A case of lichenoid drug eruption associated with relugolix

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INTRODUCTION

The gonadotropin-releasing hormone (GnRH) analogue drug class consists of both GnRH agonists and antagonists, and is primarily used for androgen deprivation therapy in the treatment of prostate cancer. Relugolix is the first and only Food and Drug Administration-approved oral GnRH antagonist for the treatment of adult patients with advanced prostate cancer. Unlike GnRH agonists, relugolix decreases serum testosterone levels without testosterone flares at treatment initiation.[1] Eliminating testosterone flares increases the tolerability of this medication by reducing side effects such as ostealgia and urinary retention. Relugolix also has a lower relative risk of cardiovascular events such as myocardial infarction and stroke when compared to GnRH agonists. Additionally, other GnRH analogues including leuprolide (GnRH agonist) and degarelix (GnRH antagonist) are administered subcutaneously or intramuscularly, and therefore carry a risk of injection site reaction.[1] Oral administration of relugolix eliminates this risk, making it a favorable option for patients. Barring an injection site reaction, the only other known skin reaction related to GnRH analogues is skin reddening during acute hot flashes.[1,2] Relugolix, compared to leuprolide, has shorter time to testosterone suppression, higher rate of sustained testosterone suppression, and faster testosterone recovery upon therapy completion.[3,4] We describe, to our knowledge, the first case of a moderate skin rash in a male patient undergoing relugolix treatment for metastatic prostate cancer.

Abbreviation used:

GnRH: gonadotropin-releasing hormone

CASE HISTORY

A 57-year-old man with metastatic prostate cancer was started on oral relugolix 120 mg daily. About 1 week after beginning therapy, the patient developed a pruritic rash on his buttocks that soon spread to his thighs, abdomen, and axilla. The rash continued to spread despite 7 weeks of treatment with triamcinolone 0.025% ointment twice daily prescribed by his treating oncologist. His oncologist then referred him to dermatology for further evaluation.

He presented to the dermatology clinic 9 weeks after relugolix treatment initiation. At the time of presentation, his long-standing daily medications included fenofibrate, omeprazole, atorvastatin, hydrochlorothiazide, nifedipine, and tamsulosin. Relugolix was the only new drug started in the 5 months prior to rash onset. His clinical exam was notable for multiple erythematous to violaceous, scaly papules coalescing into thin plaques, covering about 5% of his body surface area (Fig 1, *A* and *B*). Oral mucosal examination revealed no lesions. The patient denied oral pain or burning sensations. Additionally, the patient had no evidence of genital lesions or nail changes. A shave biopsy of a lesion on his left thigh revealed lichenoid dermatitis with eosinophils (Fig 2). He was treated with clobetasol

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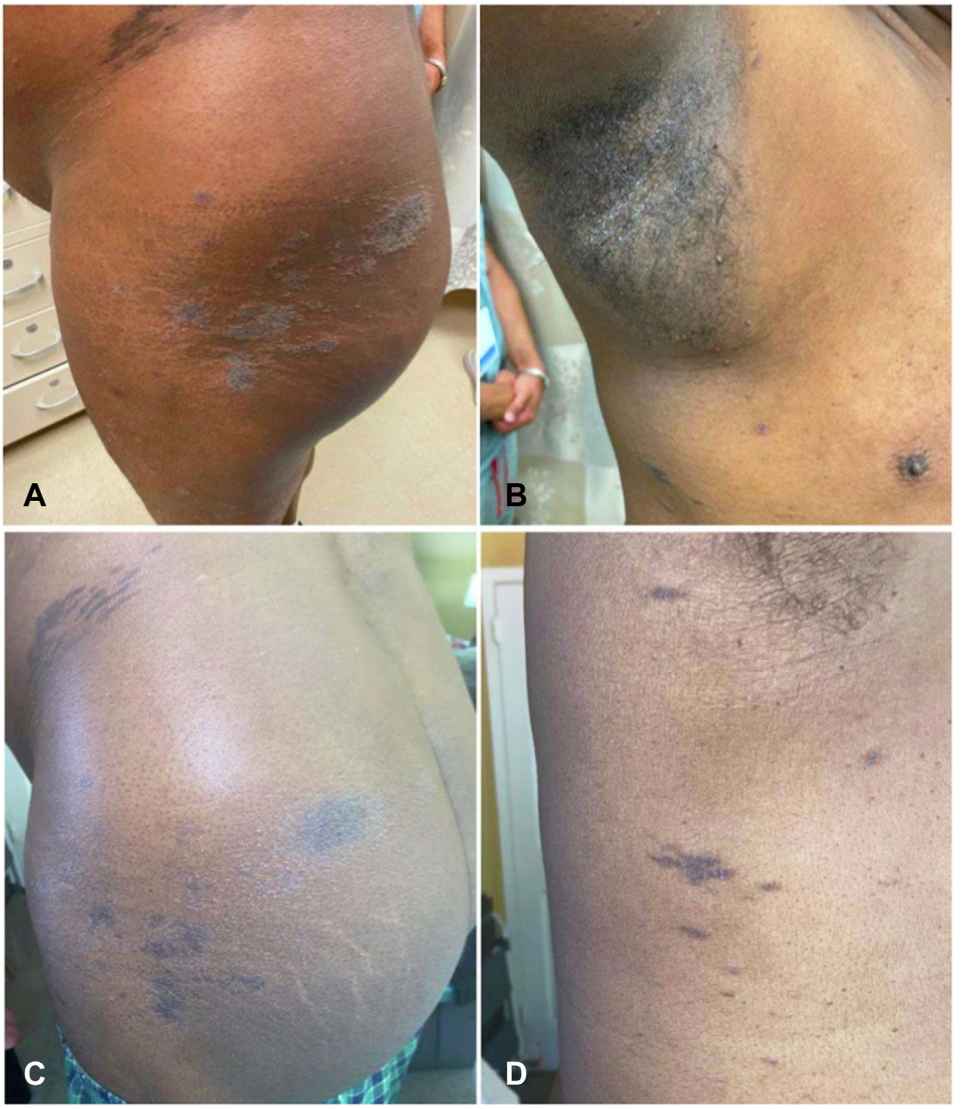

Fig 1. A, Left buttock and (**B**) right axilla before treatment with clobetasol 0.05% ointment for 2 weeks, demonstrating erythematous to violaceous, scaly papules coalescing into thin plaques. **C,** Left buttock and (**D**) right axilla after treatment, demonstrating hyperpigmented macules and patches consistent with postinflammatory pigment alteration.

0.05% ointment twice daily, and relugolix was continued without interruption. Over the course of 2 weeks, his pruritus resolved and the rash improved, with only postinflammatory hyperpigmentation visible (Fig 1, *C* and *D*).

DISCUSSION

This is, to our knowledge, the first report of a biopsy-confirmed skin toxicity associated with a GnRH analogue. The diagnosis was favored to be a lichenoid drug eruption, as opposed to idiopathic lichen planus, given the lack of mucosal involvement and generalized, symmetric distribution of the rash, which spared classic sites of lichen planus such as the flexor forearms and presacral area. The presence of eosinophils in the biopsy suggests a lichenoid drug eruption,[5] providing further support that the rash was associated with relugolix therapy in this case.

Common drugs known to cause lichenoid drug eruptions include angiotensin-converting enzyme inhibitors, thiazide diuretics, antimalarials, and beta blockers.[5] Our patient denied any other recent medications besides relugolix in the last 5 months. While the pathophysiology is still unclear, lichenoid drug eruption may involve inflammatory interactions of the offending drug with immune system mediators including T cells and cytokines.[6] The impact of sex

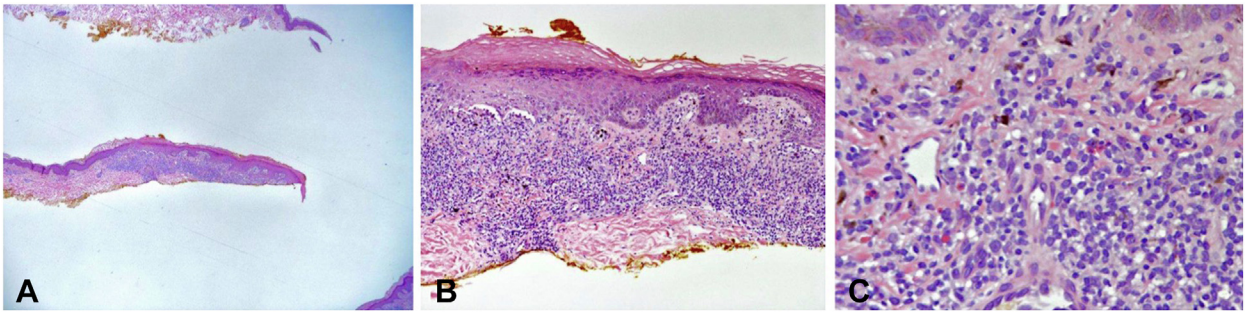

Fig 2. A, Low magnification (hematoxylin and eosin [H&E], 4×) and (**B**) medium magnification (H&E, 10×) show lichenoid interface dermatitis with mixed inflammatory infiltrate, necrotic keratinocytes, vacuolar interface change, and melanophages. **C,** High magnification (H&E, 40×) shows the infiltrate is composed of lymphocytes and eosinophils.

hormones on the pathophysiological conditions of the skin is also an important consideration, given that relugolix reduces systemic testosterone levels.[1] Sex hormones have various effects on the skin and modulate signaling pathways involved in inflammation. Testosterone in particular has been shown to have suppressive effects on inflammation. This is supported by the previously reported finding that male atopic dermatitis patients have lower testosterone levels when compared to controls.[7] Similarly, in a clinical study that compared sex hormones in psoriatic and non-psoriatic males, males with psoriasis exhibited lower testosterone levels.[8]

Lichenoid drug eruptions are typically first managed with discontinuation of the offending medication, and self-resolve within a few weeks to months. If the patient cannot discontinue the drug, or has prolonged or extensive disease, therapies for idiopathic lichen planus are utilized. These include topical, intralesional, and systemic corticosteroids, topical calcineurin inhibitors, narrowband UV-B phototherapy, and systemic retinoids.[5] In this case, we successfully treated the lichenoid drug eruption with clobetasol 0.05% ointment twice daily, without discontinuing the important oncologic therapy. Given that relugolix has robust use in prostate cancer and emerging clinical utility in other pathologies such as endometriosis and leiomyomas,[9] patients and clinicians alike should be aware of this possible side effect for clinical counseling and management.

Conflicts of interest

None disclosed.

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