Erythropoietic Protoporphyria and Terminal Hepatic Failure

DANIELA BRUCH-GERHARZ[1], KLAUS BOLSEN[1], CLAUS-DIETER GERHARZ[2] and GÜNTER GOERZ[1]

Departments of [1]Dermatology and [2]Pathology, Heinrich-Heine-University of Duesseldorf, Germany

We report on a 44-year-old patient with erythropoietic protoporphyria who could effectively control his photosensitivity for 22 years with oral carotinoids. The clinical course of his disorder was complicated by liver involvement, initially expressed as marginally raised serum transaminase levels for several years. Terminal hepatic failure with fatal outcome developed 22 years after manifestation of his liver function abnormalities. Hepatic involvement represents an inconstant and unpredictable feature of erythropoietic protoporphyria, determining the prognosis of an otherwise clinically benign disorder. *Key words: liver; porphyrins; photosensitivity; ferrochelatase.*

Erythropoietic protoporphyria (EPP) is a hereditary disorder of porphyrin metabolism characterized by a decreased activity of the mitochondrial enzyme ferrochelatase (FeCh) and excessive concentrations of protoporphyrin in red blood cells, plasma, bile and faeces (1, 2). Until recently, this condition was thought to be inherited as an autosomal dominant trait with variable penetrance (3); recent data, however, suggest an autosomal recessive mode of inheritance in some cases (4).

EPP patients usually present with a history of disabling photosensitivity, with both acute phototoxic skin reactions and chronic hyalinosis-like cutaneous lesions at the light-exposed areas due to photoexcitation of protoporphyrin by UVA and visible light. Most cases manifest in early childhood after the first longstanding exposure to sunlight; the clinical features, thereafter, tend to aggravate in spring and summer (5).

The liver is occasionally affected in EPP and reveals a spectrum of histopathologic features ranging from moderate inflammation to fibrosis. Nearly all EPP patients suffer from cholelithiasis, but only rarely is serious liver disease recorded, culminating in fatal liver cirrhosis (6). Therefore, it has been hypothesized that protoporphyrin exerts a light-independent toxic effect on the liver; nevertheless, the exact pathophysiological mechanisms underlying progressive liver damage are still incompletely understood (7).

We report on an EPP patient with terminal hepatic failure 22 years after manifestation of his liver dysfunction. The insidious evolvement of hepatic failure observed in our patient emphasizes the potentially fatal role of liver complications in patients with EPP.

CASE REPORT

EPP was first diagnosed in our patient in 1971 at the age of 22 years. Since early childhood the patient had experienced moderate cutaneous photosensitivity, characterized by burning and painful discomfort followed by a transient erythema of sun-exposed skin. Episodes typically occurred in spring and summer, with the skin lesions and symptoms becoming apparent within minutes or hours subsequent to sun exposure. Family history revealed only a half-brother with similar skin changes and solar intolerance. The other family members had no evidence or history of a photodermatosis or porphyria.

At his first presentation in our clinic in 1971, the 22-year-old patient exhibited erythematous phototoxic skin reactions on the dorsal aspects of both hands in areas not protected by his gloves (Fig. 1a) and lichenified hyalinosis cutis-like lesions on the dorsa of his nose, hands and fingers (Fig. 1b), as well as pseudorhagades surrounding the vermilion border. Elevated protoporphyrin concentrations in erythrocytes were demonstrated by porphyrin analysis (2760 nmol/dl; normal, <72). Fluorescence microscopic examination revealed orange-red fluorescence of red blood cells, the so-called fluorocytes (Fig. 1c). Blood cell count was normal, whereas routinely performed laboratory investigations revealed abnormal values for AST (32 U/l; normal, <18), ALT (36 U/l; normal, <22) and total serum bilirubin (1.48 mg/dl; normal, <1.2). Moderately increased serum transaminase levels had already been observed at the age of 18 years for the first time. Carotinoid therapy (daily oral doses of 75–150 mg beta-carotene or canthaxanthine) provided effective photoprotection. Repeated controls of liver function revealed no abnormalities, although the patient reported intermittent alcohol abuse since 1979.

During the next 15 years the patient was not available for follow-up until he was readmitted to our Department in 1994. On examination, the 44-year-old patient revealed marked jaundice, ascites, peripheral oedemas, enlarged liver at palpation and venous collaterals, indicating severe hepatic insufficiency. Laboratory investigations showed increased levels of serum alkaline phosphatase (464 U/l; normal, 65 to 220), AST (232 U/l) and a mild iron deficiency anemia (hemoglobin 10.3 g/dl; normal, 12 to 16) and elevated IgG level. Antinuclear antibodies (ANA), hepatitis antigens and antibodies were negative. The patient showed markedly increased erythrocyte porphyrin concentrations (5135 nmol/dl), a FeCh activity in leukocytes reduced to approximately 20% of normal, elevated total bilirubin levels (13.5 mg/dl) as well as hyperammonemia (484 µg/dl; normal, 15 to 60). Abdominal ultrasonography revealed liver cirrhosis, splenomegaly, an 8 mm in diameter gallstone in the gall-bladder, but no evidence of biliary tract obstruction. Severe phototoxic skin reactions could be demonstrated in chronically light-exposed areas, such as the dorsa of the hands (Fig. 1d), nose and parts of the face. The patient reported an increase of phototoxicity in parallel to the progression of his liver disease.

The liver function continued to deteriorate during the next days, and the patient died after an acute hemorrhage from esophageal varices. Autopsy revealed cholecystolithiasis and a black stained liver with cirrhosis (Fig. 2a). Histological evaluation showed complete cirrhosis (Fig. 2b) with foci of hepatocellular necrosis and Mallory bodies (Fig. 2c), compatible with ethanol-induced injury. In addition, there was an excessive accumulation of red-brown pigment within Kupffer cells, hepatocytes and bile canaliculi. Polarization showed this pigment to be red birefringent (Fig. 2d), and crystalline-like configurations could be identified. Ultrastructural examination of liver specimens revealed aggregates of crystalline structures that were straight or slightly curved and erratically arranged in the cytoplasm of hepatocytes (Fig. 2e,f). Finally, the postmortem liver specimen contained 483 nmol protoporphyrin/g liver, i.e. a 150-fold increased concentration in comparison to normal liver.

DISCUSSION

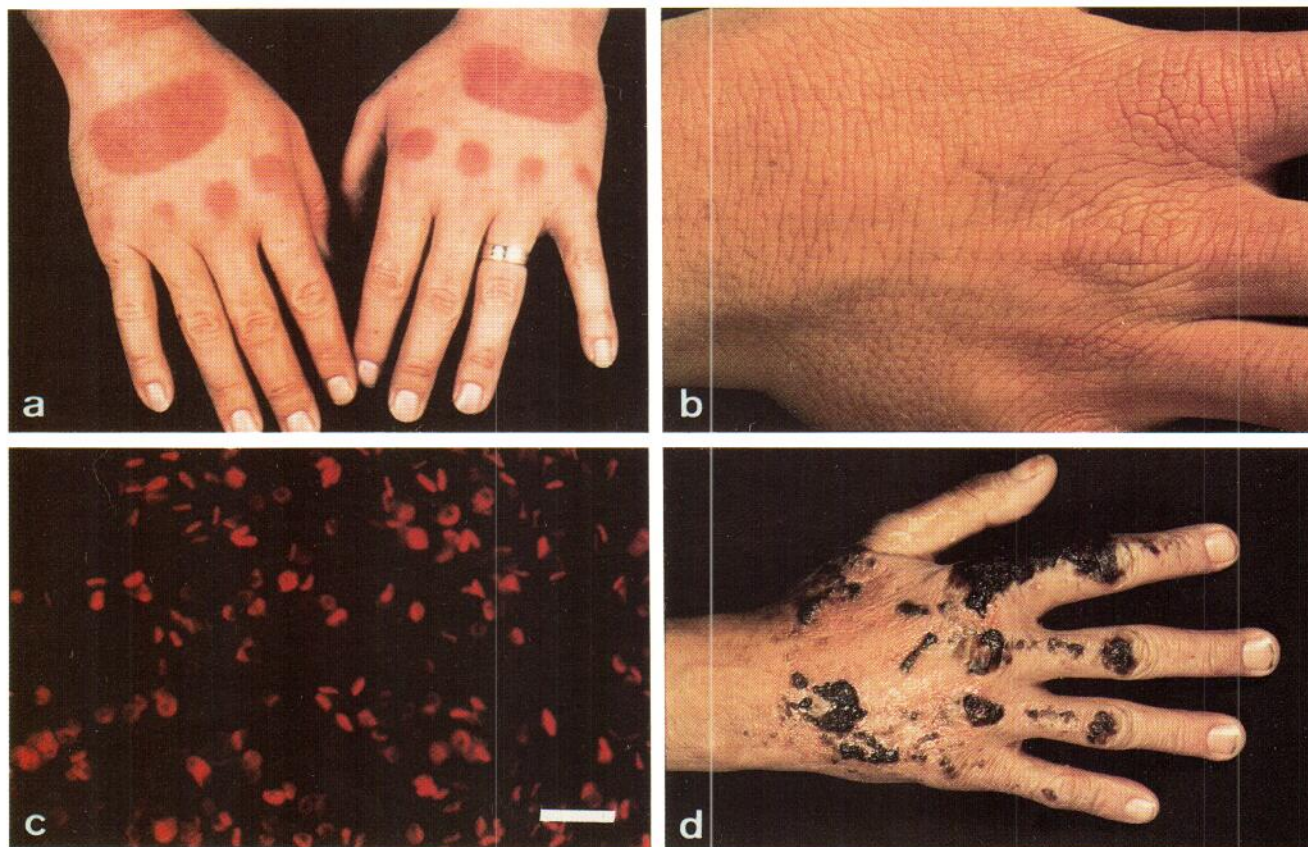Although EPP is generally regarded as a benign metabolic disorder, it may occasionally be associated with severe,

Fig. 1. Aspects of protoporphyrin deposits in skin (*a,b,d*) and erythrocytes (*c*). (*a*) Erythematous phototoxic skin reactions on the dorsa of both hands in areas not protected by the patient's gloves. (*b*) Hyalinosis-like lichenoid skin lesions on the dorsa of the hands and fingers at the age of 22 years. (*c*) Bright orange-red fluorescence of protoporphyrin in erythrocytes by fluorescence microscopy (bar = 40 μm). (*d*) Phototoxic reaction in the 44-year-old patient: bullous phototoxic skin reactions have been transformed into dark-brown crusts on the dorsa of the hands and fingers within 3–4 days.

progressive and fatal liver injury. Unfortunately, our patient was not available for follow-up for 15 years prior to the manifestation of his liver failure. Thus, a therapeutic intervention with chenodeoxycholic acid or cholestyramine was not possible.

Histopathological examination of liver biopsies from EPP patients with overt liver disease reveals inflammation and fibrosis extending from the portal areas as well as bile thrombi indicative for cholestasis. Furthermore, granular deposits of protoporphyrin birefringent upon examination with polarized light can be found in hepatic parenchymal cells, Kupffer cells and bile duct epithelia. Ultrastructurally, they appear as slightly curved crystals, often arranged in typical rosettes within phagolysosomes (8, 9). Interestingly, the protoporphyrin deposits can also be demonstrated in the liver cells of patients without apparent liver abnormalities (10). Ongoing liver damage finally results in micronodular cirrhosis with loss of normal architecture and cholestasis. In our patient, however, chronic alcohol abuse had most probably contributed to the progression of liver injury.

The pathophysiological mechanisms of liver injury in EPP are still a matter of controversy. Clinicopathological and experimental studies indicate that liver damage in EPP is associated with an accumulation of protoporphyrin in hepatobiliary structures (11), resulting in a light-independent formation of active oxygen species, which in turn cause toxic damage

to hepatic tissue (5). The role of the liver itself as a production site of protoporphyrin in EPP, however, has not yet conclusively been elucidated, since the erythropoietic and hepatic production of protoporphyrin cannot be quantitated separately (12). Hepatic protoporphyrin production has been suspected in only a few reports on EPP (13, 14), whereas most clinical and experimental observations suggest that the erythropoietic tissue is the major source of excessive protoporphyrin (15–19). Analysis of porphyrin metabolism after liver transplantation in EPP patients could give some insight into the role of the liver in the production of protoporphyrin. Indeed, the transplanted liver has normal FeCh activity and cannot, therefore, produce increased amounts of protoporphyrin. Thus, a long-term follow-up of liver transplant recipients could greatly contribute to a better understanding of the pathogenesis of progressive liver disease in EPP. Unfortunately, reports on liver transplantation in EPP patients so far only present data on porphyrin metabolism obtained shortly after liver transplantation (16–22). These short-term data on porphyrin metabolism, however, are blurred by the effects of massive blood transfusion prior to and during liver transplantation, which per se reduces the mean level of erythrocyte protoporphyrin concentration.

It is currently impossible to make any reliable prediction of the individual risk of an EPP patient for the development of hepatic failure. In view of the poor prognosis of clinically
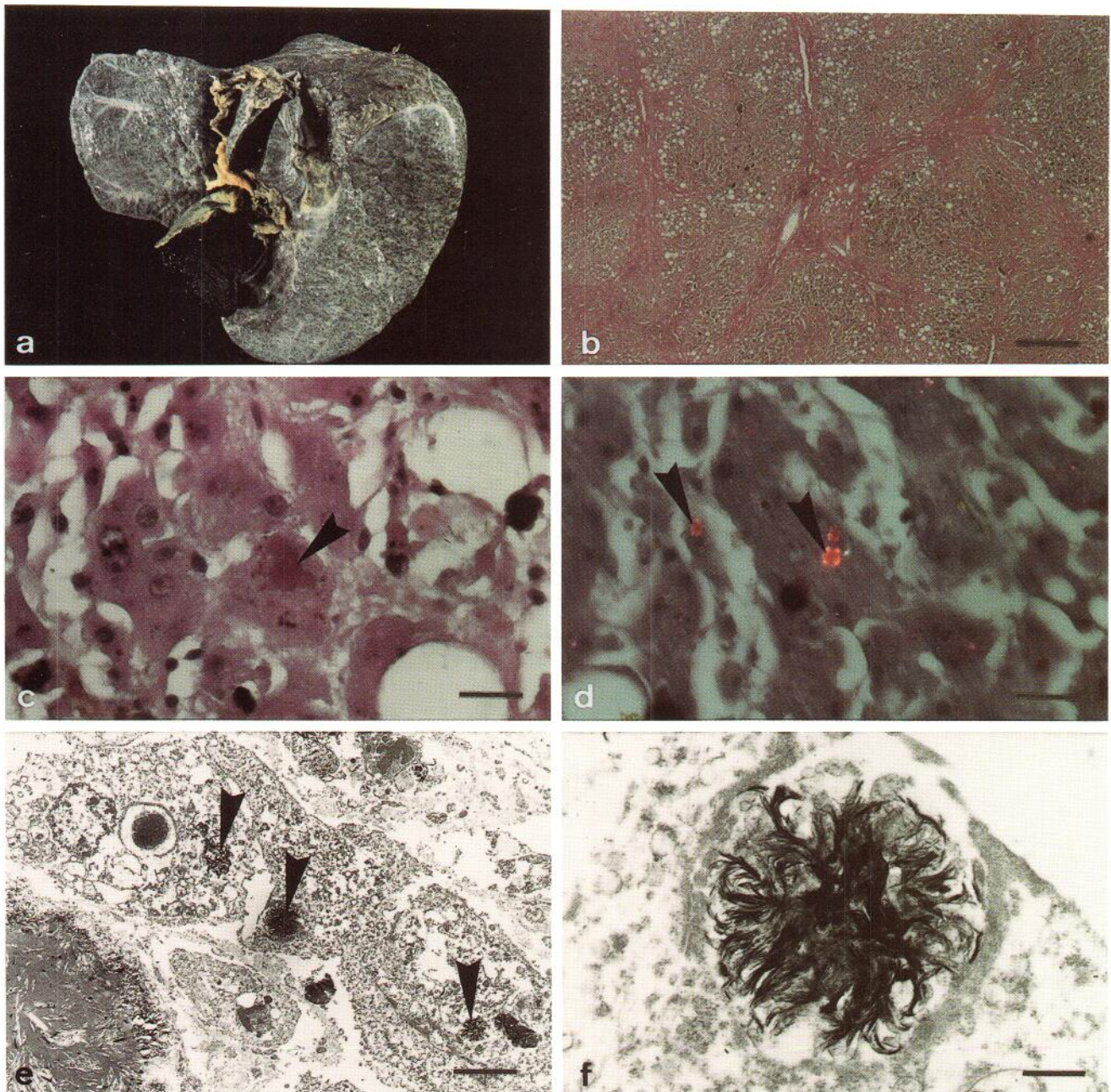
Fig. 2. Morphological aspects of liver involvement. (*a*) Massive black pigmentation of liver parenchyma and cirrhosis. (*b,c,d*) Light microscopical aspects of cirrhotic liver parenchyma (*b*) showing Mallory bodies (*c,arrow*) and birefringent protoporphyrin pigments with crystalline-like configurations (*d,arrows*), (*b*: bar = 0.5 mm; *c,d*: bar = 40 μm), (*e,f*) Transmission electron microscopical aspect of a hepatocyte, showing abundant crystalline deposits of protoporphyrin (*e,arrows*), shown in more detail in (*f*), (*e*: bar = 10 μm; *f*: bar = 1.5 μm).

overt liver disease and the risks of liver transplantation (20–22), EPP patients should have regular liver function tests and periodic liver biopsies that might permit earlier recognition of progressive liver damage, so that prophylactic treatment could be initiated.

REFERENCES

1. Kosenow W, Treibs A. Lichtüberempfindlichkeit und Porphyrin-ämie. Z Kinderh 1953; 73: 82–91.
2. Magnus IA, Jarett A, Prankerd TAJ, Rimington C. Erythropoietic protoporphyria: a new porphyria syndrome with solar urticaria due to protoporphyrinaemia. Lancet 1961; ii: 448–451.
3. Went LN, Klasen EC. Genetic aspects of erythropoietic protoporphyria. Ann Hum Genet 1984; 48: 105–117.
4. Norris PG, Nunn AV, Hawk JLM, Cox TM. Genetic heterogeneity in erythropoietic protoporphyria: a study of the enzymatic defect in nine affected families. J Invest Dermatol 1990; 95: 260–263.

5. Baart de la Faille H, Bijlmer-Iest JC, van Hattum J, Konings-berger J, Rademakers LHPM, van Weelden H. Erythropoietic protoporphyria: clinical aspects with emphasis on the skin. Curr Probl Dermatol 1991; 20: 123–134.

6. Mercurio MG, Prince G, Weber FL Jr., Jacobs G, Zaim MT, Bickers DR. Terminal hepatic failure in erythropoietic protopor-phyria. J Am Acad Dermatol 1993; 29: 829–833.

7. Koningsberger JC, van Asbeck BS, van Hattum J, Wiegman LJ, van Berge Henegouwen GP, Marx JJ. The effect of porphyrins on cellular redox systems: a study on the dark effect of porphyrins on phagocytes. Eur J Clin Invest 1993; 23: 716–723.

8. MacDonald DM, Germain D, Perrot H. The histopathology and ultrastructure of liver disease in erythropoietic protoporphyria. Br J Dermatol 1981; 104: 7–17.

9. Bonkovsky HL, Schned AR. Fatal liver failure in protoporphyria: synergism between ethanol excess and the genetic defect. Gastroenterology 1986; 90: 191–201.

10. Rademakers LHPM, Cleton MI, Kooijman C, Baart de la Faille H, van Hattum J. Early involvement of hepatic parenchymal cells in erythropoietic protoporphyria? An ultrastructural study of patients with and without overt liver disease and the effect of chenodeoxycholic acid treatment. Hepatology 1990; 11: 449–457.

11. Morton KO, Schneider F, Weimer MK, Straka JG, Bloomer JR. Hepatic and bile porphyrins in patients with protoporphyria and liver failure. Gastroenterology 1988; 94: 1488–1492.

12. Nordmann Y. Erythropoietic protoporphyria and hepatic com-plications. J Hepatol 1992; 16: 4–6.

13. Scholnick P, Marver HS, Schmid R. Erythropoietic protoporphy-ria: evidence for multiple sites of excess protoporphyrin formation. J Clin Invest 1971; 50: 203–207.

14. Lamon JM, Poh-Fitzpatrick MB, Lamola AA, Frykholm BC, Freeman ML, Doleiden FH. Hepatic protoporphyrin production in human protoporphyria. Effects of intravenous hematin and analysis of erythrocyte protoporphyrin distribution. Gastro-enterology 1980; 79: 115–125.

15. Schwartz S, Johnson JA, Stephenson BD, Anderson AS, Edmondson PR, Fusaro RM. Erythropoietic defects in protopor-phyria: a study of factors involved in labelling of porphyrins and bile pigments from ALA-^{3}H and glycine ^{14}C. J Lab Clin Med 1971; 78: 411–434.

16. Samuel D, Boboc B, Bernuau J, Bismuth H, Benhamou JP. Liver transplantation for protoporphyria: evidence for the predominant role of the erythropoietic tissue in protoporphyrin overproduction. Gastroenterology 1988; 95: 816–819.

17. Polson R, Lim CK, Rolles K, Calne RY, Williams R. The effect of liver transplantation in a 13-year-old boy with erythropoietic protoporphyria. Transplantation 1988; 46: 386–389.

18. Bloomer JR, Weimer MK, Bossenmaier IC, Snover DC, Payne WD, Ascher NL. Liver transplantation in a patient with protopor-phyria. Gastroenterology 1989; 97: 188–194.

19. Steinmüller T, Doss MO, Steffen R, Blumhardt G, Bechstein WO, Frank M, et al. Liver transplantation in erythrohepatic protopor-phyria. Dtsch Med Wochenschr 1992; 117: 1097–1102.

20. Shehade SA, Chalmers RJG, Prescott RJ. Predictable and unpre-dictable hazards of erythropoietic protoporphyria. Clin Exp Dermatol 1991; 16: 185–187.

21. Herbert A, Corbin D, Williams A, Thompson D, Buckels J, Elias E. Erythropoietic protoporphyria: unusual skin and neuro-logical problems after liver transplantation. Gastroenterology 1991; 100: 1753–1757.

22. Meermann L, Verwer R, Sloof MJH, van Hattum J, Beukeveld GJJ, Kleibeuker JH, Haagsma EB. Perioperative measures during liver transplantation for erythropoietic protoporphyria. Trans-plantation 1994; 57: 155–158.