PORPHYRIA IN HODGKIN'S DISEASE*

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Varied and perplexing skin lesions are found in the course of Hodgkin's disease. A survey of the world literature shows that 20 - 50% of patients have significant complaints referable to the skin; no cases with concomitant porphyria have as yet been reported.

Although porphyrin was referred to and described as far back as the last century[1,2] and the term *porphyria* was first used by Waldenström[3] more than 30 years ago, many aspects of this enigmatic condition still await clarification. Indeed, even the classification of porphyrias must await more knowledge regarding their inter-relationships, and is constantly being revised. The most useful current classification is shown in Table I.[4]

The following case report draws attention to a hitherto unpublished concomitant metabolic disorder occurring during the course of Hodgkin's disease.

TABLE I. CLASSIFICATION OF PORPHYRIAS (1970)[4]

1. Erythropoietic porphyria
   (*a*) recessive (classical congenital porphyria)
   (*b*) dominant (*porphyria erythropoietica et hepatica* or erythropoietic protoporphyria or coproporphyria)
2. Acute intermittent porphyria
   (*a*) manifest
   (*b*) latent
3. Hepatic cutaneous porphyria
   (*a*) hereditary
      (*i*) *porphyria cutanea tarda* or protocoproporphyria
      (*ii*) mixed porphyria
      (*iii*) variegate porphyria
   (*b*) acquired
      (*i*) symptomatic *porphyria cutanea tarda*
      (*ii*) Bantu porphyria
      (*iii*) hexachlorobenzene porphyria
      (*iv*) griseofulvin porphyria
      (*v*) porphyria of hepatic adenoma
4. Experimental porphyria

CASE REPORT

A 39-year-old diamond cutter was referred to our clinic with the diagnosis of Hodgkin's disease of mixed cell type (Luke's classification). Biopsies were performed on an enlarged lymph gland in the left inguinal area and skin from the pubic area. About 4 months previously he started complaining of pruritus, weight loss, fever and sweating.

When the patient was first seen in our clinic he was found to be very ill with a deep jaundice, severe nausea, and pain over the right hypochondrium and lower back. He further complained of loss of appetite and a moderate 'dead feeling' of all fingers. Examination showed bilateral multiple enlarged lymph glands of the groins as well as a large, hard swelling of the anterior pubic area, and hepatomegaly. A severe ichthyosis of the whole body was present.

The following laboratory results were obtained at this

*Date received: 28 August 1970.

time: Haemoglobin 13·5 g/100 ml, platelets 229 000/mm³, white cells 25 000/mm³ with a differential count of 90% polymorphonuclear cells, 4% lymphocytes and 6% monocytes. The Coombs test was negative, and a bone-marrow examination showed no abnormalities. Blood urea was 34 mg/100 ml, uric acid was 3·8 mg/100 ml, creatinine was 1·5 mg/100 ml, serum calcium was 10·6 mg/100 ml, and serum copper was 190 μg/100 ml. The sedimentation rate was 40 mm (Westergren), bilirubin direct/indirect was 1·5/0·8 mg/100 ml, SGOT was 23 Cabaud units, alkaline phosphatase 32 KA units, serum albumin 2·6 g/100 ml, serum globulin 4·7 g/100 ml and serum gammaglobulin 1·5 g/100 ml. A marked bilirubinuria was present.

Intensive combination chemotherapy was started immediately. By the 8th day of treatment the liver was no longer palpable, the adenopathy was very much smaller and the pubic swelling half the initial size. Both pruritus and pain had cleared, and the generalized ichthyosis was only mild. The patient's appetite improved. The icterus was only mild, sedimentation rate was down to 10 mm, bilirubin was normal, SGOT was 12 Cabaud units, serum albumin 3·3 g/100 ml, serum globulin 4·2 g/100 ml, alkaline phosphatase 22 KA units. Serum copper was still 200 μg/100 ml.

By the 28th day the jaundice had cleared, there was no bilirubinuria, serum albumin was 3·7 g/100 ml and serum globulin 3·3 g/100 ml. Alkaline phosphatase was still above normal (20 KA units). Serum copper was 162 μg/100 ml. Serum electrophoresis remained normal and the alkaline phosphatase gradually became normal. An occasional abnormal value was still periodically recorded for SGOT and SGPT tests. By day 169 all tests indicative of liver function were normal, and they have remained so up till the present time. On day 176 the patient complained of blisters on both hands. He was found to have several large (up to 1·5 cm by 0·5 cm) subepidermal bullae, mainly on the dorsae of both hands (Figs. 1 and 2). These bullae contained a colourless fluid, and in other areas the blisters were broken and crusted over. No bullae occurred on the rest of the body.

Urine and faeces were positive for porphyrins. Quantitative and qualitative tests were performed. The faeces showed an increased coproporphyria of 50·86 μg/g dry faeces, and an increase of protoporphyrins to 71·87 μg/g dry faeces. No uroporphyrins were present. In the urine the coproporphyrins were greatly increased to 152·66 μg/litre urine, while no uroporphyrins were found.

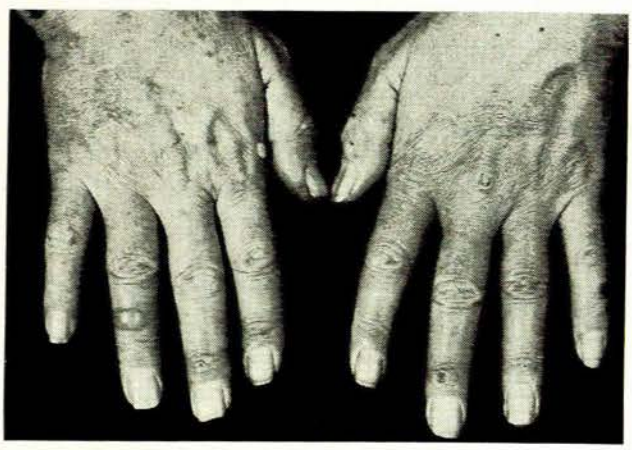

Fig. 1. The typical appearance of the patient's hands. A large unruptured bulla can be seen on the ring finger of the right hand.

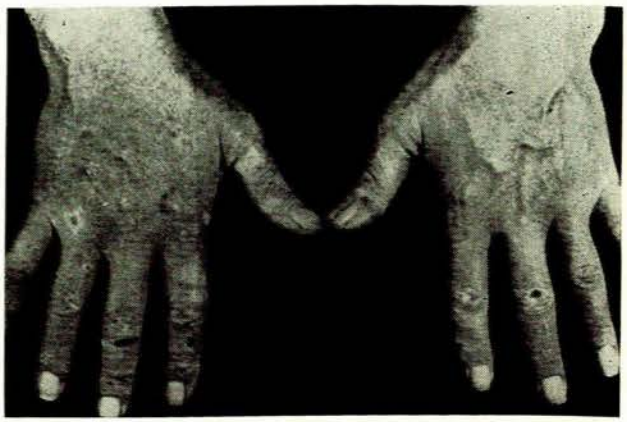

Fig. 2. Scarring and depigmentation as well as crusted, ruptured bullae are clearly visible on the dorsae of both hands.

The patient was in complete remission from the Hodgkin's disease 170 days after treatment was started and is still in complete remission 10 months after the commencement of treatment. The cutaneous porphyria has remained present, which is rather irksome in his work.

DISCUSSION

In this patient several skin lesions occurred: specifically Hodgkin's disease of the skin (as was shown by the biopsy of the pubic area), the non-specific ichthyosis of Hodgkin's disease (which cleared on successful treatment of the Hodgkin's disease) and lastly, an unusual concomitant porphyria with typical skin lesions. When the porphyria presented shortly after grossly abnormal liver function was restored, it was thought to be an acquired symptomatic form of porphyria cutanea tarda based on malfunction of the liver. An interesting aetiological aspect observed by Gajdos-Török[5] is the rather frequent appearance of cutaneous porphyria in patients with rare diseases of haematological character. This could also fit in with our patient. The age and sex of this patient, absence of serious photosensitivity, no family history of porphyria, the fact that administration of barbiturates had had no adverse effects on him, and of course the acquired liver malfunction, suggested a symptomatic porphyria cutanea tarda. Differentiation between symptomatic porphyria and genetic porphyria on purely clinical grounds may be impossible.[6,7] Quantitative and qualitative biochemical findings in the excreta (increased copro- and protoporphyrins with absence of uroporphyrins) indicate that this patient probably has a porphyria cutanea tarda hereditaria (protocoproporphyria of Waldenström) or else the so-called 'variegate' porphyria of White South Africans.

The aetiological mechanism for the development of porphyria awaits clarification. An elevation of the porphyrins or their precursors in urine and faeces is the chemical hallmark of the porphyrias; this may be caused either by a block in haem biosynthesis or, more likely,

by increased production of porphyrin precursors. Investigations suggest that increased amounts of glycine or delta-aminolaevulinic acid are available for porphyrin biosynthesis. Since δ-aminolaevulinic acid is a common precursor for both porphyrin and purine biosynthesis, it has been suspected that an abberation in purine metabolism may represent part of the hepatic porphyrias. Since the first symptoms of cutaneous porphyria the patient's serum uric acid has remained elevated, ranging from 7·5 to 8·8 mg/100 ml. The coexistence of porphyria and hyperuricaemia may seem paradoxical, if a block in the manufacture of purines is a defect in porphyria. However, metabolic defects like gout and porphyria are not incompatible,[8] and the presence of hyperuricaemia does not necessarily negate the possibility that a block exists in the formation of purines.

The case reported here presents a complex problem regarding the aetiology of the porphyria: (*i*) this may be a patient with porphyria variegata, totally unrelated to the Hodgkin's disease; (*ii*) the porphyria may be part of the Hodgkin's disease—although concomitant porphyria and Hodgkin's disease have never before been documented, id reactions of bullae and vesicles during the course of Hodgkin's disease have been reported,[9,10] but the cases were not investigated for porphyria (hydroa aestivale is not at all uncommon in Hodgkin's disease, and it has been noted[11] that some cases of so-called hydroa aestivale or polymorphous light eruption may well be due to porphyria); (*iii*) lastly, the question arises whether a chemotherapeutic agent may have been a precipitating factor in a patient with a genetic defect. The porphyria occurred when the patient was already in complete remission with normal liver function; 3 weeks had elapsed since intensive combination chemotherapy had been stopped; and he had been receiving chlorambucil as maintenance therapy for 1 week before the appearance of the bullae.

Chlorambucil (N-N-di(2-chloroethyl)-p-amino-phenyl-butyric acid) is one of the oldest alkylating agents and has been in clinical use since 1954. It has been given for long periods in a vast number of patients throughout the world, and has never precipitated an attack of porphyria. This may perhaps be because the incidence of porphyria is only 0·2%[12] or 0·07% for South African genetic porphyria.

SUMMARY

Skin lesions are very common in Hodgkin's disease, but no cases with concomitant porphyria have as yet been reported. A case is presented where protocoproporphyria with typical skin involvement occurred when the patient with advanced Hodgkin's disease and severe liver involvement was in complete remission. Biochemical differentiation between symptomatic porphyria cutanea tarda and genetic porphyria showed that this patient has the latter form. The possible interrelationship between Hodgkin's disease and the metabolic defect of porphyrin metabolism is discussed.

We wish to thank Dr J. L. Meiring, pathologist, for the quantitative and qualitative porphyrin determinations.

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