SKIN

BRIEF ARTICLE

A Case of Dasatinib-Induced Keratosis Pilaris

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ABSTRACT

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) indicated for treatment of chronic myeloid leukemia (CML). Dasatinib targets several proteins specific to cancer pathogenesis such as Bcr-Abl, Src, c-kit and PDGFRb. Cutaneous reactions are a well-documented side effect of many TKIs, however, there are limited reports and characterization of dasatinib induced rash. We report a case of keratosis pilaris and follicular epithelial thinning in a 19-year-old patient one month after beginning dasatinib for treatment of CML. This report suggests a possible role of dasatinib in the induction of epithelial follicular instability via reduced Src activity and subsequent down regulation of EGFR.

INTRODUCTION

Dasatinib is a second-generation tyrosine kinase inhibitor (TKI) that is indicated for treatment of chronic myeloid leukemia (CML). Mechanistically, it targets several proteins specific to cancer pathogenesis as they are involved in differentiation, proliferation, and survival. The main proteins targeted are Bcr-Abl, Src, c-kit and PDGFRβ.[1] Dasatinib is structurally similar to the first-generation kinase, imatinib, but has a 325-fold greater potency and is effective against most imatinib-resistant kinase domain mutations.[1]

Although, dasatinib has a high safety profile and is generally well tolerated, Drucker et al found a 23.3% incidence of all-grade rashes and 1.1% incidence of high-grade rashes associated with dasatinib.[2,3] Clinical presentation of rashes from this study were described as pruritic, keratosis pilaris-like eruptions.[2] Cutaneous reactions are a well-documented side effect of first and second-generation TKIs, however, there are limited reports of dasatinib induced rash.[4,5] Further, the mechanism of rashes due to TKIs are theorized to be pharmacologic rather than immunologic as symptoms are generally dose-dependent and resolve upon cessation of dosing.[6] Unfortunately, it is not always possible to discontinue TKI treatment and therefore cutaneous side effects may be treated pharmacologically. As of now, evidence-based guidelines have not been established for management of dasatinib induced cutaneous side effects, but eruptions that are suggestive of inflammatory processes can be managed with topical corticosteroids.[2,7]

CASE REPORT

We report a case of persistent keratosis pilaris occurring in a young male that was

exacerbated upon beginning treatment of CML with dasatinib.

A 19-year-old-male was diagnosed in August 2017 with CML that was confirmed through bone marrow biopsy resulting in BCR/ABL fusion in 91% of the nuclei. At that time, he was started on chemotherapy consisting of imatinib 400 mg daily. The patient was switched from imatinib to dasatinib because of lack of documented cytogenic/molecular remission after 2.8 years on imatinib.

Throughout the duration of imatinib treatment, the patient experienced an intermittent mild, pruritic papular rash over his upper extremities that spread to his abdomen and chest. Once the patient switched to dasatinib, the severity of the rash worsened significantly. The patient described it as extremely pruritic and exacerbated by heat. The patient briefly took himself off the medication for an entire month (February 2021) without resolution of the rash and has since restarted dasatinib. The patient presented to dermatology in May 2021, with abundant uniform spiky follicular papules covering the trunk, arms, thighs, back and face (**Figure 1**). Clinically, our patient's rash was consistent with keratosis pilaris.

A punch biopsy was taken. Histopathological analysis revealed follicular epithelial thinning affecting mainly the upper portion of the hair follicle, leading to free hair shafts with a mild associated reactive inflammatory infiltrate. The overlying follicular ostia contained parakeratotic debris with mild associated perifollicular acanthosis (**Figure 2**).

The patient was started on triamcinolone 0.1% cream twice daily, applied to affected areas and over the counter ammonium lactate lotion applied all over, every day.

DISCUSSION

It is well known that one of the most common non-hematologic adverse effects of TKIs cutaneous reactions, however, there is little evidence of cutaneous side effects associated with dasatinib.[8] Although, keratosis pilaris-like eruptions are the most common adverse cutaneous effects reported from dasatinib treatment, they have not been well characterized as morphologies are varied.[2,5,9] Bergman, et al. describes a case of neutrophilic dermatosis associated with dasatinib that presented as recurrent erythematous plaques on the face, neck, chest, arms and back. Biopsies showed a variably cellular, superficial, and deep perivascular and interstitial predominantly neutrophilic infiltrate without evidence of vasculitis.[9]

In our case, biopsy remarkably revealed destabilization of follicular epithelium characterized by follicular epithelial thinning leading to follicular rupture on histopathology. The typical epidermal hyperkeratosis, hypergranulosis and plugging of individual hair follicles of regular keratosis pilaris was not observed, despite our patient's clinical presentation being consistent with keratosis pilaris. Differential diagnosis of keratosis pilaris includes other follicular disorders such as follicular hyperkeratotic spicules, trichodysplasia spinulosa, disseminate and recurrent infundibular folliculitis, disseminated spiked hyperkeratosis and multiple digitate hyperkeratosis. Characteristics of these diseases in respect to clinical manifestations, histopathological findings and their associated conditions are summarized in **Table 1**.

Follicular destabilization is thought to underlie the common acneiform rash that can be seen with TKI therapy, especially those

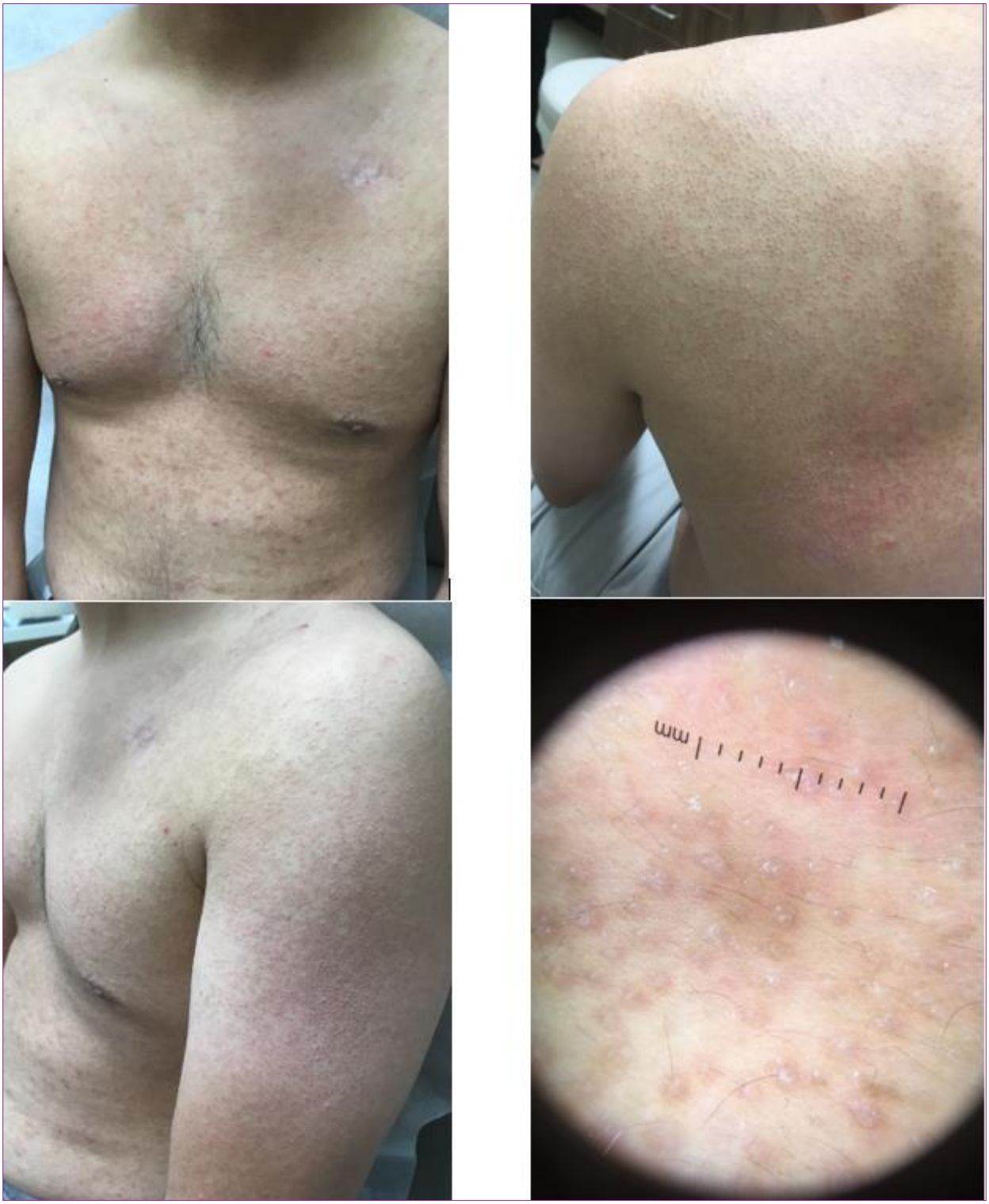

Figure 1. Uniform spiky follicular papules covering the chest, abdomen, arms, and back

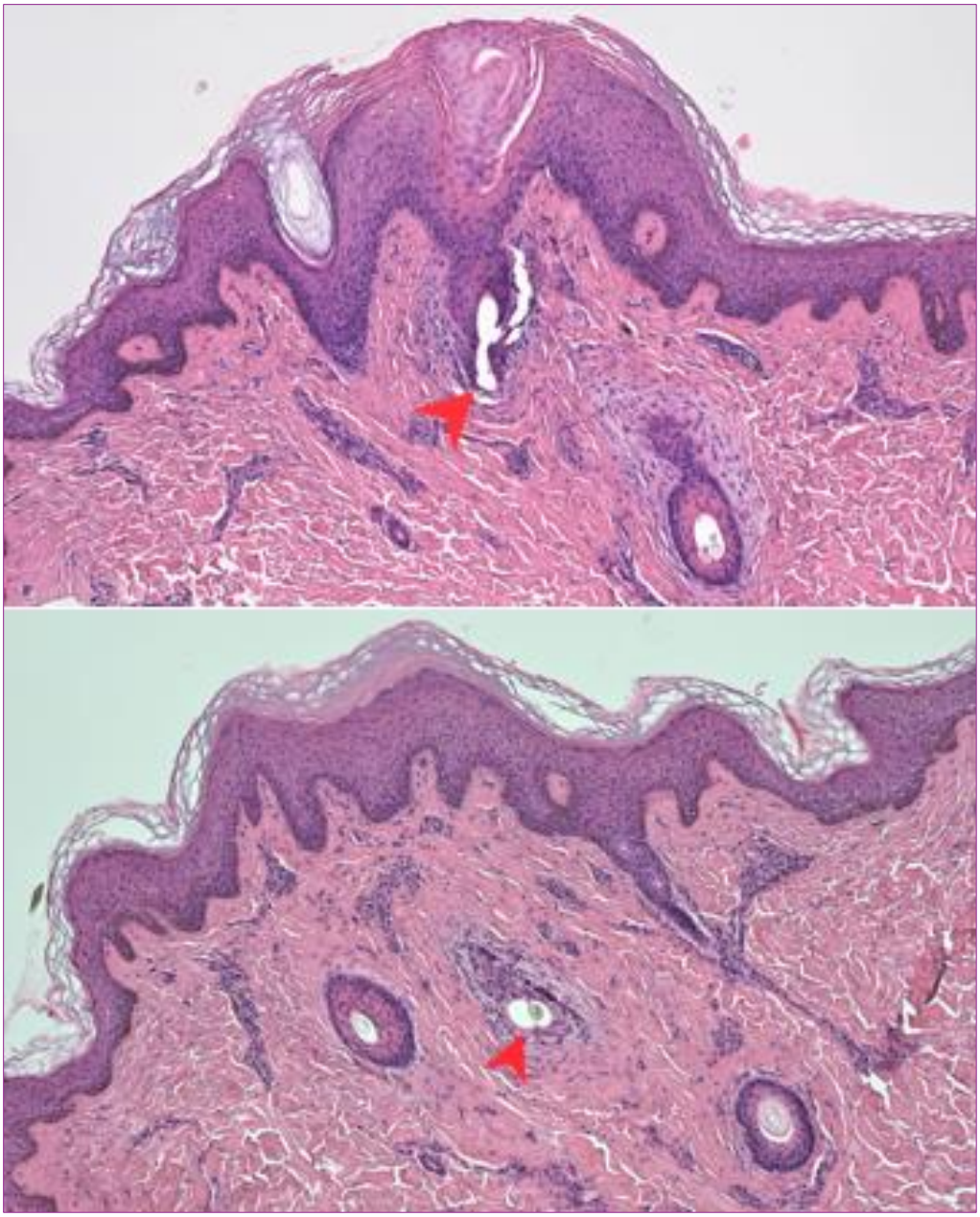

Figure 2. follicular epithelial thinning affecting mainly the upper portion of the hair follicle, leading to free hair shafts with a mild associated reactive inflammatory infiltrate. The overlying follicular ostia contained parakeratotic debris with mild associated perifollicular acanthosis

Table 1. Clinical findings, histopathology, and associations of the differential diagnosis for keratosis pilaris

Diseases	Clinical Findings	Histopathology	Associations
Follicular hyperkeratotic spicules	Tiny hyperkeratotic spicules in follicular distribution and predominantly on the face	Infundibular hyperkeratosis, focal parakeratosis, and mild acanthosis with evidence of follicular plugging	Multiple myeloma
Trichodysplasia spinulosa	Numerous keratotic spicules on follicular erythematous papules, disproportionately affects the face	Follicular hyperkeratosis and multiple vellus hairs enveloped by a keratotic sheath within a dilated hair follicle	Viral associations in immunocompromised hosts
Disseminate and recurrent infundibular folliculitis	Hundreds of uniform, skin-colored papules likened to “goose bumps”. Presents on the trunk, neck, and upper extremities	Mild inflammation of the follicular infundibulum	Primarily seen in adults with darkly pigmented skin
Disseminated spiked hyperkeratosis	Widely disseminated small spikes of keratin that are unrelated to hair follicles	Digitate orthokeratosis with moderate epidermal cell hyperplasia and a normal underlying dermis	Familial, early adulthood
Multiple digitate hyperkeratosis	Fine filiform hyperkeratotic lesions. Predominately affects the trunk and extremities	Nonfollicular, focal columns of orthokeratosic hyperkeratosis emerging from a raised epidermis with significant stratum granulosum	Familial, sporadic, post-inflammation, paraneoplastic

that modulate the epidermal growth factor receptor (EGFR) pathway, as EGFR signaling is important in hair follicle homeostasis.[7,10,11] Although dasatinib does not result in direct inhibition of EGFR, targeted activity against Src down-regulates EGFR activity.[10,12] This suggests a possible role of dasatinib in the induction of follicular instability via reduced EGFR activity, leading to a phenomenon similar to that seen in patients on EGFR inhibitors.

CONCLUSION

We report a case of keratosis pilaris induced by dasatinib treatment that histologically revealed evidence of follicular destabilization, characterized by follicular epithelial thinning, leading to follicular rupture. This specific characterization has not yet been reported and proposes further questioning of the relationship between reduced Src and EGFR down regulation.

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