Imatinib-induced lichenoid eruption: A case report and a review of literature.

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ABSTRACT:

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Imatinib is the first generation tyrosine kinase inhibitor which consisted of bcr-abl, c-kit, and platelet-derived growth factor receptors (PDGFRs). Its tolerability in the treatment of malignancies is higher than the conventional chemotherapy. However, various adverse cutaneous reactions are the most common side effect of imatinib. Nevertheless, lichenoid eruption is an uncommon cutaneous reaction from imatinib. The clinical manifestation is violaceous, flat-topped papules or plaques involving mainly trunk and extremities. Oral and genital mucosal involvement is a distinctive feature. There were no specific histopathological findings, but usually not a typical characteristic of lichen planus. Due to high prevalence of cutaneous rash, the pathogenesis may be related to pharmacological effect than hypersensitivity reaction. Dosage decrement of imatinib is a choice of treatment, or switch to the second or third generation tyrosine kinase inhibitors. Acitretin was successfully used to treat imatinib-induced lichenoid eruption in our patient and enabling the continuation of the high imatinib dosage for her hematologic malignancy.

Key words: Imatinib, lichenoid eruption, tyrosine kinase inhibitor

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บทคัดย่อ:

ธีรพงษ์ เมฆวิไลพันธุ์, ณัฏฐา รัชตะนาวิน รายงานการเกิดผื่นชนิดไลเคนนอยด์ ในผู้ป่วยที่ได้รับยาอิมมาทินิบ และการทบทวนวรรณกรรม วารสารโรคผิวหนัง 2560; 33: 329-335.

สาขาวิชาตจวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

อิมมาทินิบเป็นยาต้านไทโรซีนไคเนสรุ่นแรกที่ผลิตขึ้นเพื่อใช้เป็นยารักษาแบบจำเพาะต่อเซลล์มะเร็งที่มีความผิดปกติของยีน BCR-ABL, c-kit, และ platelet-derived growth factor receptors (PDGFRs) ทำให้ผู้ป่วยสามารถทนต่ออาการข้างเคียงได้มากกว่ายาเคมีบำบัด แต่พบอาการข้างเคียงทางผิวหนังได้บ่อยในผู้ป่วยที่ได้รับยาอิมมาทินิบ อย่างไรก็ตามการเกิดผื่นชนิดไลเคนนอยด์พบได้ไม่บ่อย อาการแสดงทางผิวหนังพบเป็นผื่นนูนสีม่วงอมแดงบริเวณลำตัว แขน และขา รวมถึงอาการแสดงที่เยื่อบุปาก และอวัยวะเพศซึ่งเป็นลักษณะเด่น ลักษณะทางจุลพยาวิทยามักไม่มีความจำเพาะเจาะจงกับโรคชัดเจน และมักไม่ใช่ลักษณะเฉพาะของไลเคนพลานัสเช่นกัน การรักษาอาจพิจารณาลดขนาดยาอิมมาทินิบ ด้วยเชื่อว่าผื่นผิวหนังแปรผันตามขนาดของยาที่ได้รับซึ่งอาจเกี่ยวข้องกับผลทางเภสัชวิทยามากกว่าการแพ้ยา หรืออาจเปลี่ยนให้กลุ่มยารุ่นที่สอง หรือสาม และมีรายงานการใช้อะซิเตรตินในการรักษาผื่นผิวหนังดังกล่าวเป็นผลสำเร็จโดยไม่ต้องลดขนาดยา ทั้งนี้เพื่อประสิทธิภาพในการรักษาโรคมะเร็งของผู้ป่วย ดังเช่นผู้ป่วยรายนี้

คำสำคัญ: การเกิดผื่นชนิดไลเคนนอยด์, ยาต้านไทโรซีนไคเนส, อิมมาทินิบ

Case report

A 47-year old Thai woman presented with multiple confluent scaly violaceous erythematous papules and plaques on trunk and extremities for 3 months. She was diagnosed of chronic myeloid leukemia with BCR-ABL gene positive since May 2016 and was treated with moderate dosage of imatinib, 400 mg/day since September 2016. Three months after treatment, there were multiple painful pustules, scaly erythematous papules confluent to form plaques on her trunk and extremities involving both palms and soles. She went to a private hospital, the skin biopsy was done and histopathological feature was compatible with chronic eczema. She was treated with topical corticosteroid and oral acitretin 50 mg/day for 1 month without improvement and experienced severe xerostomia from acitretin, so it was decreased to 25 mg/day. She came to Ramathibodi Hospital for dermatological consultation. Physical examination revealed multiple confluent scaly violaceous erythematous papules and plaques on her trunk and extremities involving both palms and soles without nail and mucosal involvement. (Figure 1)

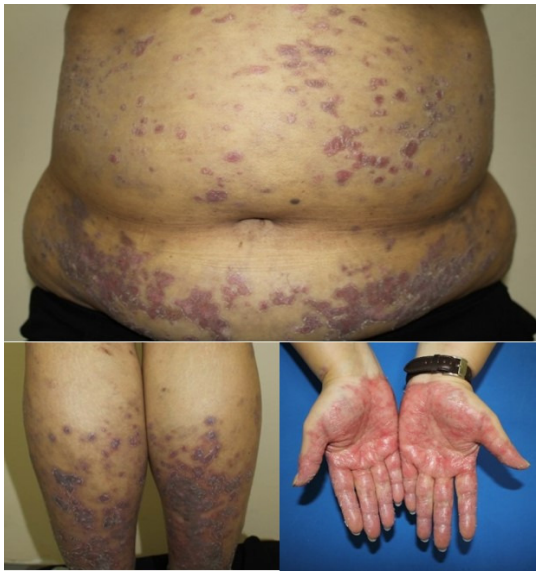

Figure 1 Multiple confluent scaly erythematous papules and plaques on trunk and extremities involving both palms and soles

The second skin biopsy was done and the histopathological feature showed psoriasiform epidermal hyperplasia in associated with wedge-shaped hypergranulosis, compact hyperkeratosis, focal parakeratosis with vacuolar alteration of basal cell layer and scattered necrotic keratinocytes in the epidermis. There were dense superficial lichenoid infiltration of lymphocytes and few eosinophils in the upper dermis. (Figure 2) She was diagnosed as imatinib-induced lichenoid eruption, classified in grade 3 according to the National Cancer Institute. (Table 1)[1]

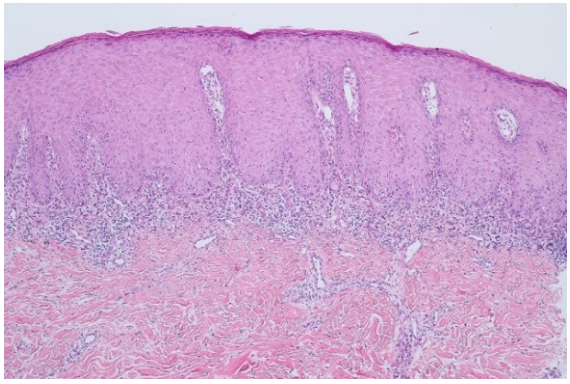

Figure 2 (H&E, 100x) Psoriasiform epidermal hyperplasia in associatied wedge-shaped hypergranulosis, compact hyperkeratosis, focal parakeratosis with vacuolar alteration of basal cell layer and scattered necrotic keratinocytes in the epidermis. There was dense superficial lichenoid infiltration of lymphocytes and few eosinophils in the upper dermis.

She was treated with oral acitretin 25 mg/day (0.3 mg/kg/day), topical corticosteroids and emollients with concurrently use of imatinib. At 1-month follow-up, the lesions gradually improved, acitretin dosage was decreased to 12.5 mg/day. Within 3 months after treatment, the rash resolved to post-inflammatory brownish patches.

Table 1 Skin and subcutaneous tissue disorders according to the National Cancer Institute[1]

Grade	Maculopapular rash
1	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)
2	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental activities of daily living
3	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care activities of daily living

Table 2 Tyrosine kinase inhibitor (TKI) classification[2]

First generation	Imatinib
	Dasatinib
Second generation	Nilotinib
	Bosutinib
Third generation	Ponatinib

Discussion

Imatinib was the first generation tyrosine kinase inhibitor (TKI) (Table 2)[2] which accounted for targeted therapy developed to inhibit the tyrosine kinases BCR-ABL in chronic myeloid leukemia (CML), c-kit in rare gastrointestinal stromal tumors, and several platelet-derived growth factor receptors (PDGFRs) in other malignancies.[3]

Although, targeted therapies improve survival and are well tolerable than traditional chemotherapeutic agents, imatinib frequently induces dermatologic adverse events[4] others than headache, diarrhea, vomiting, muscle spasm, elevated transaminases, anemia, and cytopenia.[5]

Various dermatologic adverse events from imatinib had been reported in 7% to 88.9% of patients in different series[5] 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.[6] The pathophysiology of imatinib-associated cutaneous reactions remains unclear. There is a correlation between the incidence and the dosage of imatinib which

may be related to the pharmacological effects.[7] The extent of cutaneous reactions was graded according to the National Cancer Institute from grade 1 to grade 3 (Table 1).[1]

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, palm, soles, and whole body can also be affected as well as mucosa[8] which is an uncommon classic lichenoid drug eruption.[9] The characteristic features is violaceous flat-topped papules, palmoplantar changes, mucous membrane lesions, and nail abnormalities.[8]

There were also reports of a few cases of nail dysplasia. The cutaneous reactions tend to be dose related given that all reports were in patients who were receiving high dosage of imatinib (> 400 mg/day) and usually appeared during 1 to 6 months after starting treatment[8] in which the more severe cutaneous reaction tend to appear earlier than the milder one.[10] The pathogenesis was proposed that these lesions may be closely correlated with the imatinib-altered expression of epidermal markers.[11]

Table 3 Histopathological findings in cutaneous reaction from imatinib[9]

Epidermis	Spongiosis	78.3%
	Acanthosis	47.8%
	Parakeratosis	36.9%
	Hyperkeratosis	36.9%
Dermis	Papillary dermal edema	82.6%
	Interface dermatitis	30.4%
Inflammatory cell infiltration	Lymphocytic infiltration	95.7%
	Histiocytic infiltration	95.7%
	Eosinophilic infiltration	36.9%
	Mast cell infiltration	30.4%

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 of mononuclear cells and eosinophils was present at the dermoepidermal junction. Multiple colloid bodies were noticed. Sparse perivascular infiltrates were also seen in the dermis.[12] Additionally, there were various histopathological findings as shown in Table 3.[10]

A dose reduction of imatinib or a short-term discontinuation can improve cutaneous conditions, but recurrence had been reported after rechallenge. A gradually increase the drug dosage may allow a reinstitution of therapy after the resolution of cutaneous eruptions.[11, 12] The use of topical corticosteroid may be a successful treatment in mild-to-moderate severity cases[13] but in severe cases, oral corticosteroid may be necessary.[14] Low-dosage acitretin 25 mg/day was be successfully used in management of imatinib-induced lichenoid eruption and enabling the continuation of the therapeutic imatinib dosage.[15] Although the cutaneous rash respond well to the treatment, but the oral eruptions tend to recur more frequently.[9]

In case of imatinib intolerability, the second- and third-generation tyrosine kinase inhibitor (TKI) may be a choice of treatment which yielded fewer cutaneous reactions than imatinib. There were 10-35% of cutaneous reactions reported from using second- generation tyrosine kinase inhibitor (TKI).[16]

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