms, but he was unresponsive to treatment and died due to sepsis six months after the diagnosis.

Different types of paraneoplastic symptoms may be seen in cholangiocarcinomas. However, according to our knowledge, a clinical picture of PCT has not previously been reported in the literature for cholangiocarcinoma. We thus report the first case in the literature of porphyria cutaneous tarda occurring in a patient with cholangiocarcinoma, which may be a rarely seen entity.

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