Imatinib Mesylate–Induced Lichenoid Drug Eruption

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PRACTICE **POINTS**

- Imatinib mesylate can cause cutaneous adverse reactions including dry skin, alopecia, facial edema, photosensitivity rash, and lichenoid drug eruption (LDE).
- Topical corticosteroids, oral acitretin, and oral steroids may be reasonable treatment options for imatinib-induced LDE if discontinuing imatinib is not possible in a symptomatic patient.

Imatinib mesylate (imatinib) is a tyrosine kinase inhibitor initially approved by the US Food and Drug Administration in 2001 for chronic myeloid leukemia (CML). Since then, the number of indicated uses for imatinib has substantially increased. It is increasingly important that dermatologists recognize adverse cutaneous manifestations of imatinib and are aware of their management and outcomes to avoid unnecessarily discontinuing a potentially lifesaving medication. Adverse cutaneous manifestations in response to imatinib are not infrequent and can include dry skin, alopecia, facial edema, and photosensitivity rash. Other less common manifestations include exfoliative dermatitis, nail disorders, psoriasis, folliculitis, hypotrichosis, urticaria, petechiae, Stevens-Johnson syndrome, erythema multiforme, Sweet syndrome, and leukocytoclastic vasculitis. We report a case of imatinib-induced lichenoid drug eruption (LDE), a rare cutaneous manifestation, along with a review of the literature.

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The authors report no conflict of interest.

The eTable is available in the Appendix online at www.cutis.com.

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Imatinib mesylate is a tyrosine kinase inhibitor initially approved by the US Food and Drug Administration in 2001 for chronic myeloid leukemia (CML). The indications for imatinib have expanded since its initial approval. It is increasingly important that dermatologists recognize adverse cutaneous manifestations associated with imatinib and are aware of their management and outcomes to avoid unnecessarily discontinuing a potentially lifesaving medication.

Adverse cutaneous manifestations in response to imatinib are not infrequent, accounting for 7% to 21% of all side effects.[1] The most frequent cutaneous manifestations of imatinib are dry skin, alopecia, facial edema, and photosensitivity rash, respectively.[1] Other less common manifestations include exfoliative dermatitis, nail disorders, psoriasis, folliculitis, hypotrichosis, urticaria, petechiae, Stevens-Johnson syndrome, erythema multiforme, Sweet syndrome, and leukocytoclastic vasculitis.

We report a case of imatinib-induced lichenoid drug eruption (LDE), a rare cutaneous side effect of imatinib use, along with a review of the literature.

Case Report

An 86-year-old man with a history of gastrointestinal stromal tumors (GISTs) and myelodysplastic syndrome presented with diffuse hyperpigmented skin lesions on the trunk, arms, legs, and lower lip of 2 weeks' duration. He had been taking imatinib 400 mg once daily for 5 months for GIST. Although

the oncologist stopped the medication 2 weeks prior, the lesions were persistent and gradually expanded to involve the trunk, arms, legs, and lower lip. He denied any pain or pruritus. Physical examination revealed multiple ill-defined, brown to violaceous, slightly scaly macules and patches on the trunk (Figures 1A and 1B), arms, and legs (Figure 1C), as well as violaceous to erythematous patches on the mucosal aspect of the lower lip (Figure 2). Two 4-mm punch biopsies were performed from the chest and back, which revealed an atrophic epidermis, lichenoid infiltration, and multiple melanophages in the upper dermis consistent with LDE (Figure 3). Direct immunofluorescence was negative. Therefore, based on the clinicopathologic correlation, the diagnosis of imatinib-induced LDE was made. He was treated with clobetasol ointment twice daily for 3 weeks with some improvement. His GIST was stable on follow-up computed tomography 3 months after presentation, and imatinib was resumed 1 month later with continued rash that was stable with topical corticosteroid treatment.

Comment

In addition to CML, imatinib has been approved for acute lymphoblastic leukemia, myelodysplastic syndromes, aggressive systemic mastocytosis, hypereosinophilic syndrome, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, and GIST. Moreover, off-label use of imatinib for various other tyrosine kinase–positive cancers and rheumatologic conditions have been documented.[2,3] With the expanding use of imatinib, there will be more occasions for dermatologists to encounter cutaneous manifestations associated with its use.

According to a PubMed search of articles indexed for MEDLINE using the terms *imatinib mesylate lichenoid drug*, there have been few case reports of LDE associated with imatinib in the literature (eTable).[4-24] Compared to classic LDE, imatinib-induced LDE has a few characteristic findings. Classic LDE frequently spares the oral mucosa and genitalia, but imatinib-induced LDE with manifestations on the oral mucosa and genitalia as well as cutaneous eruptions have been reported.[4-9] In fact, the first known case of imatinib-induced LDE was an oral eruption in a patient with CML.[4] In patients with oral involvement, lesions have been described as lacy reticular macules and violaceous papules, erosions, and ulcers.[4,5,12] Interestingly, of those cases manifesting as concomitant oral and cutaneous LDE, the oral eruptions recurred more frequently, with 3 of 12 patients having recurrence of oral lesions after the cutaneous manifestations resolved.[8,16] Genital manifestations of imatinib-induced LDE were much less common.[9,11]

To date, subsequent reports of imatinib-induced LDE have documented skin manifestations consistent with classic LDE occurring in a diffuse, bilateral, photodistributed pattern.[10,15,16] One case presented with diffuse hyperpigmentation associated with LDE in a Japanese patient.[20] The authors suggested this finding may be more prominent in patients with skin of color,[20] which is consistent with the current case. Nail findings such as subungual hyperkeratosis and longitudinal ridging also have been reported.[9,11]

The latency period between initiation of imatinib and onset of LDE generally ranges from 1 to 12 months, with onset most commonly occurring between 2 to 5 months or with dosage increase (eTable). Imatinib-induced LDE primarily has been documented with a 400-mg dose, with 1 case of a 600-mg dose and 1 case of an 800-mg dose, which suggests dose dependency. Furthermore, reports exist of several patients responding well to dose reduction with subsequent recurrence on dose reescalation.[13,15]

Historically, LDE resolves with discontinuation of the drug after a few weeks to months. When discontinuation of imatinib is unfavorable or patients report symptoms including severe pruritus or pain, treatment should be considered. Topical or oral corticosteroids can be used to treat imatinib-induced LDE, similar to lichen planus. When oral corticosteroids are contraindicated (eg, due to poor patient

Figure 1. Widespread violaceous, hyperpigmented, slightly scaly macules and patches on the chest (A), back (B), and leg (C).

Figure 2. Lacy, violaceous to erythematous patches on the mucosal surface of the lower lip.

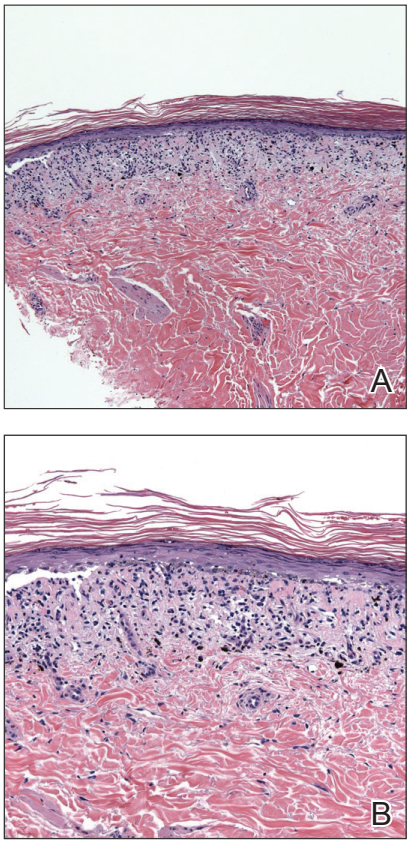

Figure 3. Atrophic epidermis, lichenoid infiltration of lymphocytes, and multiple melanophages in the upper dermis on histopathology (A and B)(H&E, original magnifications ×40 and ×100).

tolerance), oral acitretin at 25 to 35 mg once daily for 6 to 12 weeks has been reported as an alternative treatment.[25]

In the majority of cases of imatinib-induced LDE, it was undesirable to stop imatinib (eTable). Notably, in half the reported cases, imatinib was able to be continued and patients were treated symptomatically with either oral and/or topical steroids and/or acitretin with complete remission or tolerable recurrences. Dalmau et al[9] reported 3 patients who responded poorly to topical and oral steroids and were subsequently treated with acitretin 25 mg once daily; 2 of 3 patients responded favorably to treatment and imatinib was able to be continued. In the current case imatinib initially helped, but because his rash was relatively asymptomatic, imatinib was restarted with control of rash with topical steroids. He developed some pancytopenia, which required intermittent stoppage of the imatinib.

Conclusion

We present a case of imatinib-induced cutaneous and oral LDE in a patient with GIST. Topical corticosteroids, oral acitretin, and oral steroids all may be reasonable treatment options if discontinuing imatinib is not possible in a symptomatic patient. If these therapies fail and the eruption is extensive or intolerable, dosage adjustment is another option to consider before discontinuation of imatinib.

REFERENCES

1. Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol*. 2006;5:228-231.
2. Kim H, Kim NH, Kang HJ, et al. Successful long-term use of imatinib mesylate in pediatric patients with sclerodermatous chronic GVHD. *Pediatr Transplant*. 2012;16:910-912.
3. Prey S, Ezzedine K, Doussau A, et al. Imatinib mesylate in scleroderma-associated diffuse skin fibrosis: a phase II multicentre randomized double-blinded controlled trial. *Br J Dermatol*. 2012;167:1138-1144.
4. Lim DS, Muir J. Oral lichenoid reaction to imatinib (STI 571, gleevec). *Dermatology*. 2002;205:169-171.
5. Ena P, Chiarolini F, Siddi GM, et al. Oral lichenoid eruption secondary to imatinib (glivec). *J Dermatolog Treat*. 2004;15:253-255.
6. Roux C, Boisseau-Garsaud AM, Saint-Cyr I, et al. Lichenoid cutaneous reaction to imatinib. *Ann Dermatol Venereol*. 2004;131:571-573.
7. Prabhash K, Doval DC. Lichenoid eruption due to imatinib. *Indian J Dermatol Venereol Leprol*. 2005;71:287-288.
8. Pascual JC, Matarredona J, Miralles J, et al. Oral and cutaneous lichenoid reaction secondary to imatinib: report of two cases. *Int J Dermatol*. 2006;45:1471-1473.
9. Dalmau J, Peramiquel L, Puig L, et al. Imatinib-associated lichenoid eruption: acitretin treatment allows maintained antineoplastic effect. *Br J Dermatol*. 2006;154:1213-1216.
10. Chan CY, Browning J, Smith-Zagone MJ, et al. Cutaneous lichenoid dermatitis associated with imatinib mesylate. *Dermatol Online J*. 2007;13:29.

11. Wahiduzzaman M, Pubalan M. Oral and cutaneous lichenoid reaction with nail changes secondary to imatinib: report of a case and literature review. *Dermatol Online J*. 2008;14:14.
12. Basso FG, Boer CC, Correa ME, et al. Skin and oral lesions associated to imatinib mesylate therapy. *Support Care Cancer*. 2009;17:465-468.
13. Kawakami T, Kawanabe T, Soma Y. Cutaneous lichenoid eruption caused by imatinib mesylate in a Japanese patient with chronic myeloid leukaemia. *Acta Derm Venereol*. 2009;89:325-326.
14. Sendagorta E, Herranz P, Feito M, et al. Lichenoid drug eruption related to imatinib: report of a new case and review of the literature. *Clin Exp Dermatol*. 2009;34:E315-E316.
15. Kuraishi N, Nagai Y, Hasegawa M, et al. Lichenoid drug eruption with palmoplantar hyperkeratosis due to imatinib mesylate: a case report and a review of the literature. *Acta Derm Venereol*. 2010;90:73-76.
16. Brazzelli V, Muzio F, Manna G, et al. Photo-induced dermatitis and oral lichenoid reaction in a chronic myeloid leukemia patient treated with imatinib mesylate. *Photodermatol Photoimmunol Photomed*. 2012;28:2-5.
17. Ghosh SK. Generalized lichenoid drug eruption associated with imatinib mesylate therapy. *Indian J Dermatol*. 2013;58:388-392.
18. Lee J, Chung J, Jung M, et al. Lichenoid drug eruption after low-dose imatinib mesylate therapy. *Ann Dermatol*. 2013;25:500-502.
19. Machaczka M, Gossart M. Multiple skin lesions caused by imatinib mesylate treatment of chronic myeloid leukemia. *Pol Arch Med Wewn*. 2013;123:251-252.
20. Kagimoto Y, Mizuashi M, Kikuchi K, et al. Lichenoid drug eruption with hyperpigmentation caused by imatinib mesylate [published online June 20, 2013]. *Int J Dermatol*. 2014;53:E161-E162.
21. Arshdeep, De D, Malhotra P, et al. Imatinib mesylate-induced severe lichenoid rash. *Indian J Dermatol Venereol* Leprol. 2014;80:93-95.
22. Lau YM, Lam YK, Leung KH, et al. Trachyonychia in a patient with chronic myeloid leukaemia after imatinib mesylate. *Hong Kong Med J*. 2014;20:464.e2.
23. Bhatia A, Kanish B, Chaudhary P. Lichenoid drug eruption due to imatinib mesylate. *Int J Appl Basic Med Res*. 2015;5:68-69.
24. Luo JR, Xiang XJ, Xiong JP. Lichenoid drug eruption caused by imatinib mesylate in a Chinese patient with gastrointestinal stromal tumor. *Int J Clin Pharmacol Ther*. 2016;54:719-722.
25. Laurberg G, Geiger JM, Hjorth N, et al. Treatment of lichen planus with acitretin. a double-blind, placebo-controlled study in 65 patients. *J Am Acad Dermatol*. 1991;24:434-437.

Case Reports of Cutaneous Imatinib Mesylate–Induced Lichenoid Drug Eruption

Reference (Year)	Age/ Sex	Disease	Imatinib Mesylate Dose, mg	Duration, mo	Cutaneous Findings	Mucosal Findings	Nail Findings	Treatments	Imatinib Mesylate Therapy	Outcome
Lim and Muir[4] (2002)	72/F	CML	ND	3	NR	Erosion plaques and ulcers of the tongue and buccal mucosa	NR	Dexamethasone mouthwash	Discontinued	Resolution
Ena et al[5] (2004)	62/M	GIST	ND	12	NR	Grey violaceous plaques on the labial and buccal mucosa	NR	Topical corticosteroids	Continued	Resolution
Roux et al[6] (2004)	52/M	CML	400	2	Disseminated eruption	NR	NR	Oral corticosteroids	Continued	ND
Prabhash and Doval[7] (2005)	50/M	CML	400	6	Maculopapular lesions on the eyelids	NR	NR	ND	Continued	Resolution
Pascual et al[8] (2006)	69/F	CML	400	2	Pruritic papules and plaques on the trunk, arms, legs, face	Oral erosions on the dorsal tongue	NR	Oral and topical corticosteroids	Tentative discontinuation (medication was discontinued and restarted with the concomitant use of topical steroid)	Resolution with recurrence of oral lesion only with reintroduction
	65/F	CML	400	3	Grey violaceous plaques on the trunk, arms, legs	Violaceous plaques on the lateral tongue with a lacy pattern	NR	Oral and topical corticosteroids	Continued	Resolution with flares of oral lesions

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Reference (Year)	Age/ Sex	Disease	Imatinib Mesylate Dose, mg	Duration, mo	Cutaneous Findings	Mucosal Findings	Nail Findings	Treatments	Imatinib Mesylate Therapy	Outcome
Dalmau et al[9] (2006)	76/M	CML	400	4	Erythema and lichenoid rash on trunk and upper arms	NR	Subungual hyperkeratosis	Oral antihistamine, topical corticosteroids	Discontinued	Resolution
	60/M	CML	400	2	Lichenoid eruption on the face, wrist, and neck	Reddish macules and erosions, erosions on the penis and anal region	NR	Oral corticosteroids, acitretin	Continued	Resolution, no relapse at 5 mo on oral prednisone 20 mg
	75/M	GIST	400	1	Generalized eruption of lichenoid papules	NR	NR	Systemic antihistamines, topical steroids, acitretin	Continued	Resolution
	50/M	CML	400	2	Generalized eruption on the face, chest, arms, legs	White reticulated macules on buccal mucosa	NR	Topical corticosteroid, oral antihistamine, acitretin	Continued	Resolution
Chan et al[10] (2007)	56/M	CML	600	3	Violaceous papules and plaques on the arms, legs, and chest	NR	NR	Oral and topical corticosteroids	Discontinued and reinitiated due to worsening of CML	Recurrence with rechallenge
Wahiduzzman and Pubalan[11] (2008)	31/M	CML	400	5	Diffuse itchy papules on the chest, palms, soles, and genitalia	Lacy eruption on the lips, buccal mucosa, and tongue	Longitudinal ridging	Oral and topical corticosteroids	Continued	Resolution

Reference (Year)	Age/ Sex	Disease	Imatinib Mesylate Dose, mg	Duration, mo	Cutaneous Findings	Mucosal Findings	Nail Findings	Treatments	Imatinib Mesylate Therapy	Outcome
Basso et al[12] (2009)	85/ND	CML	400	5	Skin eruption on the arms and legs	Ulcer on the lower lip	NR	Oral corticosteroids	Discontinued, restarted and discontinued due to recurrence of rash	Resolution
	55/M	CML	ND	3	NR	Erosions on the tongue, lower lip, and buccal mucosa	NR	Topical and oral corticosteroids	Continued	Near-complete remission at 3 mo
Kawakami et al[13] (2009)	53/M	CML	400	2	Generalized, violaceous, mildly pruritic papules and plaques on the abdomen and proximal arms	NR	NR	Topical corticosteroids	Dose adjustment of imatinib to 200 mg	Remission, recurrence with dose increase to 400 mg
Sendagorta et al[14] (2009)	71/M	GIST	400	3	Violaceous, scaly plaques on the flank and upper arms	Violaceous erosions on tongue and labia	NR	ND	Discontinued	Resolution
Kuraishi et al[15] (2010)	57/M	CML	400	2	Lichenoid eruption on the arms and legs, palmoplantar keratosis	White streak with erosion of buccal mucosa	NR	Topical corticosteroids, oral antihistamine	Tentative discontinuation, restarted with dose adjustment	Partial remission

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Reference (Year)	Age/ Sex	Disease	Imatinib Mesylate Dose, mg	Duration, mo	Cutaneous Findings	Mucosal Findings	Nail Findings	Treatments	Imatinib Mesylate Therapy	Outcome
Brazelli et al[16] (2012)	60/F	CML	400	12	Photoinduced dermatitis	Radiating striae on oral mucosa and tongue	NR	Topical and oral corticosteroids	Discontinued and restarted with corticosteroids	Resolution with intermittent recurrence of oral lesions
Ghosh[17] (2013)	63/M	CML	400	2	Numerous well-defined, violaceous, discrete and coalescing papules and plaques on arms, legs, abdomen, chest, and back	No lesions	NR	Topical corticosteroids	Stopped and reintroduced with few new lesions controlled with topical steroids	Resolution but recurrence with rechallenge
Lee et al[18] (2013)	77/M	GIST	400	NR	Violaceous pruritic papules on both legs progressing to whole-body involvement	NR	NR	Switch to sunitinib with improvement; no other therapy reported	Imatinib was discontinued in favor of sunitinib with improvement of eruption, but kidney function worsened so imatinib was reintroduced at lower doses of 200 mg	Patient was maintained at time of publication on 200 mg of imatinib with continued cutaneous eruption

Reference (Year)	Age/ Sex	Disease	Imatinib Mesylate Dose, mg	Duration, mo	Cutaneous Findings	Mucosal Findings	Nail Findings	Treatments	Imatinib Mesylate Therapy	Outcome
Machaczka and Gossart[19] (2013)	48/M	CML	400	2	Multiple erythematous skin lesions with peeling of skin, particularly on the fingertips and palms, with erythematous plaques in axilla and bright red maculopapular lesions on back, penis, and groin	NR	NR	NR	After initial reduction to 300 mg was not helpful, the drug was discontinued and dasatinib therapy introduced	Resolution
Kagimoto et al[20] (2014)	58/F	GIST	400	3	Violaceous and hyperpigmented papules and plaques on face, back, and limbs	Violaceous plaques on buccal mucosa	NR	Topical corticosteroids	Continued	No resolution, no further data
Arshdeep et al[21] (2014)	47/F	CML	800	3	Pruritic lichenoid papules and plaques with minimal scale photodistributed on neck, chest, back, and dorsal hand; erythematous plaques on palms and soles; scalp with bright erythema	Lower mucosal lip	All 20 nails showed subungual hyperkeratosis, onychomadesis and onycholysis	Oral prednisolone 0.5 mg/kg with 4-mo taper	Continued	Resolution

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Reference (Year)	Age/ Sex	Disease	Imatinib Mesylate Dose, mg	Duration, mo	Cutaneous Findings	Mucosal Findings	Nail Findings	Treatments	Imatinib Mesylate Therapy	Outcome
Lau et al[22] (2014)	86/M	CML	400	3	Pruritic skin rash with white streaks and scaling over face, scalp, trunk, and limbs	NR	Trachyonychia with onycholysis	Topical steroid	Stopped and nilotinib started	Resolution
Bhatia et al[23] (2015)	72/M	CML	600	9	Pruritic lesion only on photoexposed areas to start with generalization of violaceous papules and plaques on neck, dorsal hands, extensor forearms, arms, and trunk	Violaceous papules on angles of mouth and lower lip; no oral or genital mucosal lesions	None	Topical corticosteroids and antihistamines	Continued	Rash was controlled with topical and antihistamine therapy
Luo et al[24] (2016)	73/M	GIST	NR	6	Lesions on face, trunk, and limbs	NR	NR	Discontinuation of drug	Stopped	Complete resolution
Current case	86/M	GIST	400	5	Hyperpigmented macules and patches on trunk, arms, legs	Lacy white to erythematous macules on the lower lip	NR	Topical corticosteroid	Discontinued and on hold due to stable condition	Improvement at 3 wk

Abbreviations: F, female; CML, chronic myeloid leukemia; ND, not documented; NR, not reported; M, male; GIST, gastrointestinal stromal tumor.