Refractory periungual stage II mycosis fungoides with novel LMNA-ROS1 fusion

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INTRODUCTION

Mycosis fungoides (MF) is the most common primary cutaneous lymphoma representing approximately 50% of skin lymphomas with a worldwide incidence of approximately 4 to 10 cases per million. Although the etiology is unknown, risk factors include African descent, obesity, smoking, and exposure to chemicals used in carpentry, painting, farming, and other industries (metal, petrochemical, and textile). This postthymic T-cell–derived malignancy is usually positive for CD4 and expresses cutaneous lymphoid antigen and chemokine receptor CCR4, cutaneous homing molecules.[1]

MF is clinically indolent affecting sun-shielded areas and often mimicking inflammatory dermatitis, which may delay diagnosis. Nail and periungual presentations are rare,[2] and progressive systemic involvement or transformation to aggressive large cell lymphoma is infrequent.

Histologically, MF is an epidermotropic lymphoma of small-to-medium–sized T cells with characteristic cerebriform nuclei. Alignment of atypical lymphocytes on the basal epidermal layer is a common early feature.[3]

Recent genetic profiling of MF has expanded treatment options. Negative prognostic mutations include *TOX*, *GTSF1*, *NOTCH1*, *CCR4*, *ITK*, *FYB*, *SYC1*, *LCK* or *miR155*, *miR21*, and *let-7i* differentially expressed genes.[4]

Monoclonal antibodies against CCR4, CD52 and CD30 alone or in combination with traditional therapy offer a promising therapeutic option. We present a clinically unusual case of subungual tumoral MF with several novel mutations.

Abbreviation used:

MF: mycosis fungoides

CASE REPORT

A 58-year-old Filipino woman with stage IIA MF presented with a 3-week history of friable ulcerations overlying several toes with resultant nail plate distortion (Fig 1) and painful, bleeding subungual lesions on several fingers. She denied fever, chills, malaise, weight loss, or similar acral lesions in the past. Previous treatment included ultraviolet B light, bexarotene, vorinostat, and pegylated interferon, all stopped because of various side effects. The patient was not on a treatment regimen at the time of her presentation. An ulcerated lesion on the left hallux was biopsied, and she was started empirically on a 10-day course of oral clindamycin. The wound culture grew *Staphylococcus aureus*. Resultant hematoxylin-eosin histology found epidermotropism and atypical lymphocytes positive for CD3, CD4, and CD5 and partially negative for CD7 (Figs 1 and 2). Scattered large cells stained positive for CD30 (up to 10%, ruling out large cell transformation of MF and cutaneous large cell anaplastic lymphoma) GMS and AFB stains were negative. Polymerase chain reaction showed a clonal T-cell

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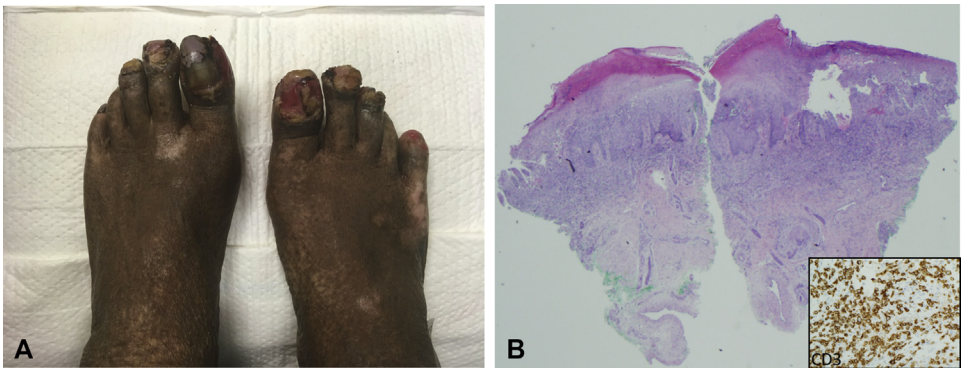

Fig 1. **A**, Periungual MF. **B**, Hematoxylin-eosin stain; original magnification: ×20. **B inset**, CD3 immunostain; original magnification ×400.

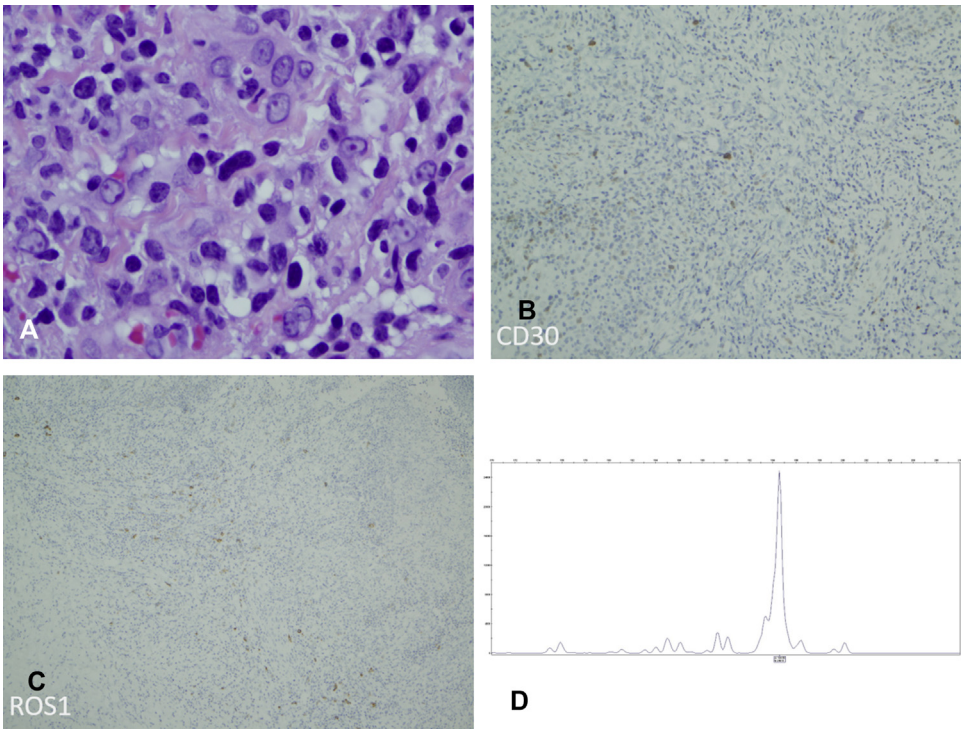

Fig 2. **A**, Hematoxylin-eosin stain; original magnification: ×1000. **B**, CD30 immunostain; original magnification: ×400. **C**, ROS1 immunstain; original magnification: ×200. **D**, Monoclonal rearrangement of T cell receptor gamma gene by polymerase chain reaction.

receptor γ gene rearrangement of identical size to prior specimens (Fig 2). Next-generation sequencing, performed at Foundation Medicine, found a novel single fusion product, lamin A/C *(LMNA)-ROS1*, in addition to 14 point mutations (*AXL A181S, CARD11 D401N, CBFB R78Q, CCND3 I209K, JARID N405S, LRP1B R353S, LRP1B T1927S, MAP3K1 M312L, MYCN A184S, MYST3 A1255G, RICTOR L177F, STK11 F354L, TSHR F130V,* and *TUSC3 G172E*) and 5 nonsense mutations (*ASXL1 R693*, CHEK2 Y212fs*1, EPHAS S534fs*41, LRP1B E553* and NOTCH2 G2086fs*8)*, unpublished in association with MF. *ROS1* immunohistochemistry was performed at ARUP laboratories and was equivocal (Fig 2). *ROS1* inhibitors for treatment were recommended. However, prior to initiation of treatment, the patient moved out of state and was lost to the Veterans Affairs hospital system.

DISCUSSION

To our knowledge, this is the first report of *LMNA-ROS1* fusion in MF. The *ROS proto-oncogene 1*, a transmembrane receptor protein kinase of unknown

function, is rearranged in many solid tumors including 1% to 2% of non–small cell lung carcinoma, cholangiocarcinoma, glioblastoma, ovarian carcinoma, gastric adenocarcinoma, colorectal carcinoma, Spitz tumors, and Spitzoid melanomas. Crizotinib, an *ROS1* inhibitor, is an effective approved therapy for non–small cell lung carcinoma. Additionally, new-generation selective *ROS1* inhibitors are being developed.

Lamin A/C (*LMNA*), the main structural nuclear envelope protein, has poorly understood oncogenic roles. *LMNA* requires cleavage by caspase 6 during apoptosis to allow nuclear condensation and may protect the cancer genome.[5] The identification of this *LMNA-ROS1* fusion suggests a potential therapeutic target. Next-generation sequencing for refractory disease, patients in high-risk categories, or patients with newly diagnosed disease could prove to be a useful tool in MF to personalize treatment options and promote exploration of new therapeutic targets.

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