Indurated Skin and Iron Overload—the Missing Link

A 62-year-old Chinese woman with a history of haemochromatosis and secondary hemosiderosis presented with gradual onset of skin hardening and increased prominence of hair follicles on bilateral forearms and back of the neck for 9 months. There was no pain or itch in the affected areas. Systemic review did not show Raynaud's phenomenon, dysphagia, dyspepsia, sicca symptoms or joint pain.

Physical examination revealed sclerodermoid, indurated plaques on forearms and arms with speckled hypo- and hyperpigmentation. Erosions were seen on the dorsum of hand and forearm (Fig. 1). On the nape, speckled hypo- and hyperpigmentation was also seen with a sharp cut-off at the collar line (Fig. 2). Skin biopsy demonstrated thickened collagen bundles in the dermis (Fig. 3). Skin induration improved with hydroxychloroquine 100 mg twice a week.

What is the most likely diagnosis?

A. Chronic actinic dermatitis (CAD)
B. Eosinophilic fasciitis
C. Porphyria cutanea tarda (PCT)
D. Scleroderma
E. Scleromyxedema

Discussion

Although the distribution (on the face and appearance of a "V" shape on the neck and forearms) fits the diagnosis of CAD (sun-exposed areas), the morphology of CAD is chronic, lichenified and eczematous plaques. Also, eosinophilic fasciitis usually presents with induration of the limbs with shallow grooves or furrows in the skin that run along the paths of underlying veins, and is usually associated with pain and swelling and inflammation of the skin.

Scleroderma has an initial oedematous phase (pitting oedema of digits) with subsequent sclerosis. It is often accompanied by Raynaud's phenomenon with synovitis and systemic involvement (cardiac, renal, gastrointestinal and pulmonary).[1] Scleromyxedema usually presents as waxy papules in a linear array. The surrounding skin is shiny and indurated, and is sclerodermoid in appearance. Typically, it affects the hands, forearms, head, neck, upper trunk and thighs.[2]

In our patient, findings of quantitative assay of blood and urine samples showed raised total urinary and erythrocyte porphyrins. Together with her clinical

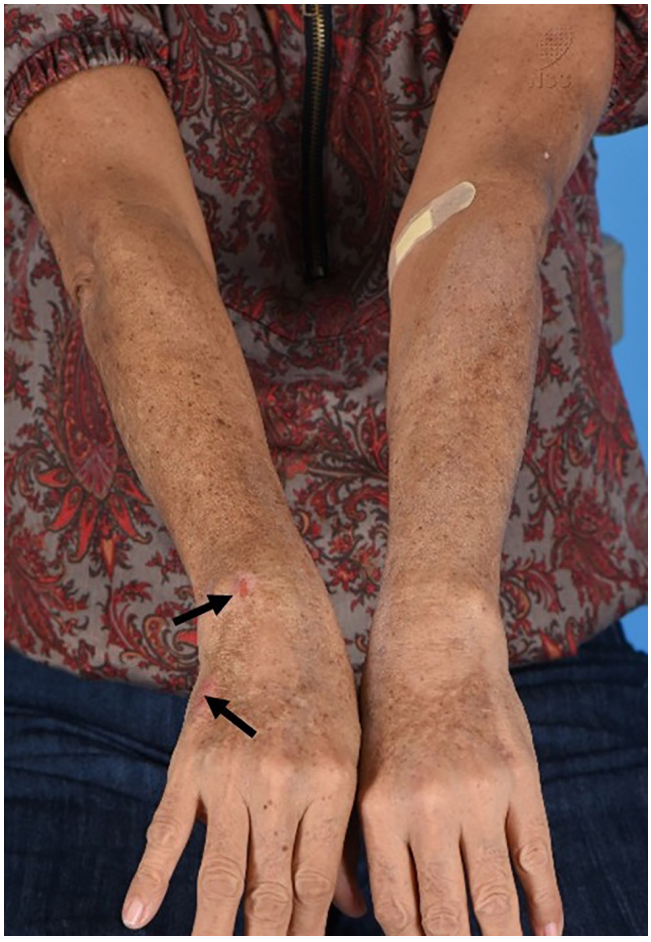

Fig. 1. Indurated plaques on forearms and arms with speckled hypo- and hyperpigmentation and erosions (black arrows).

Correct answer: C

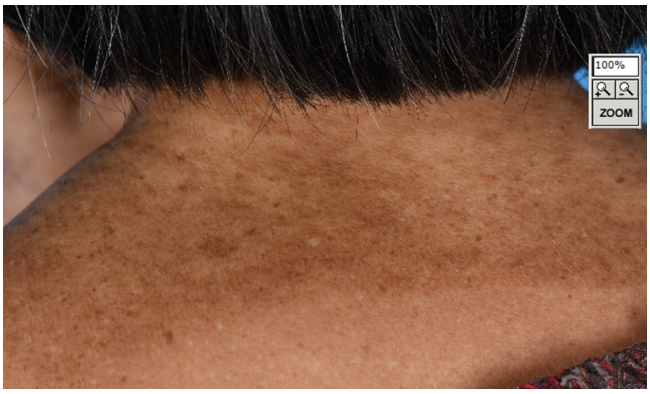

Fig. 2. Indurated plaques with speckled hypo- and hyperpigmentation with a sharp cut-off at the collar line.

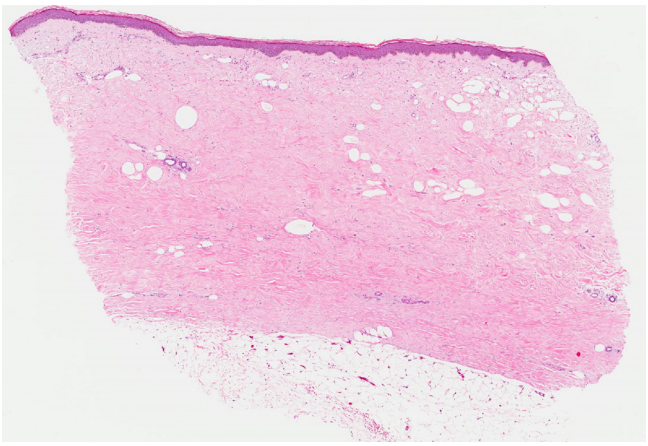

Fig. 3. Dermis shows widespread thickened collagen bundles. Fusion of adjacent collagen bundles and loss of intercollagenous cleft spaces are seen in some areas. The eccrine glands are compressed and appear high-lying due to collagen that is laid down below which extends to the dermosubcutaneous junction with a flat edge (hematoxylin and eosin stain, magnification × 40).

presentation, the results confirmed the diagnosis of PCT. PCT is the most common form of porphyria seen in dermatological practice and its clinical features include sclerodermoid plaques, erosions, vesicles and hyperpigmentation in sun-exposed areas. It is also associated with hypertrichosis.[3]

PCT is characterised by reduced activity of uroporphyrinogen decarboxylase (UROD) enzyme, which could be attributed to inherited genetic defects or acquired factors that caused inactivation of the normal enzyme. There are 3 types of PCT. Type 1 (sporadic) is the most common form and accounts for 80% of cases and occurs in the absence of UROD gene mutation. Type 2 (familial) is characterised by a UROD mutation that affects 1 allele. Type 3 (familial) is also characterised by familial inheritance, but UROD mutation is absent and it may be attributed to other hereditary factors such as haemochromatosis gene mutation.[4]

In all 3 types of PCT, hepatic UROD activity is decreased and leads to accumulation of porphyrins in the liver. Porphyrins are then transported from the liver to the skin, where they absorb sunlight and enter an excited state (photoactivation). This abnormal activation results in characteristic damage to the skin (blister formation and skin hardening from dermal fibrosis).

Several factors can predispose individuals to become more susceptible to the development of PCT. They include alcohol use, smoking, hepatitis C, human immunodeficiency virus and oestrogen supplementation.[5] However, the most important factor is iron overload that occurs in conditions such as haemochromatosis.[6,7] Increased hepatic iron facilitates the formation of oxygen free radicals that contribute to oxidative formation of a UROD inhibitor.

Full blood count is usually normal while serum aminotransferase levels are elevated. Urine test will yield a pink fluorescence when it is illuminated under Wood's light. In PCT, urine porphyrin excretion is increased. The excreted porphyrins are predominantly uroporphyrin and heptacarboxyl porphyrin. Quantitative assay of porphyrins can be performed in specialised centres.[8]

All patients with PCT who have active skin lesions should receive primary therapy including phlebotomy or low-dose hydroxychloroquine. In a prospective pilot study that involved 48 consecutive patients with PCT, time required to normalise plasma porphyrin levels—a predictor of clinical improvement—was similar for both treatments.[9]

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