Nail Irregularities Associated With Sézary Syndrome

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PRACTICE **POINTS**

- Nail changes are frequently observed in patients with Sézary syndrome.
- Nail changes in patients with cutaneous T-cell lymphoma may result from the disease process or physical symptoms of advanced disease, or they may present secondary to treatment.

Sézary syndrome (SS) is the leukemic form of cutaneous T-cell lymphoma (CTCL) and can be associated with various nail irregularities, though they are infrequently reported. In this retrospective study, we reviewed medical records from a CTCL clinic database at the University of Texas MD Anderson Cancer Center (Houston, Texas) for reported nail abnormalities in patients with a diagnosis of SS. Findings for 2 select cases are described in more detail and are compared to prior case reports to establish a comprehensive list of nail irregularities that have been associated with SS.

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Sézary syndrome (SS) is an advanced leukemic form of cutaneous T-cell lymphoma (CTCL) that is characterized by generalized erythroderma and T-cell leukemia. Skin changes can include erythroderma, keratosis pilaris–like lesions, keratoderma, ectropion, alopecia, and nail changes.[1] Nail changes in SS patients frequently are overlooked and underreported; they vary greatly from patient to patient, and their incidence has not been widely evaluated in the literature.

In this retrospective study, we reviewed medical records from a previously collected CTCL clinic database at the University of Texas MD Anderson Cancer Center (Houston, Texas) and found nail abnormalities in 36 of 83 (43.4%) patients with a diagnosis of SS. Findings for 2 select cases are described in more detail; they were compared to prior case reports from the literature to establish a comprehensive list of nail irregularities that have been associated with SS.

Methods

We examined records from a previously collected CTCL clinic database at the University of Texas MD Anderson Cancer Center. This database was part of an institutional review board–approved protocol to prospectively collect data from patients with CTCL. Our search yielded 83 patients with SS who were seen between 2007 and 2014.

Results

Of the 83 cases reviewed from the CTCL database, 36 (43.4%) SS patients reported at least 1 nail abnormality on the fingernails or toenails. Patients ranged in age from 59 to 85 years and included 27 (75%) men and 9 (25%) women. Nail irregularities noted on physical examination are summarized in Table 1. More than half of the patients presented with nail thickening (58.3% [21/36]), dystrophy (55.6% [20/36]), or yellowing (55.6% [20/36]) of 1 or more nails. Other findings included 15 (41.7%) patients with subungual hyperkeratosis, 3 (8.3%) with Beau lines, and 1 (2.8%) with multiple oil spots consistent with salmon patches. Five (13.9%) patients had only 1 reported nail irregularity, and 1 (2.8%) patient had 6 irregularities. The

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average number of nail abnormalities per patient was 2.88 (range, 1–6). We selected 2 patients with extensive nail findings who represent the spectrum of nail findings in patients with SS.

Patient 1—A 71-year-old white man presented with a papular rash of 30 years' duration. The eruption first occurred on the soles of the feet but progressed to generalized erythroderma. He was found to be colonized with methicillin-resistant *Staphylococcus aureus*. Over the next 9 months, the patient was diagnosed with SS at an outside institution and was treated with cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone, gemcitabine, etoposide, methylprednisolone, cytarabine, cisplatin, topical steroids, and intravenous methotrexate with no apparent improvement. At presentation to our institution, physical examination revealed pruritus; alopecia; generalized lymphadenopathy; erythroderma; and irregular nail findings, including yellowing, thickened fingernails and toenails with subungual debris, and splinter hemorrhage (Figure 1). A thick plaque with perioral distribution as well as erosions on the face and feet were noted. The total body surface area (BSA) affected was 100% (patches, 91%; plaques, 9%).

TABLE 1. Nail Irregularities Presenting in Sézary Syndrome (N=36)

Nail Irregularity	No. of Patients (%)[a]
Nail thickening	21 (58.3)
Dystrophy	20 (55.6)
Yellowing	20 (55.6)
Subungual hyperkeratosis	15 (41.7)
Onycholysis	7 (19.4)
Ridging	6 (16.7)
Splinter hemorrhage	6 (16.7)
Beau lines	3 (8.3)
Onychomadesis	3 (8.3)
Pitting	1 (2.8)
Salmon patch	1 (2.8)
Subungual hematoma	1 (2.8)

[a]Patients may have more than 1 nail irregularity.

At diagnosis at our institution, the patient's white blood cell (WBC) count was 17,800/μL (reference range, 4000–11,000/μL), with 11% Sézary cells noted. Biopsy of a lymph node from the inguinal area indicated T-cell lymphoma with clonal T-cell receptor (TCR) β gene rearrangement. Biopsy of lesional skin in the right groin area showed an atypical T-cell lymphocytic infiltrate with a CD4:CD8 ratio of 2.9:1 and partial loss of CD7 expression, consistent with mycosis fungoides (MF)/SS stage IVA. At presentation to our institution, the WBC count was 12,700/μL with a neutrophil count of 47% (reference range, 42%–66%), lymphocyte count of 36% (reference range, 24%–44%), monocyte count of 4% (reference range, 2%–7%), platelet count of 427,000/μL (reference range, 150,000–350,000/μL), hemoglobin of 9.9 g/dL (reference range, 14.0–17.5 g/dL), and lactate dehydrogenase of 733 U/L (reference range, 135–214 U/L). Lymphocytes were positive for CD2, CD3, CD4, CD5, CD25, CD52, TCRα, TCRβ, and TCR VB17; partial for CD26; and negative for CD7, CD8, and CD57. At follow-up 1 month later, the $CD4^+CD26^-$ T-cell population was 56%, which was consistent with SS T-cell lymphoma.

Skin scrapings from the generalized keratoderma on the patient's feet were positive for fungal hyphae under potassium hydroxide examination. Nail clippings showed compact keratin with periodic acid–Schiff–positive small yeast forms admixed with bacterial organisms, consistent with onychomycosis. At our institution, the patient received extracorporeal photopheresis, whirlpool therapy (a type of hydrotherapy), steroid wet wraps, and intravenous vancomycin for methicillin-resistant

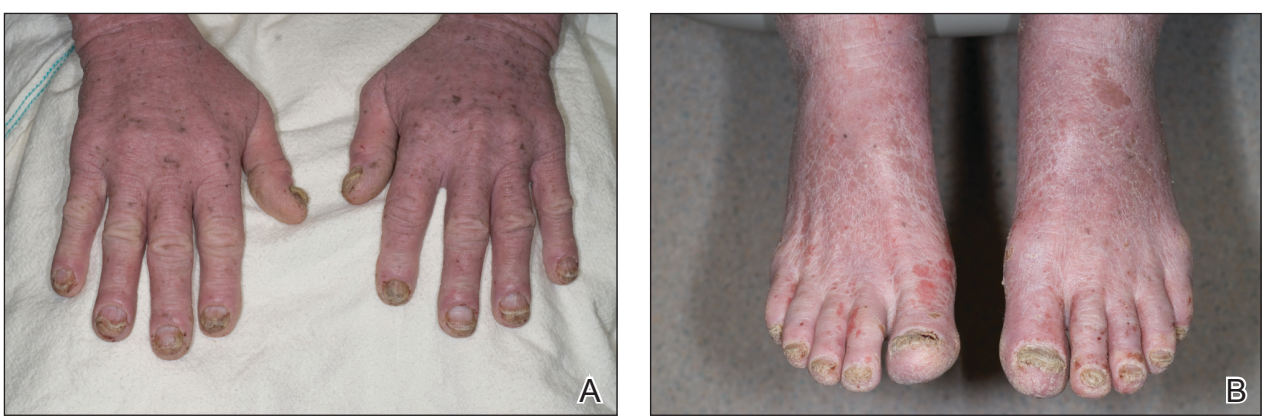

FIGURE 1. Sézary syndrome. A, Thickening and yellowing of the fingernails. B, Erythroderma and subungual debris also were noted on the toenails.

S aureus. He also received bexarotene, levothyroxine sodium, and fenofibrate. After antibiotics and 2 sessions of photopheresis, the total BSA improved from 100% to 33%. The feet and nails were treated with ciclopirox gel and terbinafine, but neither the keratoderma nor the nails improved.

Patient 2—An 84-year-old white man with B-cell chronic lymphocytic leukemia also was diagnosed with SS at an outside institution. One year later, he presented to our institution with mild pruritus and swelling of the lower left leg, which was diagnosed as deep vein thrombosis. There was bilateral scaling of the palms, with fissures present on the left palm. The fingernails showed dystrophy with Beau lines, and the toenails were dystrophic with onycholysis on the bilateral great toes (Figure 2). Patches were noted on most of the body, including the feet, with plaques limited to the hands; the total BSA affected was 80%. Flow cytometry showed an elevated Sézary cell count ($CD4^+CD26^-$) of 4700 cells/μL. Complete blood cell count with differential included a hemoglobin level of 11.4 g/dL, hematocrit level of 35.3% (reference range, 37%–47%), a platelet count of 217,000/μL, and a WBC count of 17,700/μL, of which 29% were neutrophils, 63% were lymphocytes, 6% were monocytes, and 2% were eosinophils. The lactate dehydrogenase level was elevated at 829 U/L. The patient had not been treated for chronic lymphocytic leukemia in the last 11 months due to adverse reactions to rituximab after 2 cycles of fludarabine, cyclophosphamide, and rituximab chemotherapy. First-line therapy for the patient was photopheresis for SS.

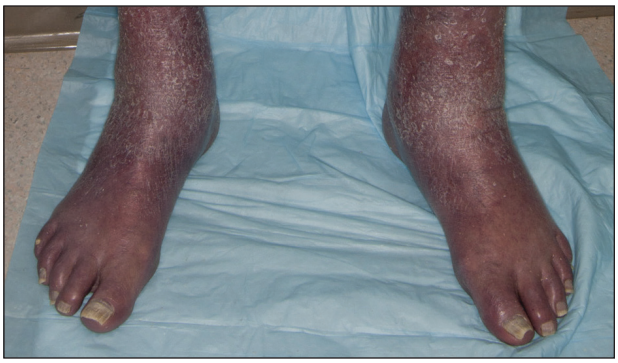

FIGURE 2. Sézary syndrome. Dystrophic toenails with onycholysis on the bilateral great toes.

Comment

Nail changes are found in many cases of advanced-stage SS but rarely have been reported in the literature. A literature review of PubMed articles indexed for MEDLINE was conducted using the search terms *Sézary*, *nail*, *onychodystrophy*, *cutaneous T-cell lymphoma*, and *CTCL*. All results were reviewed for original reported cases of SS with at least 1 reported nail finding. A total of 7 reports[2-8] met these requirements with a total of 43 SS patients with reported nail findings, which are summarized in Tables 2 and 3.

Our findings are generally consistent with those previously described in the literature. Nail thickening, yellowing, subungual hyperkeratosis, dystrophy, and onycholysis are consistently some of the most common nail findings in patients with SS. In 2012, Martin and Duvic[9] found that 52.9% (45/85) of SS patients with keratoderma on physical examination were positive for dermatophyte hyphae when skin scrapings were done under potassium hydroxide examination, a considerably greater incidence than in the general population (10%–20%). The nail changes seen in our SS patients were identical to those found in dermatophyte infections, including discoloration, subungual debris, nail thickening, onycholysis, and dystrophy.[10] In patient 1, nail clippings were positive for onychomycosis, a common nail condition that is especially prevalent in older or immunocompromised patients.[9,10]

Interestingly, findings not observed in the literature included salmon patches and Beau lines. Beau lines are horizontal depressions in the nail plate and often are indicative of temporary interruption of nail growth, such as due to an underlying disease process, severe illness, and/or chemotherapy.[11,12] In our review, patient 2 had clinical findings of Beau lines. Because the average time for fingernail regrowth is 3 to 6 months,[13] it is reasonable to assume that physical findings associated with fludarabine, cyclophosphamide, and rituximab chemotherapy treatment would no longer be demonstrated 11 months after completion of therapy. On the other hand, paronychia was frequently observed by Damasco et al[8] (63.2% [12/19] of their cases), yet it was not found in our database or the other literature reports we reviewed. Perhaps these differences are due to differences in patient populations and/or available therapies, lack of documentation, or small sample size and limited reports in the literature.

A common question is: Are the nail irregularities caused by the physical symptoms of advanced CTCL or by the underlying disease process in response to the atypical T cells? Erythroderma has been speculated to cause many of the clinical findings of nail abnormalities found in CTCL patients.[2,3] However, Fleming et al[14] described an MF patient who experienced onychomadesis without erythroderma, which suggests that a different mechanism may cause these nail changes. The wide range of nail abnormalities in CTCL can cause problems with diagnosing the specific cause underlying the nail alteration.

To further complicate the issue, numerous therapies for CTCL also may cause nail changes, such as the previously described Beau lines. In 2010, Parmentier et al[4] reported a patient with nail alterations that had been present for more than 1 year, with 9 of 10 fingernails demonstrating anonychia, onychomadesis, subungual distal hyperkeratosis, and onycholysis. In this case report, the authors were able to exclude phototherapy as the

TABLE 2. Nail Irregularities Presenting in Sézary Syndrome in the Literature (N=43)

Reference (Year)	Total No. of SS Patients	Nail Finding	No. of Patients Affected (%)[a]
Sonnex et al[2] (1986)	5	Splinter hemorrhage	5 (100)
		Yellowing	4 (80)
		Subungual hyperkeratosis	3 (60)
		Nail thickening	2 (40)
		Large irregular indentations	1 (20)
Tosti et al[3] (1990)	1	Nail thickening	1 (100)
		Yellowing	1 (100)
Parmentier et al[4] (2010)	1	Anonychia	1 (100)
		Onycholysis	1 (100)
		Onychomadesis	1 (100)
		Subungual hyperkeratosis	1 (100)
Ogilvie et al[5] (2012)	1	Dystrophy	1 (100)
Booken et al[6] (2013)	15	Yellowing	7 (46.7)
		Dystrophy	6 (40)
		Nail thickening	6 (40)
		Subungual hyperkeratosis	4 (26.7)
		Onychomadesis	3 (20)
		Trachyonychia	2 (13.3)
Bishop et al[7] (2015)	1	Nail thickening	1 (100)
		Yellowing	1 (100)
Damasco et al[8] (2018)	19	Paronychia	12 (63.2)
		Leukonychia	8 (42.1)
		Onycholysis	8 (42.1)
		Trachyonychia	6 (31.6)
		Subungual hyperkeratosis	5 (26.3)
		Splinter hemorrhage	5 (26.3)
		Nail thickening	5 (26.3)
		Yellowing	4 (21.1)
		Distal notching of nail	3 (15.8)
		Onychoschizia	3 (15.8)
		Anonychia	1 (5.3)
		Longitudinal melanonychia	1 (5.3)

Abbreviation: SS, Sézary syndrome.
[a]Patients may have more than 1 nail irregularity.

TABLE 3. Comparison of Nail Irregularities and Incidence in the CTCL Database vs Literature Review

	No. of Patients (%)[a]	
Nail Irregularity	CTCL Database (N=36)	Literature Review (N=43)
Anonychia	0 (0)	2 (4.7)
Beau lines	3 (8.3)	0 (0)
Distal notching of nail	0 (0)	3 (7.0)
Dystrophy	20 (55.6)	7 (16.3)
Large irregular indentations	0 (0)	1 (2.3)
Leukonychia	0 (0)	8 (18.6)
Longitudinal melanonychia	0 (0)	1 (2.3)
Nail thickening	21 (58.3)	15 (34.9)
Onycholysis	7 (19.4)	9 (20.9)
Onychomadesis	3 (8.3)	4 (9.3)
Onychoschizia	0 (0)	3 (7.0)
Paronychia	0 (0)	12 (27.9)
Pitting	1 (2.8)	0 (0)
Salmon patch	1 (2.8)	0 (0)
Splinter hemorrhage	6 (16.7)	10 (23.3)
Subungual hematoma	1 (2.8)	0 (0)
Subungual hyperkeratosis	15 (41.7)	13 (30.2)
Trachyonychia	6 (16.7)	8 (18.6)
Yellowing	20 (55.6)	17 (39.5)

Abbreviation: CTCL, cutaneous T-cell lymphoma.
[a]Patients may have more than 1 nail irregularity.

cause of onycholysis (visible separation of the nail plate from the nail bed) and other clinical nail findings in the SS patient based on the onset of nail changes prior to beginning psoralen plus UVA therapy and complete sparing of 1 finger.[4] The findings in our patient 1, who had no history of psoralen plus UVA therapy at the time the irregular nail findings presented, supports this observation. Total skin electron beam therapy for MF also has been reported to cause temporary nail stasis and thus must be taken into account when considering nail changes in patients with MF/SS.[15]

A nail matrix biopsy may provide clues to the definitive cause of the clinically observed nail changes; however, this procedure typically is not performed due to patient concerns of postoperative complications including pain and nail dystrophy.[16] Histopathology features were similar in reported nail biopsies of 2 SS patients.[3,4] Tosti et al[3] reported that longitudinal biopsy showed a dense lymphocytic infiltrate of atypical lymphocytes with involuted nuclei and notable epidermotropism. Parmentier et al[4] reported a longitudinal nail biopsy in an SS patient that presented with atypical lymphocytes, epidermotropism, and Pautrier microabscess formation. Immunostaining showed CD3 positivity within the distal nail matrix, nail bed, and hyponychium. One-third of the cells stained positive for CD4, while the majority stained positive for CD8. Most notably, the skin, nails, and blood showed identical clonal rearrangement of TCRγ.[4] Nail matrix biopsies in MF patients rarely have been reported in the literature, but those that are available show similar features to those seen in SS patients. Harland et al[17] summarized the findings of 4 case reports of CTCL patients that included nail biopsies by stating, "[a]ll histopathologic findings from

nail biopsies showed a dense subepithelial infiltrate of lymphocytes with marked epitheliotropism." These histopathologic abnormalities are akin to skin biopsies in MF patients, thus providing an essential link to the disease state of MF and the nail abnormalities found within SS patients.

Treatment of the nail problems found within SS is challenging due to limited research. Parmentier et al[4] noted an SS patient who was treated with topical mechlorethamine applied directly to the nail. In this case, topical mechlorethamine was effective at treating onychomadesis, subungual distal hyperkeratosis, and onycholysis within 6 months.[4] Another SS patient, who presented with thickening and yellowing of the nail, had reported a proximal nail plate that resolved after chemotherapy. The patient did not survive long enough to note complete improvement of the nail.[3] In our study, patient 1 was treated with ciclopirox gel and terbinafine, which did not result in nail improvement. Nail treatments in SS patients have yet to show much improvement and thus need more research and focus in the literature.

Conclusion

Sézary syndrome is a rare CTCL that can present with clinical features that may be mistaken for other diseases. Nail abnormalities in SS patients may be related to fungal involvement, medical therapy, or the underlying disease process of SS. We report one of the largest populations of SS patients with specific reported nail abnormalities, thus expanding the possibilities of nail changes that accompany the disease. Continued research and studies involving SS can provide a better understanding of nail involvement and successful treatment of these clinical findings.

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