Case 25
A 47-year old Thai woman from Bangkok

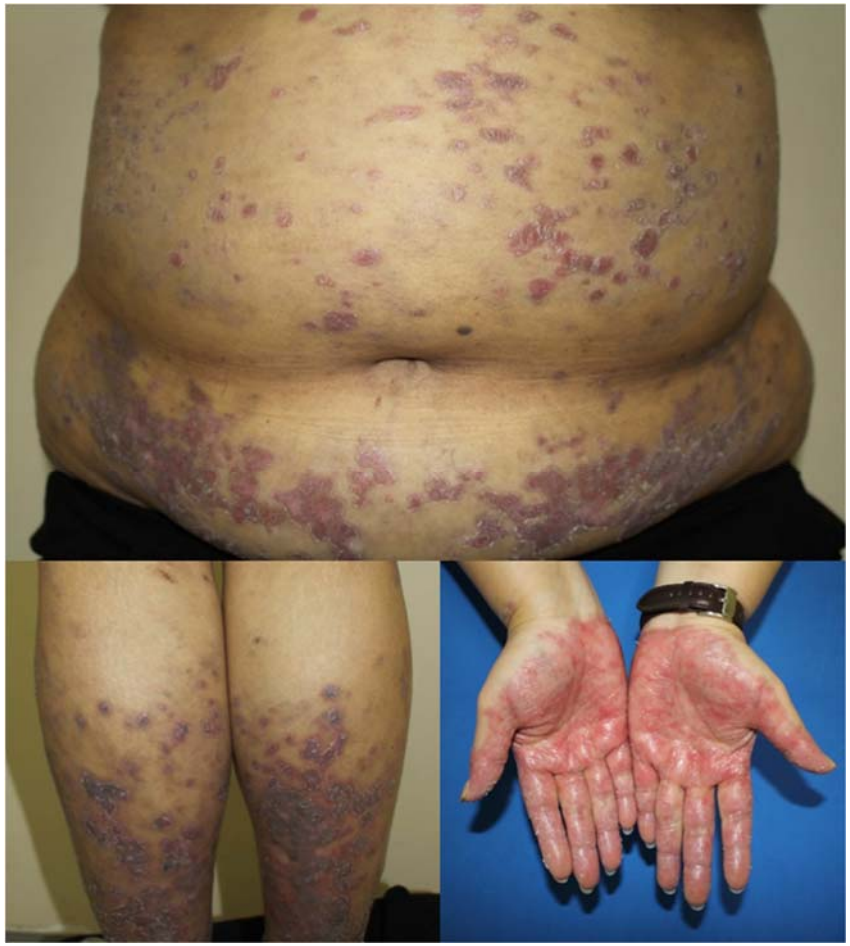
Chief complaint: Multiple confluent scaly erythematous papules and plaques on trunk and extremities for 3 months

Present illness:
She was a known case of chronic myeloid leukemia with BCR-ABL gene positive since May 2016, treated with imatinib 400 mg/day since September 2016.

3 months after that, there were multiple painful pustules, scaly erythematous papules confluent to form plaques on trunk and extremities involving both palms and soles. She went to a private hospital and was treated with topical corticosteroid and oral acitretin 25-50 mg/day for 2 months without improvement. The skin biopsy was done and histopathological feature was compatible with chronic eczema. So, she sought for a second dermatological opinion at Ramathibodi Hospital.

Past history: She had no previous history or family history of psoriasis.

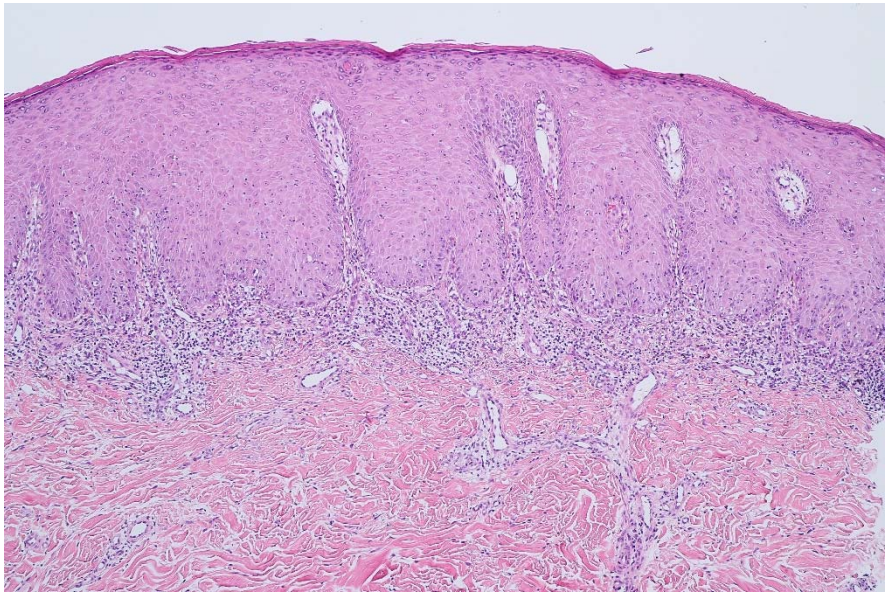
Physical examination:
V/S: T 37°C, P 70/min, RR 20/min, BP 120/80 mmHg
HEENT: mildly pale conjunctivae, anicteric sclerae
Lymph node: not palpable
Other systems: unremarkable



(Fig. 25.1)

Dermatological examination: (Fig. 25.1)
Multiple confluent scaly erythematous papules and plaques on trunk and extremities involving both palms and soles

Histopathology (S17-4266A, Hip) (Fig. 25.2)



(Fig. 25.2)

- Psoriasiform epidermal hyperplasia, wedge-shaped hypergranulosis, with compact hyperkeratosis, and focal parakeratosis
- Dense superficial lichenoid infiltrate of lymphocytes and few eosinophils with vacuolar alteration of basal cell layer and scattered necrotic keratinocytes

Laboratory investigation:
- CBC: Hb 10.3 g/dl, Hct 30.7%, WBC 4,110 cells/µL (N 66 %, L 19 %, Mo 9 %, Eo 5 %, Ba 1 %), Platelet 121,000 cells/µL
- BUN: 9 mg/dL, Cr: 0.5 mg/dL
- LFT: ALP 52 U/L, GGT 16 U/L, AST 31 U/L, ALT 37 U/L, TP 76 g/L, Alb 40 g/L, TB 0.4 mg/dL, DB 0.2 mg/dL, Chol 188 mg/dL

Diagnosis: Imatinib-induced lichenoid eruption (Grade 2)
Treatment:
- Oral acitretin 25 mg on alternate day
- 0.05% clobetasol propionate apply lesions on palms and soles twice daily
- 0.1% triamcinolone acetate in 10% urea cream applied lesions on trunk and extremities daily
- Mineral oil and 10% urea cream applied twice daily

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Discussion:

Imatinib was the first-generation tyrosine kinase inhibitor which accounted for targeted therapy developed to inhibit the tyrosine kinases *bcr-abl* in chronic myeloid leukemia, c-kit in rare gastrointestinal stromal tumors, and several platelet-derived growth factor receptors (PDGFRs) in other malignancies.[1]

Although, targeted therapies improve survival and are better tolerated than traditional chemotherapeutic agents, imatinib can also induce dermatologic adverse events[2] others than headache, diarrhea, vomiting, muscle spasm, elevated transaminases, anemia, and cytopenia.[3]

Dermatologic adverse events from imatinib had been reported in 7% to 88.9% of patients in different series[3] including superficial edema, macular-papular eruption, pigmentary disorders, hypopigmentation/depigmentation, hyperpigmentation, **lichenoid reactions**, psoriasis and psoriasiform eruption, pityriasis rosea-like

eruption, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, urticaria, neutrophilic dermatosis, photosensitivity, porphyria, pseudoporphyria.[4] The pathophysiology of imatinib-associated skin reactions is unclear. The high prevalence and dose relationship suggest that skin rash may be related to the pharmacological effects of imatinib.[5]

The cutaneous reactions were classified according to the National Cancer Institute common toxicity criteria ranging from grade 1 to grade 4 (Table 1).[6]

Table 1 Cutaneous adverse reactions according to the National Cancer Institute criteria

Grade	Skin lesion
1	Macular or papular eruption or erythema without associated symptoms
2	Macular or papular eruption or erythema with pruritus covering < 50% of body surface area
3	Symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering > 50% of body surface area
4	Generalized exfoliative dermatitis or ulcerative dermatitis

Adapted from Valeyrie L et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. J Am Acad Dermatol 2003;48:201-6.

Lichenoid eruption is an uncommon cutaneous reaction from imatinib. The lesions may occur on the skin mainly on trunk and extremities, but sometimes the face, neck, palmaris et plantaris and whole body can also be affected as well as mucosa[7] which is unlikely to classic lichenoid drug eruption that frequently spares the oral mucosa and genitalia.[8]

There were also reports of a few case of nail dysplasia. These reactions appear to be dose dependent given that all reports were in patients who were receiving high doses of the drug (> 400 mg/day) and usually appeared during 1 to 6 months after starting treatment.[7]

The pathogenesis was proposed that these lesions may be closely correlated with the imatinib-altered expression of epidermal markers.[9]

The characteristic features is violaceous, flat-topped papules; palmoplantar changes; mucous membrane lesions; and nail abnormalities.[7]

The histopathological feature reveals hyperkeratosis with focal parakeratosis, irregular acanthosis and focal wedge-shaped hypergranulosis. Focal basal cell degeneration and pigment incontinence were found. An upper dermal band-like infiltrate comprising mononuclear cells and eosinophils was present at the dermoepidermal junction. Multiple colloid bodies were noticed. Sparse perivascular infiltrates were also seen in the dermis.[10]

A dose reduction in imatinib or a short-term discontinuation can be considered to improve cutaneous conditions, and a gradual increase in the dose may allow a reinstitution of therapy after the resolution of cutaneous eruptions.[9] The use of a systemic or topical corticosteroid and a gradual increase in the imatinib dose may be a useful and practical approach to permit the continuation of treatment with imatinib.[10] Acitretin 25 mg/day may be successfully used to treat imatinib-induced lichenoid eruption, enabling the continuation of the effective imatinib dosage.[11] Although the cutaneous manifestations respond well to the treatment and has been resolved, but the oral eruptions can recur more frequently.[8]

This patient was categorized as grade 2 cutaneous reactions according to the National Cancer Institute common toxicity criteria. She was treated with oral acitretin 25 mg on alternate day, topical corticosteroids and emollients with concurrently use of imatinib. At 3-month follow-up, the lesions gradually improved and became asymptomatic brownish patches.

References:

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