Extensive pigmented abdominal plaque in a diabetic patient

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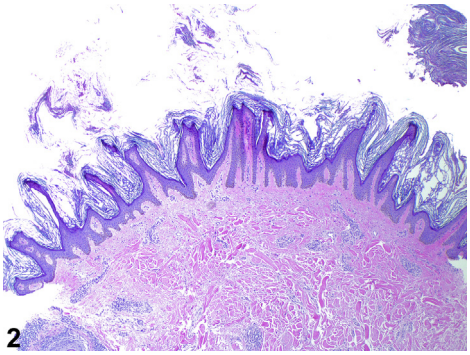

A 42-year-old man of South-Asian descent with insulin-dependent type 2 diabetes mellitus presented with a 2-year history of an asymptomatic hyperpigmented plaque on his lower abdomen. He described a 10-year regimen of self-injecting insulin aspart, 60 U, and insulin detemir, 120 U, subcutaneously, twice daily to his lower abdominal area exclusively without rotating areas of injections. Clinical examination found an extensive diffuse hyperpigmented and hyperkeratotic dark-brown corrugated plaque on his lower abdomen (Fig 1).

A skin biopsy from the abdominal plaque found epidermal hyperplasia and mild hyperkeratosis (Fig 2).

Question 1. Considering the above clinical and histopathologic images, what is the most likely diagnosis?

A. Acquired ichthyosis

B. Retention hyperkeratosis

C. Confluent and reticulated papillomatosis (CARP)

D. Drug-induced acanthosis nigricans (AN)

E. Erythrasma

Answers:

A. Acquired ichthyosis — Incorrect. Acquired ichthyosis is associated with conditions such as lymphoma, HIV, inflammatory disorders, and malnutrition. The histology consists of mild orthokeratosis, hyperkeratosis with a diminished granular layer, and negative staining for filaggrin.

B. Retention hyperkeratosis — Incorrect. This condition occurs with abnormal desquamation and is typically associated with poor hygiene. Retention hyperkeratosis can usually be removed with an alcohol swab.

C. CARP — Incorrect. The typical onset of CARP occurs during pubertal development with lesions manifesting as brown verrucous coalescing papules with a reticulated appearance at the peripheral margins. A classic histopathologic feature is bulbous epidermal rete ridges that protrude into the

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papillary dermis, which is not supported by the skin biopsy taken.

D. Drug-induced AN — Correct. Typically, AN presents as thick hyperpigmented verrucous/velvety plaques commonly over the neck and axillae and is associated with diabetes and obesity. The features of AN on histopathology include hyperkeratosis, dermal papillomatosis, and mild acanthosis.[1,2] In this case, the AN was induced by injected insulin.

E. Erythrasma — Incorrect. Erythrasma typically presents as brown-to-erythematous plaques and is more prevalent in diabetic patients. It is caused by *Corynebacterium minutissimum*. Erythrasma often occurs in intertriginous areas and fluoresces a coral-pink color on Wood's lamp examination. Histology shows a sparse superficial perivascular lymphocytic infiltration and orthokeratosis within which blue staining organisms (rods and filaments) may be seen on hematoxylin-eosin staining.

Question 2. Which of the following contributes to the pathogenesis of drug-induced AN?

A. Induction by insulin and insulin-like growth factor (IGF)

B. Inflammation secondary to *Malassezia furfur*

C. Genetic predisposition

D. Underlying malignancy

E. Impairment of the barrier skin function

Answers:

A. Induction by insulin and IGF — Correct. The pathogenesis of AN, when benign, is likely related to the induction of insulin and IGF, which stimulates the proliferation of keratinocytes and fibroblasts.[2] Compensatory hyperinsulinemia secondary to insulin resistance (from type 2 diabetes) is a pathogenic factor that is considered to drive this condition. It is believed that long-term exogenous insulin injections to the subcutaneous tissue stimulates epidermal cell growth, leading to the development of AN over these injected areas.[3,4]

B. Inflammation secondary to *M furfur* — Incorrect. Fungal organisms do not contribute to the development of this condition.

C. Genetic predisposition — Incorrect. There is no clear evidence suggesting genetic predisposition plays a contributing role in drug-induced AN, which is in contrast to hereditary benign AN that can manifest in an autosomal dominant fashion.

D. Underlying malignancy — Incorrect. Benign insulin-induced AN is not related to more worrisome variants of AN, which are often associated with aggressive malignancies.

E. Impairment of the barrier skin function — Incorrect. This is not considered to contribute to drug-induced AN development.

Question 3. Other than insulin, which of the following medications is most likely to cause a drug-induced AN?

A. Methotrexate

B. Fusidic acid ointment

C. Vancomycin

D. Testosterone

E. Nicotinic acid

Answers:

A. Methotrexate — Incorrect. This medication has not been reported to cause AN.

B. Fusidic acid ointment — Incorrect. Fusidic acid is a bacteriostatic antibiotic that inhibits translocation in protein synthesis and is effective in treating gram-positive bacteria especially *Staphylococcus aureus* and *Streptococcus pyogenes*. Although this medication has been reported in one case to cause AN from topical application, it is not the most likely to cause drug-induced AN.

C. Vancomycin — Incorrect. To our knowledge, there have been no reported cases of vancomycin-induced AN.

D. Testosterone — Incorrect. There have been a few cases of testosterone-induced AN, although this is not a common side effect of this medication.

E. Nicotinic acid — Correct. It is estimated that as many as 20% of patients on oral nicotinic acid will have drug-induced AN at some point.[5]

Abbreviations used:

AN: acanthosis nigricans
CARP: confluent and reticulated papillomatosis
IGF: insulin-like growth factor

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