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NILOTINIB INDUCED SKIN RASH IN CML PATIENT

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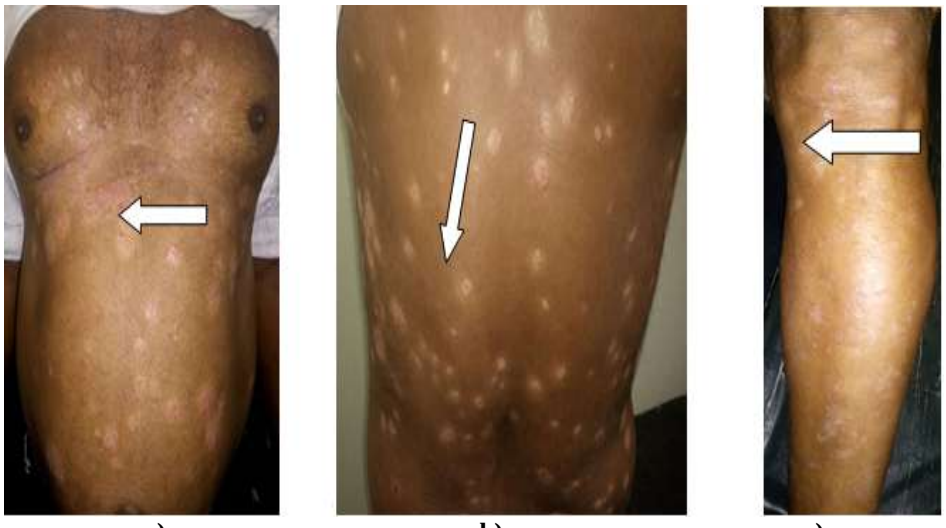
ABSTRACT
Chronic myeloid leukemia (CML) is a myeloproliferative disorder resulting from the clonal expansion of abnormal hematopoietic progenitor cells, characterized by a reciprocal translocation between the long arms of chromosomes 9 and 22 which creats the Philadelphia chromosome. Since the approval of Imatinib in 2001, Nilotinib have been approved for use in Imatinib resistant or intolerant as well as front line treatment for CML patients.[1-3] The most common side effects of Nilotinib include myelosuppression, mild skin rash, QTc prolongation nausea, vomiting, diarrhea, but serious allergic reactions are rare. Here, we present a case of Nilotinib induced psoriatic skin changes.

KEYWORDS: Nilotinib; Rash; Chronic Myeloid Leukemia; Psoriasis.

CASE 1: A 50-year-old man, known case of Imatinib resistant chronic myeloid leukemia, being treated with Nilotinib 400 mg (Tasigna), twice daily for 4 months, presented with multiple erythematous scaly plaques over his trunk and extremities for 1 month. The lesions gradually increased in size and number and spread over the body with mild itching. There was no family history of similar skin lesions. He was not taking other medications and denied any other illness. Examination revealed many bilaterally symmetrical, erythematous well-defined plaques of varying sizes with peculiar silvery-white scales over the scalp, upper limbs, trunk and lower limbs.



a) **b)** **c)**

Figure 1: Multiple bilaterally symmetrical erythematous plaques of varying sizes with characteristic silvery-white scales over the abdomen, back and lower limbs. Nails and joints were normal.

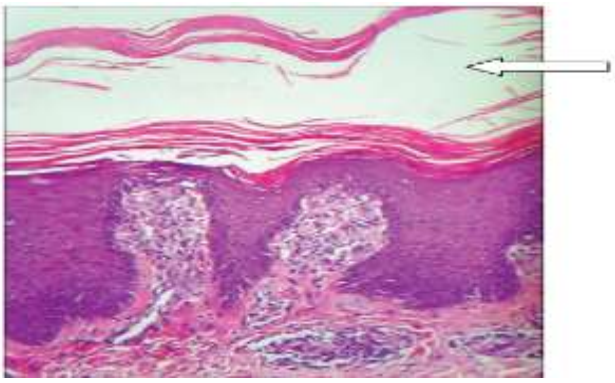
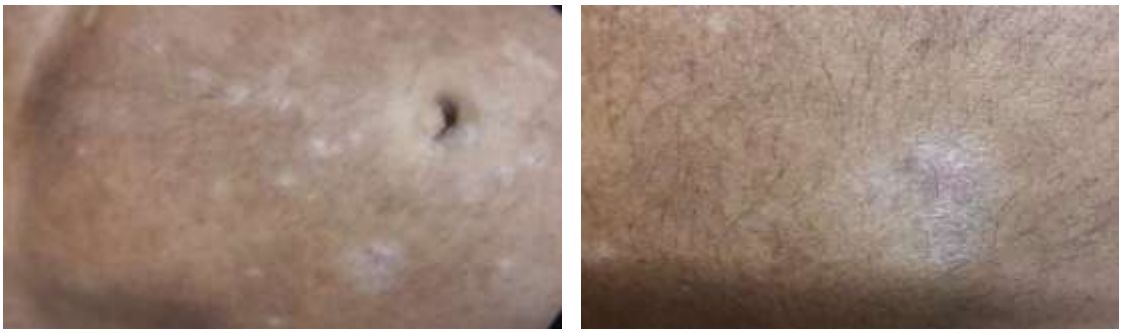


Figure 2: Histopathological examination revealed hyperkeratosis, acanthosis, dilated papillary dermal vessels, loss of granular layer, supra-papillary thinning and a perivascular chronic inflammatory infiltrate in the dermis along with few dermal neutrophils, consistent with psoriasis vulgaris without interface changes, exocytosis of lymphocytes, no eosinophils or plasma cells could be observed in the dermis.

Treatment with topical Calcitriol ointment and topical Fluticasone propionate and was initiated. However, after 2 weeks of topical treatment, there was no much improvement. He was treated with 0.5 mg/kg of Prednisolone daily. This was continued for the next 4 weeks with close monitoring, along with topical Fluticasone propionate cream.



a) **b)**

Figure 3: Skin lesions improved after treatment.

Currently his psoriatic lesions are well controlled with treatment. Nilotinib has been continued without any change in the dose and patient is asymptomatic even after 1 year of completion treatment for psoriasis and is in MMR at 12 months of treatment with Nilotinib.

DISCUSSION

Nilotinib, a second-generation tyrosine kinase inhibitor, is indicated for Imatinib resistant or intolerant as well as front line treatment for CML cases.[1-3] It is having higher binding affinity than Imatinib for tyrosine kinase Bcr-abl. Cutaneous side effects constitute the commonest non-hematological adverse events observed with Nilotinib, and most of these it are mild to moderate in severity. [4,5] The incidence of rash with Nilotinib varies from 20 to 62%, usually manifesting as morbilliform eruption, keratosis pilaris like lesions, erythema and scaling, and multiple milia-like lesions, associated with pruritus in 75% cases.[5,6] Other rare adverse effects published include development of Sweet's syndrome, an intensified inflammatory reaction of actinic keratosis after 5-fluorouracil (5-FU) treatment, dry skin, alopecia and rosacea-like eruption,.[5-7] The uncommon adverse effects like eczema, urticaria, skin ulcer, petechiae, photosensitivity, hyperhidrosis, erythema nodosum, ecchymosis, and swelling of face that have been reported with Nilotinib.[8]

Several reports describe aggravation or development of psoriasis with Imatinib[4,9], although paradoxical improvement of psoriasis has also been described with it. Nagai *et al.*[10] reported the index case of psoriasis in a patient of chronic myeloid leukemia on Nilotinib therapy who had responded to topical vitamin D3 analogs and steroids, and Nilotinib administration could be continued without interruption.

Psoriasis is a chronic relapsing remitting inflammatory disease in which lymphocytes like Th1, Th17, and cytokines play an important pathogenetic role. Normally, Treg cells are able to inhibit the immunological response and maintain cutaneous immunological homeostasis, thereby preventing an autoimmune response against self-antigens. In psoriasis, the suppressor activity of Treg cells is reduced, either due to a reduction in the number of these cells, a decreased ability of Treg cells to produce suppressive cytokines or "resistance" of T effector cells to their inhibition.[10,11]

Both Imatinib and Nilotinib have been demonstrated to impair the function of Treg cells. Chen *et al.* and Larmonier *et al.* demonstrated that the proliferation of Treg cells and their immunosuppressive effect is inhibited by Imatinib at a concentration achieved clinically (2.5-5 μM).[12, 13] Similarly, Nilotinib has been shown to inhibit phytohemagglutin in induced CD8+ T cell proliferation in therapeutic concentrations (0.5-4 μM)[14] and also to reduce lymphocyte-specific protein tyrosine kinase and function of T cell. However, Fei *et al.* concluded that Nilotinib suppressed function and proliferation of Treg cells in a higher concentration *in vitro* (>10 μM), and was not found to hamper the function of Treg cells.[15] These findings, therefore, raise the concern that the tyrosine kinase inhibitors, blocks signaling in both Treg cells and effector T cells, can have an important pathogenic role in the development of psoriasis, still, the exact mechanism involved awaits further studies.

CONCLUSION

Nilotinib is a newer effective chemotherapeutic drug for the treatment of chronic myeloid leukemia, optimal management of adverse effects requires prompt recognition and collaboration between dermatologists and hematologists.

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