

# Rare Side Effects of Imatinib – Lichenoid Dermatitis - A Case Report

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## ABSTRACT

**Introduction:** The treatment for gastrointestinal stromal tumors remains surgery and small molecule tyrosine kinase inhibitor like imatinib.

**Case report:** A 54 years adult male with Gastrointestinal stromal tumor (GIST) of small intestine with liver metastases was started on Imatinib. On treatment, the patient developed multiple well defined hyperpigmented plaques associated with pruritus all over the body. Imatinib was suspended which resulted in remission of symptoms. On restarting Imatinib, resurgence of lesions were observed. Skin biopsy revealed it to be lichenoid dermatitis. Patient was treated with topical steroid and after remission of lesions, Imatinib was restarted with periodic escalation of dose from 200mg to 400mg per day which had a stable response of the tumor in primary and secondary sites with maintained remission of skin lesions.

**Conclusion:** This rare side effect of imatinib can be effectively managed with brief suspension of imatinib and steroid therapy.

**Keywords:** Imatinib, stromal tumors, lichenoid dermatitis, topical steroids.

## INTRODUCTION

Imatinib is an inhibitor of multiple tyrosine kinases like c-kit, Abl, Scf, and platelet-derived growth factor (PDGFR) receptors implicated in carcinogenesis and is used to treat Chronic myeloid leukaemia (CML), Gastrointestinal stromal tumour (GIST) and Dermatofibrosarcoma protuberans.<sup>1</sup> Adverse cutaneous reaction are common in imatinib treated patients. Varying proportions of cutaneous reactions to Imatinib have been reported in different case series. Commonest non haematological adverse effects of imatinib are non-lichenoid cutaneous reactions. Lichenoid drug eruption (LDE) associated with Imatinib has rarely been reported in the literature.<sup>2</sup> This report is about imatinib induced lichenoid dermatitis in a patient with gastrointestinal stromal tumour.

## CASE REPORT

A 54 years male, known diabetic on oral hypoglycemic drugs, was diagnosed with Gastrointestinal stromal tumor from small intestine, with liver metastases in the Department of Medical Oncology, Madras Medical College and Hospital Chennai. The patient belonged to high risk according to revised NIH risk stratification system. He was started with Tab. Imatinib 400 mg PO daily. After 6 months the patient was found to have multiple well defined hyperpigmented plaques associated with pruritus all over the body, predominantly in the lower abdomen, lumbosacral area, trunk and along the flexor creases and oral cavity, as shown in the figure 1,2.

Imatinib was suspended, after which the intensity of the hyperpigmented lesion and pruritus decreased. When imatinib was restarted after one month with the same 400mg daily dose, the intensity of the lesion and pruritus increased. Imatinib was

stopped once again and was advised for skin biopsy, which then subsequently revealed lichenoid dermatitis. Patient was advised with topical steroids like clobestol propionate twice a day along with systemic oral antihistamines and the hyperpigmented plaques responded by flattening along with intensity of pigmentation and pruritus also got reduced.

Skin biopsy, revealed lichenoid dermatitis.

Histopathological examination revealed flaky hyperkeratosis, prominent granular layer, irregular acanthosis, basal cell degeneration in some areas, pigment incontinence and melanocytes seen throughout the upper dermis (Figure 3). Focal collection of inflammatory infiltrates close to epidermis consisting of lymphocytes and histiocytes were also seen in dermis around blood vessels, suggestive of lichenoid dermatitis. Imatinib was restarted once again after 1 month at a lower dose of 200mg per day along with topical corticosteroids (clobestol propionate) twice daily and antihistamines. Imatinib was resumed to 400mg at dose increments every fortnight with one dose level (ie., 200mg/day to 300mg/day, then 300 mg/day to 400mg/day). Primary and secondary sites showed stable response along with continued maintenance of remission of the lichenoid lesions (Figure 4).

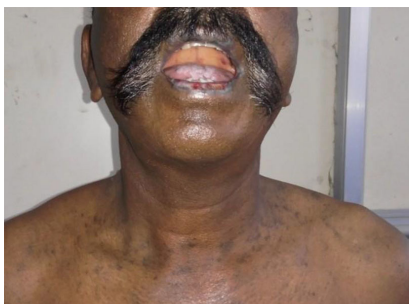
## DISCUSSION

Imatinib toxicity commonly presents as bullous reactions, including erythema multi-forme and Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, vasculitis and mycosis fungoides-like eruption.<sup>1,3,4</sup> Lichenoid eruptions are caused by a list of drugs, in that Imatinib is relatively a new addition. Lichen planus-like or lichenoid eruptions comprises a spectrum of cutaneous reactions similar to lichen planus. Lichenoid drug eruptions (LDE) typically appear symmetrically on the trunk and extremities with localized or generalized eczematous papules and plaques and variable desquamation, but with characteristic differences. Dose-dependent relationship of this drug with rash is a result of its pharmacological effect. Imatinib induced pharmacological effect, by altering signal transduction mechanisms rather than its immunological effect, is responsible for the dose-dependent relationship of this drug with the rash. Lichenoid rash generally appears after 1 to 6 months of imatinib therapy. A photo-distributed pattern is generally seen,<sup>5</sup> with lesions healing with hyperpigmentation.<sup>6</sup> But in our patient, the lesions were seen in the trunk and flexor creases which

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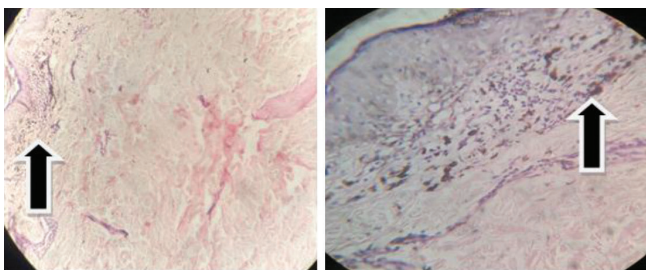
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**Figure-1:** Mucocutaneous lesions



**Figure-2:** Characteristic lesions with imatinib



**Figure-3:** HPE showing hyperkeratosis and pigment incontinence



**Figure-4:** Reduction of intensity of skin lesions- Post steroids and dose reduction of imatinib

also healed with hyperpigmentation. Extensive mucocutaneous involvement, seen in this patient, is quite uncommon for a lichenoid eruption and has not been reported with imatinib so far.<sup>7</sup>

Histopathologically, a number of findings are more typical of Lichenoid drug eruptions (LDE) and comprise focal parakeratosis, presence of eosinophils and plasma cells, and a deeper perivascular and periadnexal infiltrate.<sup>8</sup> In this patient skin biopsy revealed flaky hyperkeratosis, prominent granular layer, irregular acanthosis, basal cell degeneration in some areas, pigment incontinence and melanocytes seen throughout the upper dermis with focal collection of inflammatory infiltrates close to epidermis.

Patients with LDE are often taking more than one medication, which may make the recognition of the causative agent difficult. Withdrawal of the drug, leading to resolution of lesions favours the diagnosis of LDE.<sup>9</sup>

In reports, some of the patients had only mucosal lesions<sup>5,9,10</sup>, some had only cutaneous lesions<sup>1,3</sup> and the remainder had both lesions.<sup>1</sup> All the patients took imatinib mesylate at a dose of 400

mg/day or above. This observation is probably in favour of the view that the Imatinib-associated LDE are dose dependent rather than being immunogenic in nature. Most common indication of Imatinib usage was Chronic Myeloid Leukemia<sup>1,3,5,9</sup> and GIST. Specific causes of imatinib induced skin lesions remain elusive. Due to its fairly low molecular weight, Imatinib is not likely to be immunogenic. The dose dependence of adverse reactions favours the assumption that imatinib related cutaneous reactions are probably due to changes in tyrosine kinase signaling rather than immunologic mechanism.

It has been also proposed that the lesions in oral LDE may be closely correlated with the altered expression of epidermal markers caused by imatinib.<sup>10</sup>

## CONCLUSION

The occurrence of such lichenoid lesions are usually dose dependant. This should be treated with topical steroids, systemic steroids, imatinib interruption, and restarting at a lower dose and dose increments in a periodic fashion, with careful watching over the lichenoid drug eruptions for exacerbations.

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