Photosensitivity and lymphoma

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A 59-year-old woman presented with anorexia, weight loss, lethargy, night sweats and lymphadenopathy. She was a lifelong teetotaler and was on no medication. Following biopsy of an inguinal node, a diagnosis of lymphocyte-depleted Hodgkin's lymphoma was established. Staging investigations showed pelvic and para-aortic node involvement (stage IIB). She went into remission following treatment with six courses of ABVD chemotherapy (adriamycin, bleomycin, vincristine, dexamethasone). During this period, she received 22 units of blood because of marked myelotoxicity.

Three years later she had a left cervical nodal relapse that was treated with local radiotherapy. She was then noted to have increased skin pigmentation. A surveillance computed tomography (CT) scan revealed multiple 1-cm low density lesions in the liver (figure 1). The liver function tests were normal. As she declined a liver biopsy, she was treated with local radiotherapy on the assumption that she had metastatic liver disease. However, there was no change in the radiological appearance of these lesions following treatment. One year later, she developed a photosensitive rash and complained of recurrent painful blistering over the nose and back of hands. The liver profile was bilirubin 9 $\mu\text{mol/l}$ (normal <17), aspartate transaminase 53 U/l (normal <40), γ -glutamyl transferase 50 U/l (normal <35), alkaline phosphatase 182 U/l (normal 40–120). The serum ferritin was 1870 $\mu\text{g/l}$ (normal 12–400). The full blood count, urea and electrolytes, albumin and clotting screen were normal.

Figure 1 Non-enhanced CT scan of the liver showing multiple, small, rounded low-density areas

Questions

- 1 What is the cause of the cutaneous symptoms?
- 2 Name one confirmatory test.
- 3 What is the treatment?
- 4 What is the aetiology of the hepatic lesions?

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Answers

QUESTION 1

Porphyria cutanea tarda, which is the most common form of porphyria in Europe and the US. The underlying biochemical defect is reduced uroporphyrin decarboxylase activity.¹

QUESTION 2

Urine porphyrins. In this situation, the coproporphyrin level was $0.95 \mu\text{mol}/24 \text{ h}$ (normal $0.05\text{--}0.3$) and uroporphyrin $8.4 \mu\text{mol}/24 \text{ h}$ (normal $0\text{--}0.05$).

QUESTION 3

Venesection or chloroquine. In this case, 3600 ml of blood was venesected over a six-month period until the haemoglobin fell to 10 g/dl. The serum ferritin was $800 \mu\text{g/l}$ and the porphyrin and liver function tests normalised. A repeat CT scan revealed that the liver lesions had disappeared.

QUESTION 4

Porphyria cutanea tarda is associated with a characteristic, diffuse, hepatic nodular infiltration. Histologically, these are granuloma-like aggregates consisting of focal necrosis with an inflammatory infiltrate, siderosis, steatosis and mild portal fibrosis.² Brown, needle-like cytoplasmic inclusions of uroporphyrin are pathognomic of porphyria cutanea tarda and are responsible for the intense red fluorescence of biopsy material under ultraviolet light. Macroscopically they appear as ill-defined bluish-brown, slightly depressed areas on the surface of the liver measuring up to 2 cm in diameter. Radiologically, they appear as hyperechogenic liver nodules on ultrasound or as hypodense masses on CT and remit following therapeutic phlebotomy or chloroquine therapy. The presentation in our patient is uncommon but significant in that it can resemble metastatic liver disease; its presence in patients with primary extrahepatic carcinoma can pose a diagnostic problem.^{3–5}

Discussion

There are two types of porphyria cutanea tarda, a sporadic and a rare inherited form. Hepatic uroporphyrinogen decarboxylase activity is

decreased by 50% in both types. The aetiology of the sporadic form is complex. The enzyme defect appears to be inherited but the pattern of inheritance is not clear. The enzyme deficiency requires interaction with additional acquired factors to produce overt porphyria. Iron overload has been implicated as the most important cofactor. The probable predisposing cause in our patient was iron overload related to prior polytransfusion. The role of iron *per se* is controversial. Although uroporphyrin decarboxylase is inhibited by iron *in vitro*, there is no evidence that it exerts the same effect *in vivo*. Indeed, the quiescence of the complaint following therapeutic phlebotomy (despite still being significantly iron overloaded) suggests that other factors may play a role.

Two years later, our patient developed a right cervical relapse that was again treated with local radiotherapy. She developed a mild recurrence of the photosensitive rash during this period. The coproporphyrin and uroporphyrin levels were 0.45 and $3 \mu\text{mol}/24 \text{ h}$, respectively. A CT scan revealed a new hepatic lesion 4 cm in size (figure 2). The patient finally consented to a liver biopsy. Histology confirmed it to be a lymphomatous deposit. The lesion regressed by 90% of its original size following local radiotherapy.

A paraneoplastic syndrome is associated with malignant tumours but not directly caused by the primary growth or its metastases. It can run a course parallel to the tumour. In our patient, the manifestations of porphyria cutanea tarda coincided with the nodal lymphomatous relapses. In all cases of porphyria cutanea tarda associated with non-Hodgkin's lymphoma described in the literature,^{6–8} lymphomatous infiltration of the liver was absent and treatment of the lymphoma with radiotherapy/chemotherapy resulted in improvement of the porphyria. Hepatic microsomal electron transport system components, in particular cytochrome P-450, have been noted to be increased in porphyria cutanea tarda and in some malignant states.⁹

The development of hepatic lymphoma 18 months after the diagnosis of porphyria cutanea tarda warrants comment. It is well known that the risk of hepatocellular carcinoma is increased in porphyria cutanea tarda. However, sufferers are also prone to develop extrahepatic tumours, and there is also a propensity for developing liver metastases in these situations. Porphyrins can bind to DNA

Figure 2 Enhanced CT scan showing a solitary hepatic lesion which was confirmed to be a lymphomatous deposit on histology

Learning points

- porphyria cutanea tarda is commonly associated with haematological conditions
- porphyria cutanea tarda is associated with a diffuse nodular hepatic infiltration which mimics metastatic liver disease but reverses with appropriate treatment
- porphyria cutanea tarda predisposes to the development of tumours, both hepatic and extrahepatic
- the course of porphyria cutanea tarda may parallel that of the underlying process

and play a role in carcinogenesis.¹⁰ The attendant liver damage contributes further to malignant liver deposit formation.

We conclude that, in patients with porphyria cutanea tarda, the search for an occult neoplasm may be of diagnostic and therapeutic value.

Final diagnosis

Porphyria cutanea tarda in a patient with Hodgkin's lymphoma.

Keywords: porphyria cutanea tarda, lymphoma, uroporphyrin decarboxylase

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A treatable cause of lymphocytic meningo-encephalitis

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A 27-year-old woman presented with a one-day history of headache, photophobia, neck stiffness and drowsiness. She had been previously well apart from minor illnesses and chicken pox aged 18 years. On examination she was pyrexial and photophobic with neck stiffness but no rash. Although drowsy she was rousable and without focal neurology. Cerebrospinal fluid (CSF) examination revealed an excess of lymphocytes, $32 \times 10^6/l$ (normal range $< 5 \times 10^6/l$) with a normal protein of 471 mg/l (100–600 mg/l), and glucose of 2.8 mmol/l (2.2–3.9 mmol/l). No bacteria were seen on Gram stain, or on subsequent culture. With treatment she steadily improved and was discharged seven days after presentation.

Questions

- 1 Name five viruses which can cause acute lymphocytic meningo-encephalitis.
- 2 What treatments are available?