

Polymorphic Skin Rash and Fatigue in a Patient with Diabetes Mellitus: A Quiz

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A 62-year-old woman presented with a several-year history of progressive cutaneous lesions involving the face, neck, gluteal region and lower extremities, accompanied by severe pruritus, pain and newly developed fatigue. Her medical history was notable for diabetes mellitus diagnosed approximately a decade earlier.

Clinical examination revealed multiple, confluent, irregularly shaped, serpiginous plaques with peripheral scaling, partially featuring blisters, erosions, haemorrhagic crusts and periorificial accentuation (Fig. 1).

Histopathological assessment demonstrated psoriasiform dermatitis with hypogranulosis, parakeratosis and distinct epidermal alterations including keratinocyte pallor and loss of intercellular adhesion (Fig. 2).

What is your diagnosis?

1: Immunoglobulin A (IgA) pemphigus

2: Acrodermatitis enteropathica

3: Necrolytic migratory erythema

4: Dermatitis herpetiformis

See next page for answer.



Fig. 1. Clinical manifestations of the patient. Multiple, coalescent, bizarrely shaped, serpiginous plaques with peripheral scaling on the face with periorificial accentuation (a), neck (b) and gluteal region (c). Multiple blisters, erosions and postinflammatory hyperpigmentation on the feet (d) and lower extremities (e).

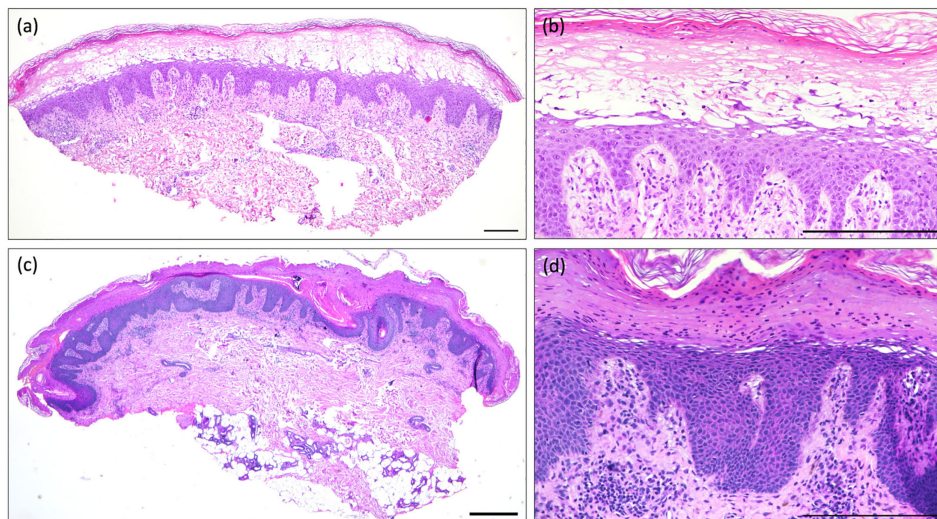


Fig. 2. Histopathological findings. Hematoxylin and eosin stain of a skin biopsy specimen demonstrates psoriasiform dermatitis, parakeratosis, absence of stratum granulosum and keratinocyte pallor with loss of intercellular adhesion (a,b). Another skin biopsy specimen from a chronic lesion reveals subtle changes including psoriasiform hyperplasia, parakeratosis with rounded nuclei and pallor of upper epidermal layers (c,d). Scale bars, 500 μ m.

ANSWERS TO QUIZ

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Diagnosis: Necrolytic migratory erythema

Direct immunofluorescence microscopy of a perilesional skin biopsy yielded no presence of tissue-bound autoantibodies. Based on the clinical and histopathological findings, a nutritional deficiency-related dermatosis was suspected. Laboratory analysis showed a markedly elevated glucagon level of 1820 pg/mL (reference, <160 pg/mL) and zinc deficiency (5.0 µmol/L; reference, 9–18 µmol/L). Her HbA1c level was 6.8 %. Magnetic resonance imaging revealed a 2.2×3.5 cm hypervascular, partially microcystic, oval-shaped pancreatic tail mass, which underwent histopathological confirmation of a moderately differentiated glucagonoma. Following surgical resection and zinc supplementation, complete resolution of the skin lesions was achieved (Fig. 3). Staging with ⁶⁸Ga-DOTATOC PET/CT revealed no evidence of metastatic disease.

Necrolytic migratory erythema (NME) is a cutaneous paraneoplastic manifestation associated with glucagonoma syndrome, which represents an exceedingly rare condition with an estimated global incidence of one in 20 million people (1). Histologically, the condition shares features with other nutritional deficiency-related dermatoses. Psoriasiform acanthosis and parakeratosis with rounded nuclei are frequently observed (2). Neutrophilic granulocytes within the parakeratotic layer and subcorneal

pustules may also be present. A hallmark feature is pallor of the upper epidermal layers with loss of keratinocyte structure, also referred to as necrolysis, along with loss of the stratum granulosum (2). The precise cellular basis of necrolysis remains unresolved, with it currently unclear whether the process is mediated by necrosis, apoptosis, or alternative mechanisms.

Glucagonoma is an extremely rare functional pancreatic neuroendocrine tumour (pNET) arising from islet alpha cells in the tail or body of the pancreas. It accounts for 2–7 % of all pNETs and was reported to display no clear sex predilection, although a more recent analysis indicates otherwise (3, 4). Increased glucagon production induces a catabolic state with enhanced gluconeogenesis and lipolysis, leading to secondary deficiencies, particularly of zinc, amino acids and essential fatty acids (1). Clinically, glucagonoma syndrome is characterized by a constellation of systemic manifestations, most notably NME, diabetes mellitus, weight loss, fatigue, anaemia, thromboembolic events and neuropsychiatric symptoms (1, 5). The exact pathophysiology underlying NME remains to be defined; however, hyperglucagonemia is considered a pivotal factor, supported by the frequent and rapid resolution of cutaneous symptoms following tumour resection or pharmacologic suppression of glucagon secretion using somatostatin analogues (1, 6). Additional hypotheses implicate metabolic and nutritional deficiencies, particularly hypoaminoacidemia, essential fatty acid depletion and zinc deficiency, as reflected in the therapeutic benefit observed with nutritional supplementation and zinc administration (3, 7, 8).

Early diagnosis of glucagonoma syndrome is crucial, as more than half of patients already present



Fig. 3. Postoperative clinical outcome: At 7 weeks following surgery, complete remission of the cutaneous manifestations was observed. Residual findings were limited to faint postinflammatory hyperpigmentation involving the perioral region (a), posterior neck (b), gluteal region (c) and lower extremities (d).

with metastatic disease, most frequently hepatic involvement, at initial diagnosis (9). Radical surgical excision remains the only curative treatment for both glucagonoma and its associated dermatologic manifestations (1). In advanced or metastatic disease, chemotherapy, peptide receptor radionuclide therapy with somatostatin analogues and liver-directed treatment modalities have been shown to achieve substantial antitumor and antisecretory activity (9).

In summary, we present a rare case of NME as an early and crucial diagnostic clue for the underlying glucagonoma. This report underscores the importance of prompt recognition of NME as part of glucagonoma syndrome for early diagnosis.

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