Case 10

Case 10A

Charussri Leeyaphan, M.D.
Woraphong Manuskiatti, M.D.

Patient
A 70-year-old Thai female from Nakhonsithammarat province

History
The patient presented with abdominal pain in January 2010. She was diagnosed with gastrointestinal stromal tumor and was treated with imatinib mesylate 400 mg/day. Ten weeks after starting the treatment, she developed a generalized pruritic violaceous eruption on her trunk, face, palms and soles.

Her underlying disease was hypertension and was previously treated with amlodipine and hydrochlorothiazide. She discontinued all medications by herself because of abdominal pain since December 2009. She had no history of previous drug allergy. There was no family history of similar skin condition.

Physical examination
GA: good consciousness, mildly pale, no jaundice, no superficial lymph node enlargement
HEENT: whitish reticulated plaques were seen on the buccal mucosa and tongue.
CVS, RS: normal
Abdomen: no hepatosplenomegaly, no palpable mass
Skin: generalized well-defined scaly violaceous papules and plaques on the trunk, face and lower lip, well-defined hyperkeratotic plaques on the palms and soles
Nails, hair and genitalia were normal.

Laboratory data
CBC: Hb 10.9 mg/dl, Hct 31.9%, WBC 4,400 /μl (N51.5%, L 22.8%, M13.2%, E 12.1%) platelet 231,000 /μl
Blood chemistry: Cr 0.8 mg/dl
LFT: within normal limits
Histopathology (S10017173)

The section reveals markedly irregular acanthosis of the epidermis with compact orthokeratosis and focal parakeratosis. There are wedge-shaped hypergranulosis with vacuolar degeneration of basal cells obscured by lichenoid infiltrate composed of lymphocytes and eosinophils. Scattered necrotic keratinocytes are found at dermoepidermal junction with melanin incontinence in the papillary dermis.

Direct immunofluorescent study: negative

Diagnosis

*Imatinib mesylate-induced lichen planus and palmo-plantar hyperkeratosis*

Discussion

Imatinib mesylate (Gleevec®) is a tyrosine kinase inhibitor. This agent blocks signaling via BCR-ABL, c-kit and platelet-derived growth factor receptor (PDGFR) by binding to the adenosine triphosphate-binding pocket that required for phosphorylation and activation of the receptor. The end result is inhibition of tumor proliferation. Gastrointestinal stromal tumor (GIST) demonstrates mutation of KIT or PDGFR proto-oncogenes. The mutation leads to abnormal protein which is activated and enables oncogenic signaling in the cell. Imatinib mesylate has been approved in the USA as the first line therapy for GIST and chronic myeloid leukemia.1,2

Most adverse reactions of imatinib mesylate including nausea, abdominal pain, diarrhea, myalgia and edema (commonly involving the periorbital areas and lower extremities) are mild to moderate.2 Approximately 31–44% of patients taking imatinib mesylate experienced cutaneous reactions.3 The most common cutaneous reaction is a maculopapular rash affecting the forearms and trunk.2 Other cutaneous reactions include hair hypopigmentation, pruritus and pityriasis rosea-like eruption.4,5 Severe cases with acute generalized exanthematous pustulosis, exfoliative dermatitis and Stevens-Johnson syndrome have also been reported.6-8

Lichenoid reaction due to imatinib mesylate is rare. It may be mild or extensive. Most cases had cutaneous lesion with or without mucosal lesion. Mucosal involvement alone was rare. The length of time before the adverse effects appeared after the initiation of the drug ranged from one to six months.9 There were few case reports with palmo-plantar hyperkeratosis after one to seven months of imatinib mesylate treatment. Nail dystrophy was also present.1,2 The incidence and severities of adverse effects tend to depend on the dosage of imatinib mesylate. Most of the patients took imatinib mesylate 400 mg/day
when developed reaction. Discontinuation or dose reduction of imatinib mesylate led to the improvement of lesions. Most of the patients could continue imatinib mesylate treatment by controlling with topical steroid. In few patients, a systemic corticosteroid was required to improve the skin symptoms. There was a report of patient whose skin lesion was successfully treated with acitretin, enabling the continuation of the effective imatinib mesylate dosage.

The mechanism of cutaneous reaction from imatinib mesylate is unclear. Patch testing and drug-induced lymphocyte stimulation test for imatinib mesylate were usually negative. The dose dependency of adverse events and its relatively low molecular weight support a hypothesis that imatinib mesylate-related cutaneous reactions are mediated by its pharmacological effect changing tyrosine kinase signaling rather than immunological mechanisms including hypersensitivity to this drug. A gradual increase in the dose may allow us to reinstitute the therapy after the resolution of cutaneous eruptions. The use of a systemic or topical corticosteroid and a gradual increase in the imatinib mesylate dose could be a practical strategy to enable the continuation of treatment with imatinib mesylate.

Although PDGF and c-kit have not been identified in normal keratinocytes, c-kit was recently found to be expressed by murine epithelial cells. Several lines of evidence have suggested that PDGF and stem cell factor may involve in the pathogenesis of psoriasis, suggesting a possible mechanism of action for imatinib mesylate in the induction of the psoriasiform palmoplantar hyperkeratosis. The possibility that altered expression of c-kit may induce epidermal inflammation and other changes in epidermal homeostasis need further investigation. Hypopigmentation due to imatinib mesylate may be related to the inhibition of melanocyte c-kit receptor tyrosine kinase.

References
Case 10B

Supapat Bunyaratavej, M.D.
Woraphong Manuskiatti, M.D.

Patient
A 49-year-old woman from Samutsakorn province

History
The patient presented with multiple pruritic, non-tender, erythematous papules on both shins and arms for 1 year. She never had any oral ulcer.

The patient did not take any medication before the skin eruption. She has been diagnosed diabetes, and has been taking metformin (500) 1 x 2, and aspirin (81) 1 x 1.

There was no other abnormal systemic symptom. There was no familial history of similar skin condition.

Physical Examination
V/S: P 80/min, BP 102/64 mmHg
GA: A middle-age Thai woman, hypersthenic built, not pale, no jaundice, no edema
HEENT: no lesion at oral mucosa
RS: clear, good air entry
CVS: normal heart sound
Abd: soft, not tender
Skin: multiple erythematous to violaceous papules with slight verrucous surface on both arms and legs, hyperpigmented patch on the right knees with some round atrophic scar on both legs

Histopathology (S10005342)
The section shows mark acanthosis of the epidermis with wedge-shaped hypergranulosis and a saw-toothed appearance of rete ridges. Keratin is compact orthokeratosis. There is basal vacuolar alteration with scattered necrotic keratinocytes and a band-like dermal lymphocytic infiltrate with scatter melanophages in close approximation to the epidermis.

Direct immunofluorescent study: not done
Diagnosis

**Hypertrophic lichen planus**

Discussion

Hypertrophic lichen planus (Lichen planus verrucosus) is one of the variations of lichen planus. It is characterized as extremely pruritic thickened, often verrucous, plaques with variable scales on the shins and dorsum of feet. Hypertrophic lichen planus is generally difficult to treat and tend to be chronic.

Clinical diagnosis alone is usually difficult since superficial inspection often suggests psoriasis or keratinocytic neoplasm instead of lichen planus, so skin biopsy is often required which exhibits considerable acanthosis, papillomatosis, hypergranulosis, and hyperkeratosis. The vacuolar alteration is accentuated at the base of rete ridge.

In spite of the knowledge that cell mediated immune response plays an important role in pathogenesis of lichen planus, the exact etiology and pathogenesis remain are not well understood. There are some reports that HIV and HCV may be associated with hypertrophic lichen planus. For example, Daramola, et al reported in 2003 that hypertrophic lichen planus in Nigerians was more prevalent with HCV infection. In addition, Rippis, et al reported in 1994 that LP in HIV-positive hosts may present with more extensive disease than in immunocompetent hosts, which is similar to the case report of Seyed Naser Emadi MD from Kenya.

The duration of hypertrophic lichen planus is the longest, when comparing with other types of lichen planus. The mean duration of typical lichen planus is 1 to 2 years, while average duration of hypertrophic lichen planus was recorded to be 6 years.

Importantly, there have been some case reports that squamous cell carcinoma, verrucous carcinoma, and keratoacanthoma may occur at long standing hypertrophic lichen planus, oral erosive lichen planus, and ulcerative lichen planus. Because the incidence of carcinoma in oral LP is about 0.3 – 3%, this may imply that the incidence of carcinoma in hypertrophic LP is low.

Similar to the treatment for cutaneous LP, treatment of hypertrophic lichen planus include topical or intralesional steroid, retinoid, etc. However, due to chronicity and thickness of the lesion, intralesional corticosteroid or topical corticosteroid with occlusion may be performed.

Initially, our patient's lesion responded very well to topical 0.05% clobetasol cream. Her lesion was resolved and only hyperpigmentation was noted while following up. However, due to the chronicity of this disease, recurrence is predictable and need to follow up for chance of turning to be malignancy.
References