Paraneoplastic scleroderma in the setting of CD30$^+$ large cell transformation of mycosis fungoides

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INTRODUCTION

Cutaneous T-cell lymphoma is a malignant non-Hodgkin T-cell lymphoma, with mycosis fungoides (MF) and Sézary syndrome being the most common subtypes. In patients with MF, transformation to large cell histology is associated with worse prognosis. Paraneoplastic scleroderma has been reported arising within the context of lung, breast, and hematologic malignancies,[1] but its association with T-cell lymphomas is exceedingly rare.[2-5] We present the case of a woman with MF with CD30$^+$ large cell transformation who also had the progressive sclerodermoid skin changes of paraneoplastic scleroderma.

CASE REPORT

A 48-year-old woman presented for evaluation of an enlarging, ulcerated tumor on the right medial thigh. Three years prior, the patient had an erythematous plaque on the left medial thigh. Biopsy then was notable for an atypical T-cell infiltrate, suggestive of MF. She was treated with topical steroids with moderate improvement. One and a half years later, symptoms of Raynaud phenomenon and areas of hyperpigmentation/hypopigmentation with progressive skin tightening developed on the arms, chest, abdomen, and neck. Scleroderma was suspected, but laboratory values were positive only for anti-nuclear antibody (1:640); anti-dsDNA, anti-Smith, anti-RNP, anti-SSA, anti-SSB, RF, anti-CCP were negative, and C3, C4, ASO, C-reactive protein, and uric acid were within normal limits. Medical history was unremarkable, and she took no medications.

Abbreviations used:

BV:	brentuximab vedotin
FGF:	fibroblast growth factor
IL:	interleukin
MF:	mycosis fungoides
Scl-70:	DNA topoisomerase I
TGF-β:	transforming growth factor β
Th2:	helper T cell 2

In the subsequent months, the patient was treated with prednisone, methotrexate, and mycophenolate mofetil for scleroderma, all of which proved ineffective. Ultimately, photopheresis every 2 weeks led to limited improvement in skin tightness, and she continued treatments for 1 year. During that time, the patient noted that a lesion on the right medial thigh was progressively enlarging. When the lesion ulcerated and began to bleed, she was referred to the Columbia University Multidisciplinary Cutaneous Lymphoma Program. On examination, the right medial thigh had a 20-cm erythematous plaque with an ulcerated tumor extending into the intergluteal crease and groin (Fig 1, *A*) as well as erythematous plaques in the left groin and buttocks. Her skin appeared waxy, shiny, and tense, not permissive to folding or wrinkling. Her face appeared mask-like with a loss of normal facial lines. Hyperpigmented and hypopigmented patches with perifollicular sparing were present on bilateral arms.

Biopsy of the right inguinal tumor showed an extensive atypical lymphocytic infiltrate with numerous giant cells of histiocytic derivation (Fig 2, *A-C*). Immunohistochemical analysis found absent staining for CD4 and CD8 but was positive for βF1, ruling out

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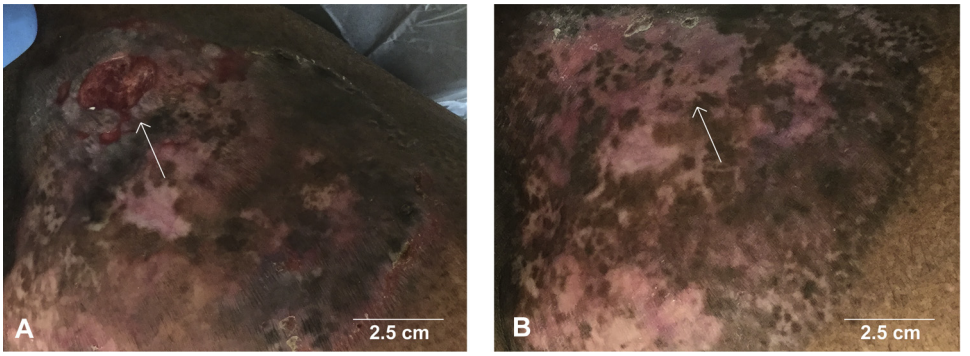

Fig 1. Mycosis fungoides tumor. **A**, On initial presentation with a large indurated scaly plaque with an ulcerated, extremely painful tumor (*arrow*) on the medial thigh. **B**, After a single dose of BV, healing of the ulcerated tumor and decreased plaque thickness and scaling. The pain completely resolved.

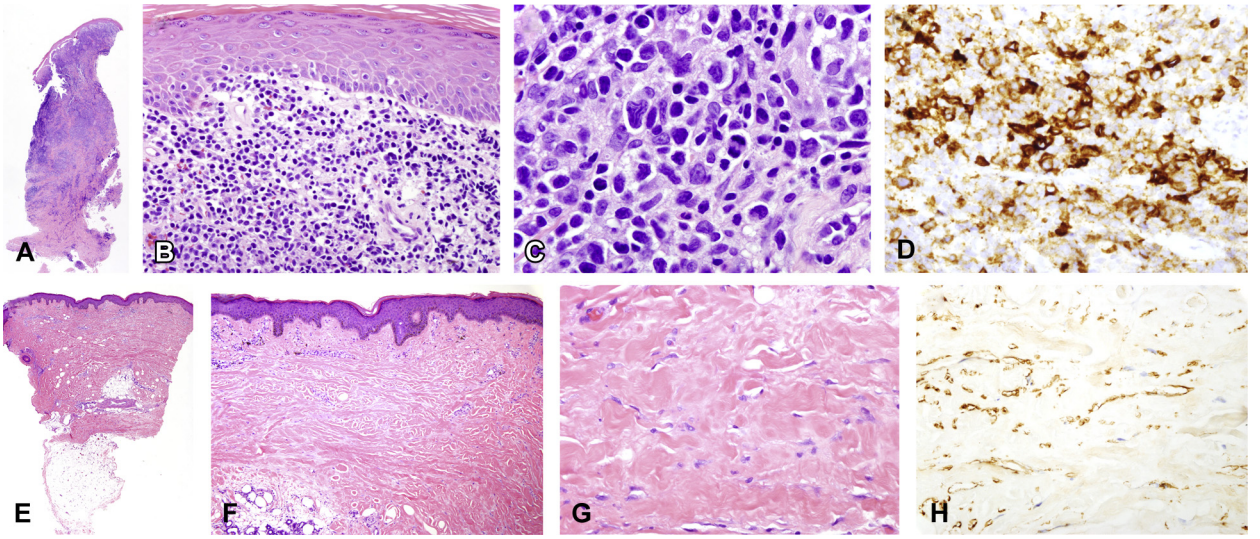

Fig 2. A-D, Biopsy of the right inguinal tumor. **A,** There is an extensive lymphocytic infiltrate throughout the epidermis and the dermis (2X). **B,** There is epidermotropism, tagging of malignant cells along the dermoepidermal junction, and a number of hyperchromatic, pleomorphic lymphocytes abutting the epidermis. There is also mild, superficial dermal fibrosis (40X). **C,** Pandermal, diffuse, and nodular infiltrate. The dermal component includes many larger cells with irregular nuclear contours, less condensed chromatin, and moderate amounts of lightly eosinophilic cytoplasm (60X). **D,** Immunohistochemistry of the right thigh tumor. Roughly 40% of the infiltrate shows immunoreactivity for CD30. There was also extensive highlighting of this infiltrate for CD2 and CD3, loss of CD5 and CD7, and no staining for CD4 or CD8 (not shown). **E-H,** Biopsy of the right forearm. **E,** Fibroplasia involving the dermis and extending into the intralobular septa of the subcutaneous fat (2X). **F,** Pandermal fibroplasia associated with profound adnexal atrophy. Collagen bundles assume a parallel disposition to the long axis of the epidermis (40X). **G,** Fibroblasts with adjacent thickened collagen bundles (60X). **H,** Positive staining for smooth muscle actin. CD34 showed a significant decrement in staining that more of less parallels the fibrosis (*not shown*).

γ/δ T-cell phenotype. Immunohistochemistry also showed loss of CD5 and CD7, increased staining for CD2 and CD3, and numerous larger $CD30^+$ cells in the dermis, consistent with transformed MF with granulomatous features (Fig 2, *D*). Biopsy of the right forearm found striking fibroplasia involving the dermis and subcutaneous fat, histologically characteristic of advanced scleroderma (Fig 2, *E-G*). A smooth muscle actin preparation showed positivity (Fig 2, *H*). CD34 showed a significant decrement in staining that paralleled the fibrosis. Her sclerodermoid findings were consistent with the subtype of limited cutaneous

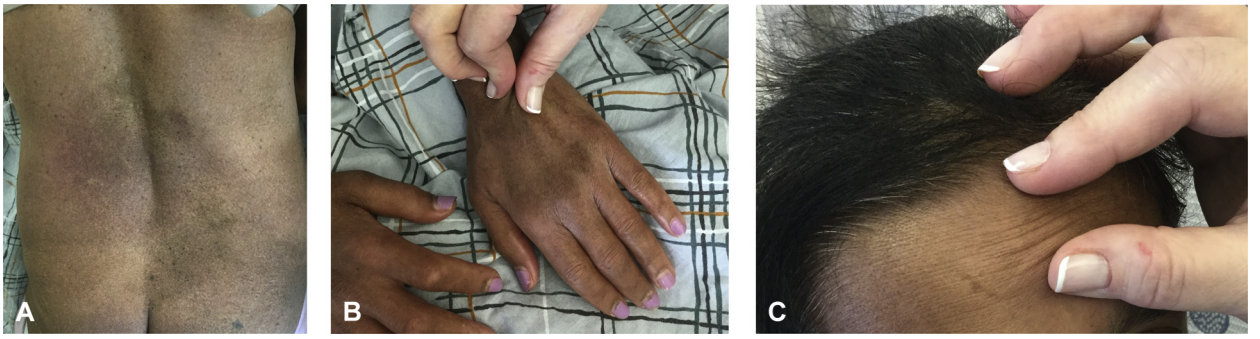

Fig 3. Improvement of MF and scleroderma after BV. **A,** Resolved, postinflammatory hyperpigmented patches. **B,** Loosening of the skin on the hands. **C,** Return of facial wrinkles on the forehead.

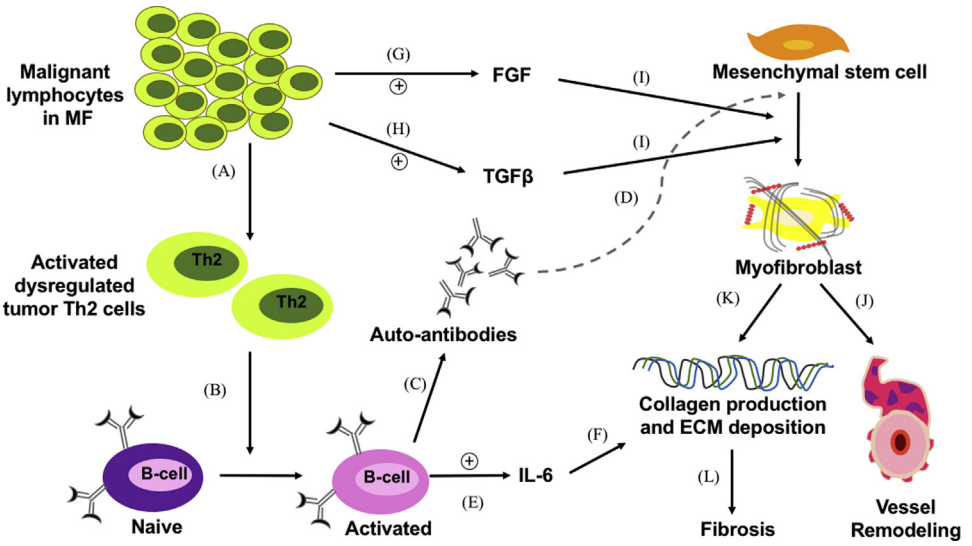

Fig 4. Intersection of MF and fibrotic pathways. **A,** MF leads to aberrant activation of dysregulated Th2 cells. **B,** Dysregulated Th2 cells promote activation and differentiation of naïve B cells into activated B cells. **C,** Activated B cells produce autoantibodies that **D,** stimulate mesenchymal stem cells. **E,** Activated B cells release pro-inflammatory cytokines including IL-6. **F,** IL-6 promotes collagen production and extracellular matrix production. At the same time, MF is associated with an increase in **G,** FGF and **H,** TGF-β. **I,** FGF and TGF-β both promote the differentiation of mesenchymal stem cells into myofibroblasts. Myofibroblasts are capable of **J,** vessel remodeling, **K,** collagen production and extracellular matrix deposition, and **L,** fibrosis.

systemic sclerosis. Peripheral flow cytometry was negative for T-cell lymphoma involvement, and other laboratory tests were negative for antinuclear antibody, DNA topoisomerase I (Scl-70), and anticentromere antibodies, but her test for RNA polymerase III antibody was positive. Positron emission tomography/computed tomography found cutaneous thickening and intense fluorodeoxyglucose uptake in the right inner thigh with hypermetabolic inguinal lymph nodes. The largest right inguinal lymph node measured 1.7 × 1.4 cm (standardized uptake value, 3.7), and the largest left inguinal lymph node measured 1.4 × 0.8 cm (standardized uptake value, 2.0). The patient was started on brentuximab vedotin (BV), and the patient achieved significant decrease in tumor size and healing of the ulcer (Fig 1, *B*). Patches resolved with residual postinflammatory hyperpigmentation, and sclerodermatous skin findings improved, including softening of the skin and return of facial lines (Fig 3, *A-C*).

DISCUSSION

Paraneoplastic scleroderma arising within the context of hematologic malignancy is rare and has only been reported once in association with MF.[4] In this case, the close temporal relationship between

onset of scleroderma and $CD30^+$ large cell transformation of MF, clinical unresponsiveness to standard therapies, RNA polymerase III positivity, and improvement of scleroderma with treatment of MF by BV support a diagnosis of paraneoplastic scleroderma.

A higher incidence of malignancy has been reported in patients with scleroderma than in the general population.[6] Within a subset of patients, an underlying malignancy may be the initiating trigger leading to development of a scleroderma-like disease process. Although paraneoplastic scleroderma is primarily a clinical diagnosis, presence of RNA polymerase I/III autoantibody has been suggested as a potential biomarker for a paraneoplastic process.[7] It has been posited that RNA polymerase I/III may resemble a tumor antigen leading to a misdirected autoimmune response. Although we cannot exclude the possibility of idiopathic scleroderma occurring coincidentally with malignancy in this patient, RNA polymerase III antibody positivity is suggestive of paraneoplastic scleroderma.

Interestingly, it appears that our patient had indolent and early-stage MF for several years before large cell transformation. However, the onset of sclerodermoid changes coincided with the escalation and transformation of her disease. In this case, we hypothesize that scleroderma onset signified a change in biological behavior of MF, representing a paraneoplastic process.

Although the exact mechanism of skin sclerosis in this patient is unknown, aberrant T-cell activation in the setting of active MF may play a role. Studies have found that patients with systemic scleroderma have increased numbers of T cells at sites of fibrosis, a predominant helper T cell 2 (Th2) response and increased levels of activated effector T cells in the peripheral blood.[8] T-cell–derived cytokines like interleukin (IL)-6 mediate development of fibrosis.

Likewise, advanced-stage MF is associated with an increase in Th2 cells. Aberrant Th2 cells activate B cells, which are capable of producing autoantibodies and releasing IL-6. Auto-autoantibodies interact with mesenchymal stem cells, stimulating their differentiation into myofibroblasts, which are capable of vessel remodeling, collagen production, and extracellular matrix deposition. IL-6 also interacts with this pathway, stimulating collagen production and extracellular matrix deposition. MF also has been associated with the release of fibroblast growth factor (FGF) and transforming growth factor beta (TGF-β).[9] FGF and TGF-β stimulate the differentiation of mesenchymal stem cells into myofibroblasts, and TGF-β in particular is thought to promote the activated scleroderma fibroblast phenotype.[10] Thus, MF may affect the fibrotic pathway at multiple levels, leading to changes similar to those seen in scleroderma (Fig 4). More research is necessary to explore the exact mechanism of paraneoplastic scleroderma onset in the setting of malignancy, but we posit that common factors including aberrant T-cell activation and cytokine release may allow interaction between malignancy and fibrotic pathways.

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