

ENDGAMES

CASE REPORT

A man with a blistering eruption and tuberculosis

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A 59 year old Chinese man was admitted for a blistering eruption. He had stopped using injected drugs and drinking alcohol three years ago after having previously drunk two cans of beer, equivalent to 2-3 units of alcohol, a week. Two years ago, he had been diagnosed with chronic hepatitis C virus (HCV) infection and had recently been diagnosed with pulmonary tuberculosis, for which he was started on isoniazid 600 mg, rifampicin 600 mg, ethambutol 1.5 g, and pyrazinamide 2 g three times a week.

Three days after starting this treatment, he developed a progressive blistering eruption over his neck and both upper limbs, which affected his lateral arms and forearms but spared the oral mucosa and other parts of his body. Nikolsky's sign was negative. He stopped all the drugs two weeks later because of a suspected drug eruption.

He had a normal blood cell count with a haemoglobin of 120 g/L (reference range 124-168). Liver enzymes were raised, with alanine aminotransferase at 65 U/L (7-36), aspartate aminotransferase at 96 U/L (14-30), alkaline phosphatase at 158 U/L (32-93), and γ -glutamyl transferase at 648 U/L (11-62), as was total bilirubin at 63 μ mol/L (14-23). Liver ultrasound was normal and his serum α fetoprotein was 2 ng/ml (<4).

No antibodies against intercellular substances and dermoepidermal junction antigens were found in his blood. A skin biopsy of a blister on his forearm showed subepidermal bullae, but immunofluorescence for hemidesmosomal protein at the dermoepidermal junction was negative.

Questions

- 1 What are the differential diagnoses?
- 2 What further investigations are needed to confirm the diagnosis?
- 3 What risk factors does this patient have that predispose him to the development of the disease?
- 4 What treatment would you recommend?

Answers

1 What are the differential diagnoses?

Short answer

Differential diagnoses include drug eruption, bullous pemphigoid, pemphigus foliaceus, and porphyria cutanea tarda.

Long answer

A two year retrospective review of adverse drug reactions from first line antituberculosis drugs reported that 5.7% of patients developed a drug eruption. However, most patients had a morbiliform rash (72.3%), which occurred within two months of starting the drug, and pyrazinamide was most commonly implicated. A bullous rash is therefore an uncommon form of drug eruption in patients on antituberculosis treatment.¹

Bullous pemphigoid is a chronic autoimmune blistering disorder. Patients present with large and tense blisters mainly over the acral areas. The lack of characteristic direct immunofluorescence for hemidesmosomal proteins at the dermoepidermal junction and eosinophilic infiltrates in the skin biopsy speak against this diagnosis.²

Pemphigus foliaceus is another autoimmune blistering disease, which is characterised by the presence of autoantibodies directed against the cell surface of keratinocytes. Patients can present just with blisters and cutaneous erosions. However, the subepidermal blister formation and the negative immunofluorescence on skin biopsy eliminated this diagnosis.

Porphyria cutanea tarda is a photosensitive dermatosis characterised by accumulation of uroporphyrin and partially decarboxylated porphyrins in the liver as a result of reduced hepatic uroporphyrinogen decarboxylase (UROD) activity, either inherited or acquired. When exposed to ultraviolet light of 400 nm, the porphyrins produce free radicals that cause skin fragility and blistering.³

Most patients with this condition present with bullae on sun exposed areas of the body, including the face, dorsal surface of the hands, and extensor surfaces of the forearms (figure).² The bullae crust over and resolve in a few weeks, leaving atrophic scars, milia, and often hyperpigmentation or hypopigmentation.⁴ A non-blistering presentation has also been reported.⁵



Blisters and erosions after rupture of blisters on the left forearm

2 What further investigations are needed to confirm the diagnosis?

Short answer

Further investigations include spot urine for porphyrins and tests for faecal porphyrins with fractionation.

Long answer

Increased concentrations of urinary uroporphyrin and heptacarboxyporphyrin are seen in porphyria cutanea tarda owing to the inactivation or inhibition of hepatic UROD. Pentacarboxylate porphyrinogen III and dehydroisocoproporphyrinogen III, which is normally a minor product, also accumulate. Increased dehydroisocoproporphyrinogen III leads to increased isocoproporphyrin III. Hence, faecal isocoproporphyrin is the biochemical hallmark of UROD deficiency.³

Plasma spectrofluorimetry and Wood's lamp examination of the urine are also helpful, especially in parts of the world where more elaborate investigations are difficult to perform.

Spectrofluorimetric scanning of the plasma can detect cutaneous porphyria during the symptomatic phase of the disease, and Wood's lamp examination of the urine will show coral pink fluorescence owing to the presence of excessive porphyrins in patients with porphyria cutanea tarda.⁶

3 What risk factors does this patient have that predispose him to the development of the disease?

Short answer

The patient has hepatitis C infection, which is closely associated with porphyria cutanea tarda. Moreover, the patient was given rifampicin.

Long answer

A strong association between HCV infection and porphyria cutanea tarda has been well established. In Western countries, the prevalence of HCV infection in patients with porphyria cutanea tarda varied from 18% to 91%. How HCV infection predisposes to the development of porphyria cutanea tarda remains unknown, although it has been proposed that HCV may decrease hepatic UROD activity,⁷ and that damaged liver cells or excess hepatic iron produce inhibitors against UROD.^{8,9} Whatever the mechanism, hepatic iron overload is a nearly

universal finding in patients with porphyria cutanea tarda and forms the basis of phlebotomy treatment.

In a case series of 10 patients from Hong Kong with sporadic porphyria cutanea tarda diagnosed from 1982 to 1997, nine had medical diseases, including two with HCV.¹⁰ Although hereditary haemochromatosis is a known risk factor for porphyria cutanea tarda, it is rare in Chinese people.

A few reports have noted an association between porphyria and pulmonary tuberculosis. Of the antituberculosis drugs that our patient was taking, only rifampicin has been reported to induce porphyria cutanea tarda.¹¹ The link between porphyria cutanea tarda and tuberculosis is unclear.

4 What treatment would you recommend?

Short answer

Identification and avoidance of precipitating factors, abstinence from alcohol, and iron reduction treatment with phlebotomy.

Long answer

Venesection and low dose chloroquine (125 mg twice weekly) are reasonable first line treatments. Venesection should aim to achieve a haemoglobin of 100 g/L or a serum iron concentration of 9 µmol/L.² Serum transferrin saturation and ferritin concentrations correlate with urinary porphyrin excretion and clinical symptoms. Chloroquine chelates the porphyrins, which is thought to make them more water soluble and to enhance their urinary excretion.³ Avoidance of precipitating factors including sunlight, alcohol, and oestrogens also helps.² Especially during the time that specific treatments are taking effect, visible light sunscreens containing pigmentary grade titanium dioxide or zinc oxide, hats, gloves, and clothes can help reduce skin damage via photoprotection. Because accumulated porphyrins are carcinogenic to the liver, it is also important to treat hepatitis C if present, with regular monitoring of liver function and the risk of developing hepatocellular carcinoma.

Patient outcome

Our patient had no other common skin features of porphyria cutanea tarda, such as hypertrichosis, skin fragility, milia, and sclerodermiform changes. His two consecutive samples of spot urine for porphyrins were raised at 919 nmol/mmol creatinine and 573 nmol/mmol creatinine (<35). Fractionation of urine porphyrins showed that uroporphyrin and heptacarboxyporphyrin were higher than normal. Fractionation of stool porphyrins showed raised isocoproporphyrin, heptacarboxyporphyrin, hexacarboxyporphyrin, and pentacarboxyporphyrin. His iron profile on presentation showed a serum iron level of 17 µmol/L (9-33), transferrin saturation of 31% (16-45%), and ferritin of 1481 pmol/L (52-738). The overall picture was in keeping with porphyria cutanea tarda. He had a total of five units of blood removed by venesection. His serum iron and haemoglobin dropped to 6.3 µmol/L and 114 g/L, respectively, and urine porphyrins normalised. Levofloxacin 500 mg daily and ethambutol 700 mg daily were gradually reintroduced after two months. His skin condition improved with no new blister formation on subsequent follow-up despite continuing antituberculosis drugs.

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