Proton pump inhibitor–induced erythema dyschromicum perstans–like pigmentation

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INTRODUCTION

Proton pump inhibitors (PPIs) are potent inhibitors of gastric acid secretion by parietal cells in gastric mucosa. Cutaneous pigmentation mimicking ashy dermatosis (AD)/erythema dyschromicum perstans (EDP) has been described with both omeprazole and esomeprazole. This report describes the presentation, histopathologic findings, and treatment of EDP-like pigmentation in the setting of lansoprazole and esomeprazole use.

Abbreviations used:

AD: ashy dermatosis
EDP: erythema dyschromicum perstans
PPI: proton pump inhibitor

CASE REPORT

A 65-year-old Venezuelan woman presented to our dermatology clinic for evaluation of dyschromia. She noted dark patches after concurrently starting venlafaxine, bupropion, lansoprazole, simvastatin, and levothyroxine. This mildly pruritic eruption initially appeared on the trunk and progressed to involve the neck, forehead, axillae, and both upper and lower extremities. On physical examination, she had many ill-defined, brown and slate-gray patches with erythematous borders, distributed as noted. A punch biopsy of the slate-gray patch on the right arm showed the presence of melanophages in the papillary dermis. EDP was suspected; she was given topical glucocorticoids, but there was no improvement for more than 10 years.

Because of the persistence of these patches (Fig 1), the patient had a repeat biopsy on the chest along the erythematous border of a slate-grey patch. Histopathologic evaluation showed a superficial perivascular lymphocytic infiltrate with vacuolar interface and numerous melanophages in the papillary dermis, again suggestive of EDP (Fig 2). Aside from a transition of lansoprazole 30 mg to esomeprazole 40 mg, there were no other medication changes during the course of her dermatologic evaluation; she continued taking all of the listed medications. Given documented associations of AD/EDP-like pigmentation with PPIs,[1-3] esomeprazole was discontinued. Soon thereafter, both pruritus and dyschromia improved. After 18 months, she reported no disease recurrence and endorsed continued improvement in cutaneous dyspigmentation (Fig 3).

DISCUSSION

First described in El Salvador as *dermatosis cenicienta*, or *ashy dermatosis*, by Ramirez in 1957, erythema dyschromicum perstans is a disorder of pigmentation frequently seen in Latin American and Asian populations and is characterized by asymptomatic, symmetric, ashy gray/blue macules and patches.[4] These lesions can appear on the trunk but may also involve the upper extremities, neck, and face. The term *erythematous dyschromicum perstans* was later coined by Sulzberger, who observed an erythematous border in active lesions.[4] Presence of this erythematous border during the

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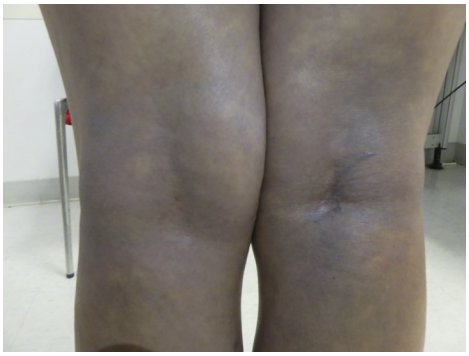

Fig 1. Multiple ill-defined, brown and slate-gray patches on the bilateral popliteal fossae.

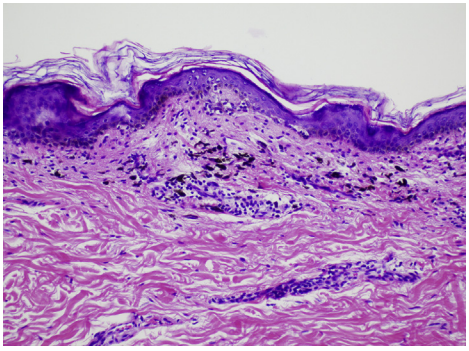

Fig 2. Histopathologic evaluation showed superficial perivascular lymphocytic infiltrate with vacuolar interface and numerous melanophages in the papillary dermis (hematoxylin-eosin; original magnification, ×200).

early active phase is the main differentiator between erythematous dyschromicum perstans and ashy dermatosis, according to a recently updated global consensus statement.[5] Histopathologic findings of early EDP include vacuolar interface with lymphocytic predominance and pigmentary incontinence, whereas older lesions may show only melanophages in the papillary dermis without interface changes. The terms *EDP* and *AD* are used when the underlying cause is unknown or considered idiopathic, whereas when a specific agent is identified as the driving mechanism, the condition is instead referred to as *AD-* or *EDP-like pigmentation* secondary to the underlying etiology.[6]

Although rare, AD- and EDP-like drug eruptions have been linked to PPIs. PPIs are H^+/K^+ adenosine triphosphatase inhibitors used to decrease gastric acid secretions, thereby treating gastroesophageal reflux and gastrointestinal ulcers.[7,8] PPIs diffuse into the parietal cells in the gastric mucosa, where they are protonated and converted to a sulfonamide, the active metabolite, which covalently binds critical cysteine residues on the H^+/K^+ adenosine triphosphatase to inhibit basal and stimulated acid

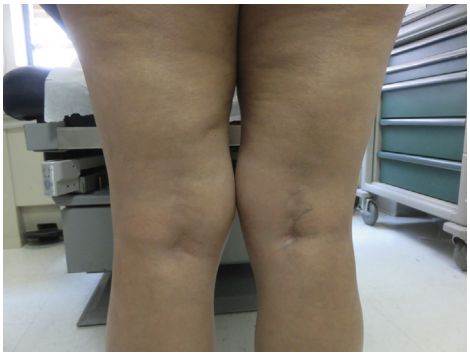

Fig 3. Resolution of erythema dyschromicum perstans–like pigmentation after cessation of all proton pump inhibitors.

secretion.[7,8] A wide variety of drug-induced cutaneous adverse reactions to PPIs have been described, including urticaria, angioedema, photoallergic dermatitis, cutaneous lupus erythematosus, drug-induced hypersensitivity syndrome, and toxic epidermal necrolysis.[9] To date, only 5 cases of AD- or EDP-like drug eruptions in association with PPIs have been reported in the literature for omeprazole and esomeprazole.[1-3] Given the erythematous border observed in this patient's early lesions, we thus present an additional case of PPI-induced EDP-like drug eruption, but we suggest that lansoprazole could also be a culprit.

In general, the pathogenesis of drug-induced hyperpigmentation is incompletely understood, although many overlapping mechanisms have been proposed. These include excessive melanin production due to exogenous medication or nonspecific inflammation with postinflammatory melanophage accumulation, deposition of iron from drug-induced vascular damage, drug-induced synthesis of non-melanin endogenous pigments, or accumulation of exogenous drug in tissues.[10] In the case of PPI-induced EDP-like pigmentation, the underlying mechanism is still not fully known, similar to the idiopathic form of EDP. One study has proposed involvement of sulfur granules in dermal macrophages, based on findings from electron microscopy and energy-dispersive radiographic microanalysis.[3]

Previous cases have shown esomeprazole 40 mg daily and omeprazole 20 mg daily to be suspected agents in AD/EDP-like pigmentation. The latency between the start of medication and development of pigmentation has been reported as 2 months to 1 year.[1-3] With removal of the offending agent, all documented cases of PPI-induced EDP-like pigmentation reported improvement[1-3]; topical glucocorticoids were used in addition to the removal of the offending agent in 1 case.[1] Although our patient was

initially given concurrent medications, we could not identify any EDP-like pigmentary changes resulting from simvastatin, venlafaxine, bupropion, or levothyroxine upon literature review. Appearance after initiation of PPIs, persistence during their use, and improvement upon cessation suggest lansoprazole and esomeprazole as the most likely causal agents in this individual's disease presentation. Therefore, continued interrogation of medications during management may prove beneficial as disease etiologies become better elucidated.

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