Specific Nail Alterations in Cutaneous T-Cell Lymphoma

Successful Treatment With Topical Mechlorethamine

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Background: Cutaneous T-cell lymphoma can be associated with clinically significant nail alterations, the presentation of which can be protean and misleading. To date, only a few reports have demonstrated direct specific tumor infiltration of the nail bed, while little is known about the efficacy of topical treatments.

Observations: We describe the case of a 93-year-old man presenting with Sézary syndrome who developed clinically significant nail alterations. Light microscopy studies and T-cell receptor rearrangement analysis demonstrated the presence of a specific lymphocytic infiltrate within the nail bed. The patient was given repeated courses of topical mechlorethamine, leading to a sustained complete remission of both skin and nail alterations.

Conclusions: Specific nail involvement should be recognized and considered in all patients with cutaneous T-cell lymphomas. Topical mechlorethamine remains an attractive therapeutic option in cases of specific nail alterations, especially for situations in which systemic therapies are either not indicated or unlikely to be well tolerated.

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NAIL ABNORMALITIES ARE A rare accompanying sign of both localized and erythrodermic forms of cutaneous T-cell lymphoma (CTCL). Their presentation can be very pleomorphic and misleading. Demonstration of specific infiltration of the nail apparatus by histologic examination and/or T-cell receptor (TCR) clonality has been very rarely reported. Moreover, although systemic therapies of CTCL are likely to improve specific nail lesions, little is known about the effect of topical treatments. Among them, mechlorethamine is an attractive alternative to use in situations in which the disease has spared lymph nodes or other hematopoietic organs.

We report the case of a patient with Sézary syndrome (SS) who developed specific nail abnormalities, confirmed histologically, immunohistochemically, and by clonal T-cell rearrangement studies, who was successfully treated with topical mechlorethamine. This observation demonstrates the usefulness for nail involvement in CTCL.

REPORT OF A CASE

A 93-year-old male patient with suspected CTCL presented at our department. He had complained of generalized and recurrent eczematous lesions for 3 years and had been treated with intermittent topical steroids. The first histologic evaluation in January 2008 showed features compatible with small-plaque psoriasis. Psoralen–UV-A (PUVA) therapy had no effect. Five months later, the eruption had spread to more than 80% of the body surface and had become partially infiltrated. Findings from a new biopsy specimen revealed a subepidermal infiltrate composed of atypical small lymphocytes with a clinically significant degree of epidermotropism but no genuine abscess formation. The infiltrate consisted mainly of CD3+ T lymphocytes (with a CD4 to CD8 ratio of 1:2), and a clonal rearrangement for the γ-chain of TCR (TCR-γ) was observed. Findings from a screening for lymph nodes or visceral and bone marrow involvement were negative. No circulating Sézary cells could be detected, but the same clonal rearrangement of the
TCR-γ was observed in the blood. The patient was considered to have stage IIIA CTCL (stage T4N0M0B0 according to the 2007 European Organisation for Research and Treatment of Cancer /International Society for Cutaneous Lymphoma criteria). In addition, he had complained of nail alterations over a 1-year period, which involved 9 of the 10 fingernails (Figure 1). Careful examination revealed anonychia (fingernail 2, right and left), onychomadesis (fingernails 1, 3, and 4, right; and fingernails 3 and 5, left), subungal distal hyperkeratosis (fingernail 1, left) and onycholysis (fingernail 5, right). Neither paronychia nor perionychium alterations were observed. There was also no discoloration or growth arrest, and the fourth left digit was normal. The patient denied any intake of systemic drugs, especially no cyclins. Histopathologic examination of a longitudinal nail biopsy (fingernail 1, left), involving the proximal nail matrix, revealed a horizontal bandlike lymphocytic infiltrate localized in the dermis of the nail bed and at the junction with the hyponychium. The atypical lymphocytes showed clinically significant epidermotropism with Pautrier microabscesses formation. No relevant modification of the proximal matrix was observed. The nail plate was proximally thin and became steadily substituted by hyperkeratosis distally (Figure 2). Periodic acid–Schiff (PAS) stains were negative for fungi. Immunostaining revealed a CD3+ lymphocytic infiltrate within the proximal matrix, the nail bed, and the hyponychium. CD4 stained only one-third of the cells, whereas CD8 showed marked staining of the majority. The TCR-γ rearrangement showed identical clones in blood as well as in skin and nail materials (Figure 3).

Because previous PUVA therapy was ineffective, local therapy with topical mechlorethamine ointment (chloromethin hydrochloride) was started. A 0.02% ointment-based mechlorethamine preparation was obtained according to the recommended procedure.1 It was applied 3 times weekly, used in alternation during the first 2 weeks, with clobetasol propionate on all the skin surface except the head. Mechlorethamine was also directly applied on the whole nail apparatus (nail plates...
and lateral and proximal nail folds). At 6 months, the skin and nails appeared to be completely healed (Figure 4). Maintenance of the success was obtained for more than 6 months while decreasing the application frequency to twice weekly.

**METHODS**

The skin and nail biopsy specimens were fixed in formalin and processed as usual. Staining with hematoxylin-eosin, PAS, Giemsa, and elastic–van Gieson stains was performed. Immunophenotyping was performed according to routine methods for skin lymphomas. For TCR-rearrangement study, genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue sections. Amplification was performed using 2 different sets of specific consensus primers that bind to different zones of the variable (V) regions in combination with consensus primers from the joining (J) regions of the TCR γ-chain gene. The 2 sets of variable region primers (consensus primers Vg1-8 and specific primers Vg9, Vg10, and Vg11) were either 5' end-labeled with 5-carboxyfluorescein or hexachloro-6-carboxy-fluorescein. Polymerase chain reaction products were analyzed by capillary electrophoresis using an ABI PRISM 3100 Avant genetic analyzer (Applied Biosystems, Foster City, California).

**COMMENT**

Though not uncommon, nail alterations in CTCL have been rarely described. Nail involvement is seen in mycosis fungoides (MF), usually in advanced stages, as well as in true SS. Ungueal involvement in plaque and tumoral stages of MF was first described as “yellow nail syndrome” of the 20 nails with pleural effusion and marked lower leg lymphedema. Yellow discoloration, slowed growth, nail thickening, and increased curvature, together with onychomadesis, were also reported in a multiple-plaque–stage MF. Yellow nails with thickening accompanied a vesiculopustular variant of palmoplantar MF, in which tumoral infiltration of the nail bed was confirmed histologically, im-

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Figure 3. Identical clonal rearrangement for T-cell receptor γ in the skin and nails. A, Polyclonal; B, D9014-08 skin abdominal biopsy specimen; C, D10439-08 nail biopsy specimen. Arrowheads indicate the direction of the major peaks.
munohistochemically, and by TCR rearrangement study. Paronychia, trachyonychia, onycholysis, and subungual hyperkeratosis were observed as a direct consequence of infiltration by a folliculotropic MF, affecting all fingernails. More recently, nail alterations in a single finger were reported in tumor-stage MF as nail plate thinning and partial obliteration of the proximal and lateral nail folds, together with soft-tissue swelling of the entire segment. Eight cases of nail alterations have been described in patients with SS. Tomsick reported isolated rough subungual hyperkeratosis of the 20 nails in a patient with circulating Sézary cells and multiple MF plaques, whereas Dalziel et al observed a similar presentation in a patient with true erythrodermic SS. The patient described in a report by Tosti et al had nonspecific thickening and discoloration of the nail plates. In a series of 5 SS cases, all patients presented with splinter hemorrhages, with subungual hyperkeratosis and/or onycholysis and 4 with distal yellow-brown discoloration.

Our case shows the coexistence of marked onycho-madesis, previously undescribed, to our knowledge, involving 9 of the 20 nails. There was neither a yellow nail discoloration nor a generalized subungual hyperkeratosis. The possibility that phototherapy was responsible for the nail alterations seems very unlikely because (1) nail changes started prior to PUVA therapy, (2) 1 finger was completely spared, and (3) onycholysis remains very rare during PUVA therapy and then induces more homogeneous alterations.

To our knowledge, treatment of nail alterations in CTCL have never been specifically studied. In the several cases reported to date, patients received a systemic treatment, resulting in partial or total improvement of the nail lesions. Topical therapies in CTCL, besides phototherapy as stand-alone or add-on treatment, rely mainly on local application of cytostatics, such as topical nitrogen mustard. Topical mechlorethamine has proved to be an efficient treatment in MF, alone or associated with topical steroids. A response was even reported in patients with a poor prognosis, such as CTCL in organ transplant recipients. However, the specific efficacy on nail alterations was never mentioned, except in the original report by Tomsick, who wrote that nitrogen mustard diluted in water induced resumption of normal nail growth. Because systemic absorption of mechlorethamine is negligible after topical administration, the observed response is likely to result from a local cytostatic effect on tumor cells infiltrating the hyponychia and/or the nail bed and/or the matrix. Topical mechlorethamine might be effective by various mechanisms of action: (1) diffusion through the nail plate, although this is likely to be minimal; (2) effect on the matrix via penetration of the proximal nail fold; and (3) direct diffusion to the nail bed favored by the distal onycholysis.

In brief, this case illustrates the wide spectrum of specific nail abnormalities that can occur in CTCL. In addition, it provides evidence for the excellent effect of topical mechlorethamine and suggests that nail involvement per se in CTCL should not be regarded as an independent criterion to start a systemic treatment if otherwise not required.

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REFERENCES


Notable Notes

Articles of Faith Variant Lighten Up Babe!

This little cherub was inspired by various folk and home remedies that have been recommended to lighten skin color (Figure). From the top, the components are saffron for its little curl; a potato for its head; plum tomatoes for its ears; almonds for its eyes; a red onion for its howling mouth (it is a baby after all); a milk bottle for its body; pieces of aloe for its arms and slices of lime for its hands; pieces of cucumber for its legs and slices of lemon for its feet; and an orange peel for its diaper.

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