LICHENOID DRUG ERUPTION ASSOCIATED WITH IMATINIB MESYLATE: TWO CASES

Ilhami Kiki[1], Mustafa Atasoy[2], Nesrin Gursan[3], Mehmet Gundogdu[1], Fuat Erdem[1], Sevki Ozdemir[2],

Atatürk University Medical Faculty, Departments of Internal Medicine[1], Dermatology[2] and Pathology[3], Erzurum, Turkey

Imatinib mesylate (STI571) is a new therapeutic agent which inhibits the tyrosine kinase of the BCR-ABL, c-kit and platelet derived growth factor oncogenes. It is used for the treatment of chronic myelogenous leukemia, Philadelphia chromosome positive acute lymphoblastic leukemia and gastrointestinal stromal tumors. Although, cutaneous side effects of this drug is common, lichenoid eruption is exceptional. We report two cases of disseminated lichenoid cutaneous reaction, which developed in two patients with chronic myelogenous leukemia treated with imatinib mesylate.

Key words: Imatinib mesylate, chronic myelogenous leukemia, lichenoid eruption

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INTRODUCTION

Imatinib is a 2- phenylaminopyrimidine derivative that shows inhibiting effect on epidermal growth factor receptor tyrosine kinase activity. It has been shown remarkable clinical activity in chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GIST), dermatofibrosarcoma protuberans and hypereosinophilic syndrome (HES) by inhibiting the tyrosine kinase activities of bcr-abl fusion protein, c-kit oncogene, platelet derived growth factor receptor alpha (PDGFRA) and the mutated genes involving in HES respectively (1,2). Owing to its oral availability, high hematological and cytogenetic response rates and a spectrum of well tolerated toxicity, it became the gold standard for treatment of CML (3).

Lichenoid eruption to imatinib is a rarely seen cutaneous adverse event (4). We report two cases of lichenoid drug eruption associated with imatinib mesylate.

CASE 1

A 33-year-old male patient with chronic phase CML who diagnosed as 3 years ago and since then receiving hydroxyurea therapy, presented with massive splenomegaly and extremely high .white blood cell count (244 x 10^9/l). Imatinib mesylate was initiated at a daily dose of 400 mg. Five weeks after the initiation of therapy; he presented with the complaints of severe itching and disseminated skin eruption. On examination, disseminated cutaneous eruption of discrete dark-purple papules located on the trunk, genital region, legs and arms were seen (Fig 1). No mucosal involvement was observed. Appearance of the lesions was suggestive of lichenoid eruption. A skin biopsy confirmed the diagnosis of lichenoid drug eruption (Fig 2). Within the 15 days cessation of drug and application of topical corticosteroids, all lesions had begun to improve and totally resolved with pigmentation by 30 days. Despite resuming imatinib at lower dosage (300 mg/day) and gradually raising to 800 mg/day in 12 months period, no recurrence in cutaneous eruptions was seen.

CASE 2

47 year-old male who started therapy with imatinib 400 mg daily for newly diagnosed CML in chronic phase, reapplied with generalized itching and disseminated skin eruption seven weeks after therapy initiated. On physical examination, disseminated cutaneous eruptions suggesting lichen ruber planus were seen (Fig 3). Mucosal surfaces

Dr. Ilhami Kiki
Atatürk Üniversitesi Tıp Fakültesi Postanesi 25240-Erzurum/Turkey
Tel: 904422361212-2106
GSM: 05324859000, Fax: 904422361301
E-mail: kikiilhami@yahoo.com

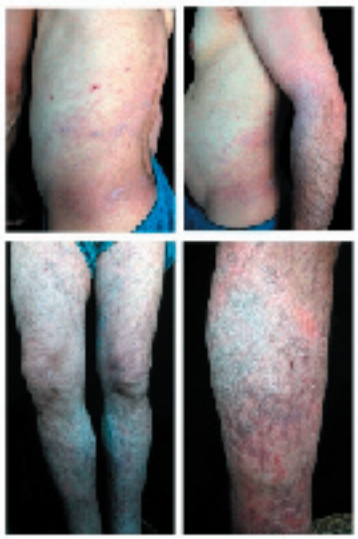

Figure 1. Disseminated cutaneous eruption of discrete dark-purple papules located on the trunk, legs and arms

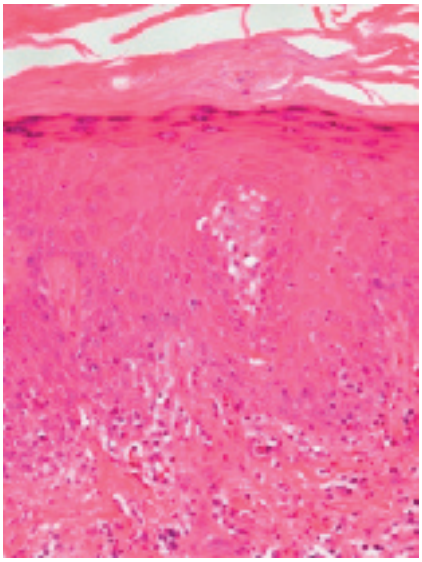

Figure 2. Lichenoid eruption characterized by compact orthokeratosis involving focal parakeratosis, thickening of the granular layer, vacuolar changes in the basal layer, and band-like lichenoid infiltration in the upper dermis which is composed of lymphocytes and eosinophils (H&E x 200).

were also uninvolved. Skin biopsy was interpreted as lichenoid drug eruption (Fig 4). Short-time cessation of imatinib and topical administration of corticosteroids resulted in the healing of all lesions. Fifteen days after, imatinib was begun again in initial dose (400 mg/day). Sustained complete remission achieved and no recurrence in lesions was observed at six month follow up. Both two patients are still under our care.

DISCUSSION

Imatinib therapy carries potential for several side effects. The most common toxicities associated with this drug are mild nausea (70%) and diarrhea (56%). The other side effects include fluid retention, muscle cramps, skin rashes, hematologic toxicity including hemolytic anemia, renal and hepatic failure ((1, 5-8).

Cutaneous reactions to imatinib are also common and have been reported 9.5% to 69% in several series. The most frequent cutaneous adverse events are maculopapular eruptions, erythematous eruptions, rashes, edema, and periorbital edema. Imatinib can also induce severe and sometimes life threatening cutaneous reactions such as Stevens Johnson syndrome and epidermal necrolysis (9-12).

Lichenoid eruption to imatinib is also an adverse cutaneous reaction that is rarely seen in patients receiving imatinib therapy. There are occasional reports of lichenoid reaction due to imatinib. In the literature review, we found three reports of imatinib associated cutaneous lichenoid eruption. Roux et al. (4) reported a case of lichenoid cutaneous eruption requiring the suspension and recurring after reintroduction of imatinib whereas Prabhash et al. (13) reported the occurrence of lichenoid skin eruption resolving without any treatment. In 2006, Dalmau et al. (14) reported four cases of imatinib induced lichenoid skin eruption consisting of 3 patients with CML and 1 with GIST. In their report; they stated that, imatinib had necessarily been discontinued in one patient; whereas improvement achieved by concomitant application of acitretin without need of imatinib dose alteration in remaining three patients.

In our cases, skin eruptions were disseminated and patients refused to continuation of imatinib. After temporarily stopping drug, eruptions dramatically relieved and did not reappear by imatinib reintroduction without any additional treatment except from topical corticosteroids. Our observation suggested that imatinib therapy should not be permanently discontinued but transiently interrupted in case of unbearable adverse reactions.

In the literature, there are also a few reports about imatinib-induced lichenoid reaction limited to oral mucosa that sometimes required discontinuation of drug (15,16).
Drug induced lichenoid eruptions has been

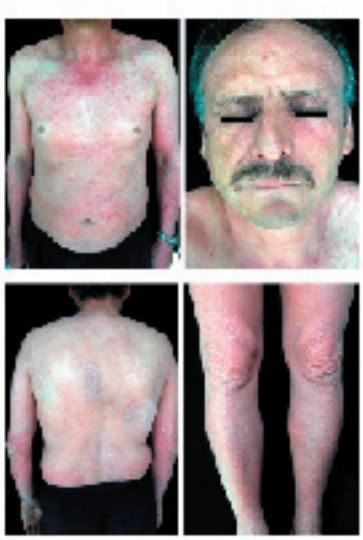

Figure 3. Numerous squamous pink-purple papules and plaques located on the face, scalp, neck, trunk, arms and legs.

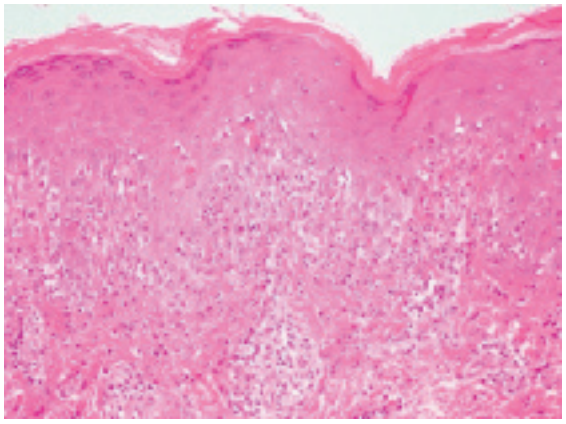

Figure 4. Histopathologyical picture showing compact orthokeratosis accompanied by focal parakeratosis, marked thickening of the granular layer, vacuolar changes in the basal layer, singly necrotic ceratocytes located in the lower epidermis and lichenoid infiltration just under the epidermis (H&E x 200).

reported to developed after a latent period that ranges between a few weeks to several months from administration Additionally, management, response to therapy and recovery of lesions has also been reported to be varying from case to case. While eruptions in some cases have shown improvement without need of suspension of drug (13, 14, 16), others have necessitated transiently or permanently discontinuation of Imatinib (14, 15).

In our cases, mucosal surfaces were intact, and duration to emergence of lichenoid eruption was 5 and 7 weeks respectively. Additionally, in both two cases, recovery was quite rapid after the discontinuation of drug even though lesions were disseminated and obliged to ceasing of Imatinib.

Cutaneous reactions to imatinib have been reported to be dose dependent pharmacologic effect of the drug rather than to hypersensitivity. Although pathophysiology of cutaneous reactions is unclear, inhibition of c-kit which is normally expressed in several skin cells has been suggested to be involved in the pathogenesis of different skin reactions (12). Therefore, temporarily dose reduction or discontinuation of drug may be reasonable in case of serious side effects.

In conclusion, we think that, low dose or standard dose imatinib re-induction following short-time discontinuation may be a reasonable therapeutic choice in case of severe and non-tolerable lichenoid drug eruption.

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