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Case Report

Nilotinib-Induced Elephantine Psoriasis In a Patient With Chronic Myeloid Leukemia: A Rare Case Report and Literature Review

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ABSTRACT

Tyrosine kinase inhibitors are anticancer drugs that disrupt signal transduction pathways in protein kinases by different mechanisms. This group of pharmacologic agents has significantly improved the outcome of patients with chronic myeloid leukemia. However, their effect is not limited to cancer cells, and various complications, particularly cutaneous reactions, have been reported. We report a very rare case of a 35-year-old female with a history of chronic myeloid leukemia who presented with elephantine psoriasis after the treatment with nilotinib.

Conclusions: This case highlights a critical side effect of tyrosine kinase inhibitors. Awareness of this subject can be useful for better management of similar patients.

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Introduction

The increasing prevalence of cancer in recent decades has led to significant advances in pharmacotherapy. Tyrosine kinase inhibitors (TKIs) have revolutionized cancer treatment. They selectively inhibit receptors with kinase activity, such as breakpoint cluster region Abelson (BCR-ABL), platelet-derived growth factor receptor (PDGFR), and receptor tyrosine kinase, which are involved in intracellular signal-transduction pathways in tumor cells, leading to the deregulation of key tumor cell functions, including proliferation and differentiation. The first TKI approved by the US Food and Drug Administration as an anticancer agent was imatinib. However, the emergence of polyclonal resistance to imatinib led to the development of second-generation TKIs such as nilotinib and dasatinib. Recent guidelines recommend any of these 3 TKIs as options for the initial treatment of cancers such as chronic myeloid leukemia (CML).[1]

These narrow-spectrum agents have minimal side effects compared with previous well-known chemotherapeutic agents. Nevertheless, the effects of these therapeutic agents are not limited to cancer cells. Cutaneous reactions are well described in TKI therapy and constitute their most common nonhematologic adverse events. Maculopapular rashes, chromatic changes in hair and skin, alopecia, pruritus, and dry skin are common adverse cutaneous effects of TKIs. Of note, the cutaneous side effects of second-generation TKIs are fewer than those of imatinib, in particular, edema and pigmentary changes. There is evidence of the role of imatinib in psoriasis development.[2] This evidence suggests that imatinib may promote the development of psoriasis; however, it remains unclear whether or not second-generation TKIs like nilotinib mediate the pathogenesis of psoriasis because there are only a few cases of psoriasis incidence in patients receiving nilotinib therapy.[3–5]

This article reports a patient treated with nilotinib due to CML who subsequently developed elephantine psoriasis. Understand-

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Table 1
Hematologic indices before and after nilotinib prescription.

Index	Before nilotinib prescription	After nilotinib prescription
White blood cells, /μL	10,900	7600
Red blood cells, mil/μL	3.9	4.12
Hemoglobin, g/dL	12	12.1
Hematocrit, %	36.3	36.3
Mean corpuscular volume, fl	93	91
Mean corpuscular hemoglobin, pg	30.8	29.4
Mean corpuscular hemoglobin concentration, g/dL	33.1	32.3
Red cell distribution width, %	14.4	14.4
Platelets, /μL	285,000	300,000

ing any possible association between these particular side effects and the range of targeted kinases may provide critical insight that could lead to better explanations about the mechanism of these side effects and skin physiopathology. Moreover, clinicians must learn about these side effects and the proper treatments to improve patients' quality of life and adherence to therapy.

Case Presentation

During April 2021, a 35-year-old woman presented to our private dermatology clinic with the chief complaint of large itchy lesions on her lower limbs. She had a history of CML from 10 years before. Due to imatinib resistance following the progression of BCR-ABL, nilotinib tablets 800 mg/d had been prescribed for her since September 2018. After 7 months, erythematous rashes appeared on her legs with mild pruritus. She had visited a general practitioner and received injectable corticosteroids 3 times over 2 months with no therapeutic response. She had not followed-up her problem until April 2021. After that, she visited us, complaining of large lesions with severe itching that intensified at night, bleeding after itching, and burning pain in her legs, especially during walking. She was in the chronic phase of CML and did not take any medication except nilotinib. She had no joint and nail involvement, allergy history, addiction, recent trauma, or family history of skin disorders. This condition upset her mood and negatively affected her relationships and sleep.

On the cutaneous examination, extensive, thick, large, scaly, symmetrical plaques were seen over the medial surface of her thighs, knees, posterior aspect of calves, and dorsum of the foot with well-defined interrupted convex borders (Figure 1). An incisional biopsy of skin lesions was performed. The histopathologic examination showed hyperkeratosis, neutrophilic parakeratosis, Munro's microabscess, psoriasiform acanthosis, dermal vascular dilatation, and perivascular lymphocytic infiltration (Figure 2). The clinical and histopathological findings were consistent with elephantine psoriasis.

The complete blood count indicies before and after nilotinib prescription are shown in Table 1. Moreover, before nilotinib prescription, BCR-ABL increased from 0.001% to 0.021%, decreasing to 0.006% after nilotinib therapy. Because of the patient's financial problem, mutation analysis was not undertaken. Nilotinib was not stopped for her on the suggestion of her doctor. Recent BCR-ABL was 0.003%, and the patient is in molecular response 4 status. Thus, we ordered methotrexate 15 mg per week subcutaneously along with topical steroids. She is presently receiving this treatment, and her monthly follow-up appointments have revealed an appropriate therapeutic response.

Discussion and Literature Review

Psoriasis is a chronic multisystemic inflammatory disorder that has been declared a serious public health challenge by the World Health Organization due to its high socioeconomic burden. In psoriasis, because of the intolerance to the suppressive effects of T effector cells, there is a reduction in suppressor cytokine production, and the number and inhibitory function of regulatory T lymphocytes. In this process, immune cell dysregulation and cytokine imbalance cause abnormal migration of keratinocytes to the skin surface and crust formation acceleration. Psoriasis is categorized morphologically into plaque, guttate, pustular, and erythrodermic types. Chronic plaque is the most common form of psoriasis and includes a few uncommon subtypes, namely annular, lichenified, and hyperkeratotic types. The hyperkeratotic form is rarely introduced in the literature, categorized into ostraceous, rupioid, and elephantine forms. Elephantine psoriasis is characterized by extensive, thick, scaly plaques, usually on the lower extremities. The report of elephantine psoriasis in this study is thus of great interest.[6–8]

The initiation of psoriasis is influenced by a wide range of internal and external factors. Stress, allergies, nutrition, infections, and skin traumas have all been implicated as extrinsic stimulants for psoriasis induction or exacerbation. Furthermore, various medications are also related to psoriasis etiology, such as interleukins, corticosteroids, rituximab, vascular endothelial growth factor antagonists, anti-PD1 immune checkpoint inhibitors, and granulocyte colony-stimulating factors. Novel medications are a significant concern from this perspective, and attention to rare reports of these cutaneous complications correlated with psoriasis is vital.[9,10]

Psoriasis development during the course of TKI therapy has been reported in several case reports.[3–5] TKIs have recently been approved as novel strategies for cancer treatment. Imatinib, a first-generation TKI, specifically targets tumoral components. Nilotinib and dasatinib, second-generation TKIs, are the choice for imatinib-resistant patients and BCR-ABL mutants. Nilotinib binds to the BCR-ABL protein and is 30 times more potent than imatinib. Nilotinib can also inhibit PDGFRb, fip1-like-1-PDGFRa, and receptor tyrosine kinase.[11] Chen et al[12,13] demonstrated that imatinib and nilotinib dose-dependently suppress the proliferation and inhibitory roles of T-reg cells. Fei et al[14] also suggested that nilotinib has a suppressive role in the proliferation and function of regulatory T lymphocytes at higher concentrations in vitro (>10 μM). These agents downregulate the autophosphorylation of tyrosine residues of proto-oncogenes, thus inhibiting the cells' proliferation and differentiation. Meanwhile, they affect not only tumoral components but also target other organs such as the cutis, leading to normal cell dysregulation and serious complications. Cutaneous reactions are the most common nonhematological side effects that appear dose-dependent. Complication management is challenging in the absence of other effective agents. Also, there are many concerns regarding arterio-occlusive events with third-generation TKIs. Nevertheless, a study presented a case of psoriasis improvement by imatinib.[15] A growing body of evidence suggests psoriasis is the most well-known dermatologic disease that can be improved by some TKIs like oral tofacitinib, proposing them as a therapeutic method for inflammatory and immune-mediated dermatoses.[16]

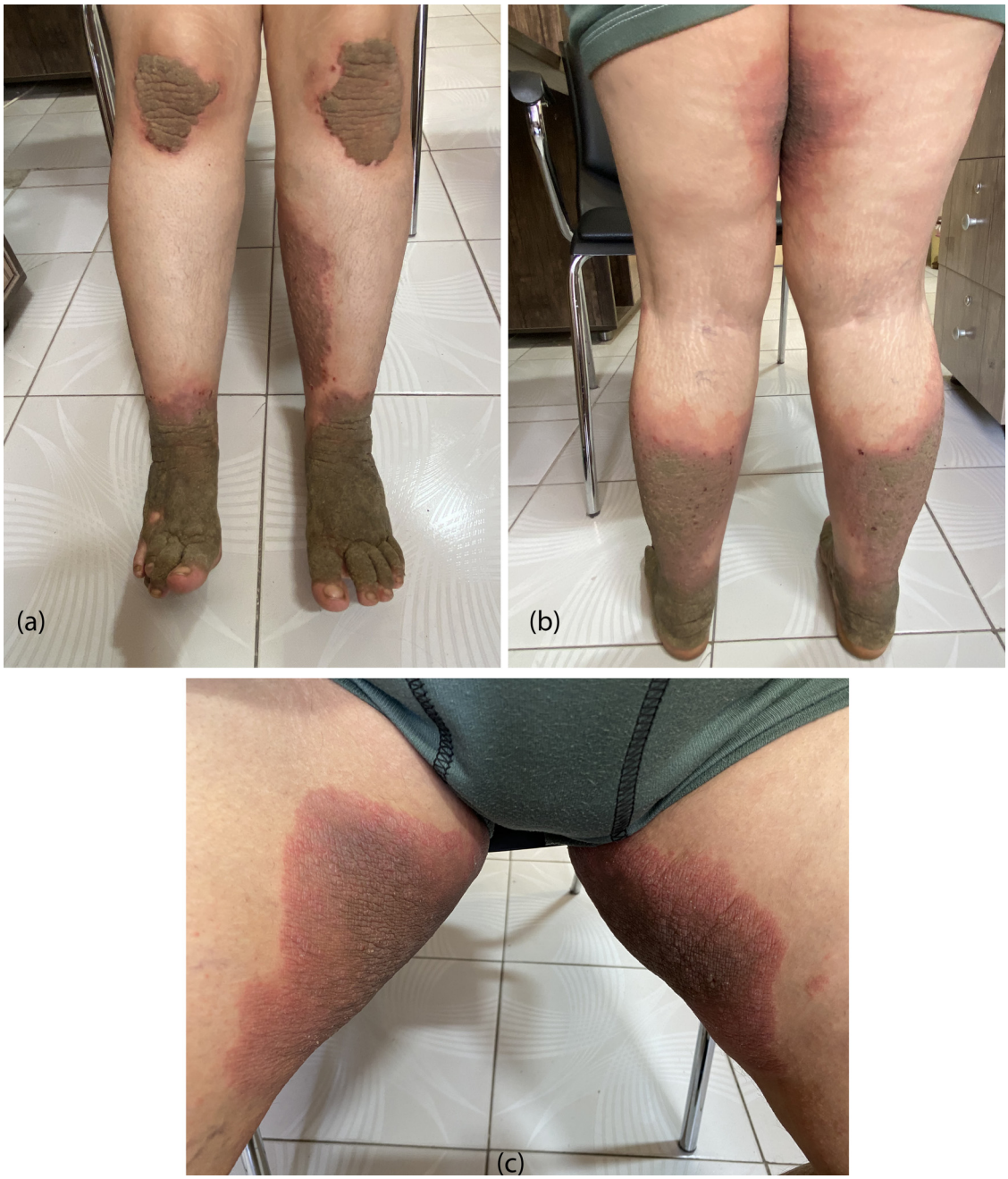

Figure 1. (A, B, and C) Extensive, thick, large symmetrical, scaly plaques of elephantine psoriasis over the lower limbs of a 35-year-old patient with chronic myeloid leukemia taking nilotinib.

In this study, we described a rare case of elephantine psoriasis development following nilotinib therapy. The most frequent dermatologic complications of nilotinib include rash (10%–28%), pruritus (17%–24%), dry skin (13%–17%), and alopecia (6%). Other cutaneous adverse reactions include Sweet's syndrome, eczema, urticaria, hyperhidrosis, erythema nodosum, skin ulcer, petechiae, photosensitivity, ecchymosis, and swollen face.[1,11] We reviewed the English literature from 2000 to 2022 based on our key words in various databases, including BMJ Journals, PubMed, Web of Science, and Google scholar. Results of our search revealed 3 similar cases. The details of these cases are summarized in Table 2. However, the cases were not found to be quite similar to the present case. Nagai et al[3] reported a case of nilotinib-induced psoriasis 26 months after administration. They argued that nilotinib probably inhibits the function of regulatory T lymphocytes and that the increased number of $CD45^+$, $CD4^+$, and $CD25^+$ cells, corresponding to the T-reg fraction, suppresses regulatory T cells. Kaur et al[4] presented a case of psoriasis 3 months into the course of nilotinib treatment. In these 2 cases, nilotinib was not discontinued.

Thekkudan et al[5] reported a patient who had developed psoriasis after 12 months of nilotinib therapy. Contrary to the previous cases, they discontinued nilotinib and started dasatinib for this patient.[5] Consequently, cutaneous lesions were exacerbated because dasatinib has more potent inhibitory effects on T-reg cells, supporting the results obtained by Fei et al.[14] In the study by Thekkudan et al,[5] skin lesions improved after dasatinib discontinuation. Although those cases described the vulgaris type of psoriasis, our case presents a unique report of elephantine psoriasis develop-

Table 2
Details of nilotinib-induced psoriasis reports in patients with chronic myeloid leukemia.

Study	Gender	Age, y	Nilotinib dosage, mg/d	Latency period, mo	Psoriasis type	Treatment options
Nagai et al,[3] 2013	Male	44	600	26	Vulgaris	Topical ointments of activated vitamin D3 derivative and corticosteroid
Kaur et al,[4] 2015	Male	30	600	3	Vulgaris	Topical fluticasone propionate 0.05%, topical calcitriol, methotrexate 15 mg weekly, folic acid 5 mg twice a week
Thekkudan et al,[5] 2017	Male	39	800	12	Vulgaris	Topical steroids, emollients, and paraffin
Current study, 2022	Female	35	800	7	Elephantine	Subcutaneous methotrexate 15 mg weekly and topical steroids

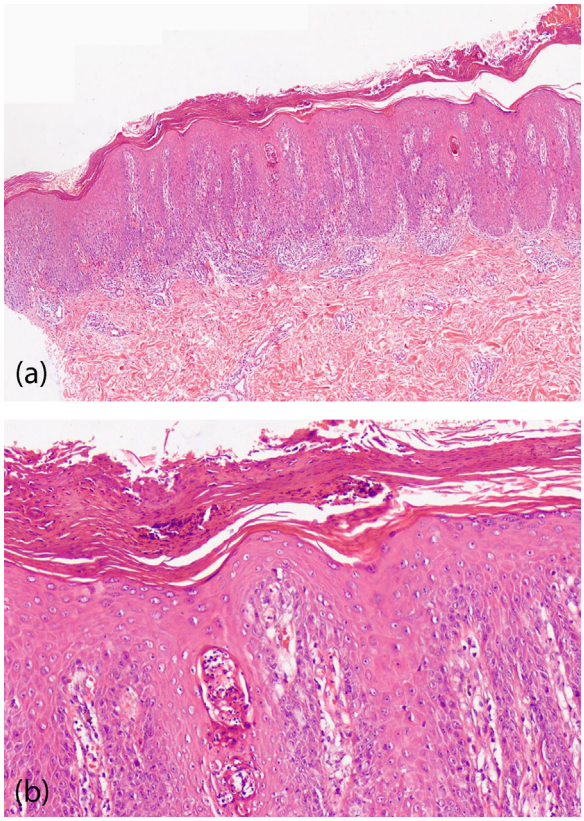

Figure 2. (A) Histopathologic examination showing psoriasiform acanthosis and parakeratosis (hematoxylin and eosin staining × 100). (B) High power reveals neutrophilic parakeratosis and Munro's microabscess (hematoxylin and eosin staining × 400).

ment after nilotinib therapy. We therefore prescribed subcutaneous methotrexate 15 mg weekly plus topical steroids. The common denominator of all the treatment strategies adopted for our patient and the mentioned cases was topical steroids and/or methotrexate, which led to effective management.

Psoriasis is among the most common cutaneous diseases worldwide, and knowing its risk factors is essential for improving management; novel medications are thus crucial from this perspective. Nilotinib, a second-generation TKI, was developed for patients with CML intolerant to imatinib. The correct diagnosis of cutaneous complications is important in patients receiving nilotinib therapy. Clinicians should be informed about the rare possible adverse effects of this treatment because it will help improve patients' quality of life and decrease their morbidity. The correlations between the clinical outcomes and severity of dermatologic complications have not yet been fully identified. Future studies are recommended to evaluate the exact mechanisms leading to psoriasis onset in patients treated with nilotinib. These facts highlight the importance of novel approaches to the safe and effective treatment of CML.

Limitations

Dasatinib was not utilized as second-line therapy in this study because dasatinib was unavailable in our country when nilotinib was prescribed. Fortunately, the patient responded well to nilotinib. Of note, dasatinib has been available over the past year, but it is costly, whereas nilotinib is free for patients with CML. Therefore, due to the patient's financial problem, dasatinib administration is not appropriate.

Blood concentrations of nilotinib should be monitored after its initiation. However, due to the economic issues and lack of required facilities, nilotinib levels are not measured routinely.

Conclusions

Elephantine psoriasis diagnosis is based on the clinical and pathological evidence presented. Considering that skin lesions developed after giving medicine to a patient who has no history of dermatologic illness and that the lesions disappear once the drug was stopped, it is plausible that these skin lesions are an adverse effect of nilotinib. As a result, to confirm the link between nilotinib and elephantine psoriasis, nilotinib had to be stopped, and the lesions had to heal before we could be sure of the correlation. Unfortunately, due to a lack of other treatment choices in our under-sanction country in the event of nilotinib withdrawal, and based on the patient's oncologist's consultation, this assurance did not take place. On the other hand, similar cases have been reported following the use of nilotinib, reinforcing the possibility of this association.

Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

CRediT authorship contribution statement

Seyedeh Fatemeh Sadatmadani: Data curation, Writing – original draft, Writing – review & editing, Visualization. **Zahra Malakoutikhah:** Investigation, Writing – original draft, Writing – review & editing, Supervision. **Fatemeh Mohaghegh:** Conceptualization, Supervision. **Mohammadsaleh Peikar:** Conceptualization, Data curation. **Mahdi Saboktakin:** Conceptualization, Data curation.

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