

Concomitant Occurrence of Kimura Disease and Mycosis Fungoides in a Lebanese Woman: Significance and Response to Rituximab

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Abstract: Kimura disease (KD) is a rare condition that predominantly affects young middle-aged Asian men. It is classically characterized by tumors in the head and neck region with associated eosinophilia and elevated serum immunoglobulin E levels. The exact pathogenesis of this condition remains unknown. Although some regard it as a reactive condition, others believe that it is a T-cell-mediated disease. T-cell clonality has been recently demonstrated in a few cases. We report a 37-year-old Lebanese woman who had both KD and mycosis fungoides (MF). T-cell receptor gene rearrangement studies using 2 different techniques did not detect any clonality for T-cell receptor in both KD and MF lesions. Due to the presence on histology of lymphoid follicles and the persistent high serum immunoglobulin E levels, we elected to attempt treatment with rituximab. Although the KD lesions persisted, they became softer and less nodular. As for the MF lesions, they flared transiently and then exhibited a sustained improvement over a follow-up period of 1 year.

Key Words: Kimura disease, mycosis fungoides, rituximab

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INTRODUCTION

First reported in 1937, Kimura disease (KD) is a rare idiopathic disorder that predominantly affects young Asian men in the second and third decades of life. It most commonly presents as asymptomatic firm nodules and tumors over the head and neck region. The salivary glands and regional lymph nodes are primarily involved, but generalized lymphadenopathy demonstrated by positron emission tomography scan may also be present.¹ Unusual sites of involvement include the oral mucosa, chest wall, extremities, and inguinal areas. Increased serum immunoglobulin E (IgE) level and peripheral blood

eosinophilia are characteristic features. Systemic complications include renal involvement, which may be present in up to half of the patients.^{2,3} Histopathology often reveals a nodular and diffuse lymphocytic infiltrate with numerous eosinophils predominantly throughout the deep dermis and subcutaneous tissue, many lymphoid follicles with associated eosinophils, fibroplasia, and small blood vessel proliferation.^{2–4} The pathogenesis of KD remains unknown but has been linked in single case reports to T-cell clonality. We report an unusual case of KD affecting the trunk of a Lebanese woman who also developed mycosis fungoides (MF) and describe the response of both conditions to rituximab therapy.

CASE REPORT

A 37-year-old white woman presented with a 20-year history of multiple persistent and disfiguring lesions over the trunk. The lesions were asymptomatic except for pruritus in one of the lesions. Her major concern was cosmetic because the disfigurement from the lesions affected markedly her quality of life. The lesions fluctuated in size over time with no specific exacerbating factor that could be elicited. Several treatments including topical, intralesional, and systemic corticosteroids were used with prompt improvement, but recurrence shortly after therapy was discontinued. There were no associated constitutional symptoms. She is known to have adult-onset hyperactive airway disease. Her medical and family history was otherwise unremarkable.

Physical examination revealed 4 soft to semifirm infiltrated subcutaneous nodules and plaques of varying sizes (3–11.5 cm in diameter) on the abdomen and back. The skin overlying these lesions was normal except for the itchy lesion over the back (the largest one), which showed skin changes characteristic of lichenification (Fig. 1). There was no associated lymphadenopathy or hepatosplenomegaly, and the rest of the physical examination was nonrevealing except for multiple symmetric digitate elongated yellow/brown patches over the back and proximal extremities (Fig. 2A). The patient reported that these lesions were asymptomatic and that they have been waxing and waning for the past few years.

Laboratory studies revealed consistently elevated serum IgE level (mean level 832.02 IU/L, normal <100 IU/L) and eosinophilia (mean level $0.8 \times 10^9/L$, normal $0.1\text{--}0.4 \times 10^9/L$) but no other white cell count abnormalities. The remaining studies including hemoglobin, blood urea nitrogen, creatinine, urinary protein level, liver function tests, erythrocyte sedimentation rate, and lactate dehydrogenase were all within normal range. Computed tomography scans of the chest, abdomen, and pelvis were normal.

An elliptical incisional skin biopsy was obtained from the largest infiltrated subcutaneous plaque over the back. Histology of the

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FIGURE 1. Lower back lesion of KD at presentation: infiltrated subcutaneous plaque with overlying lichenification.

subcutaneous plaque over the back revealed a dense deep dermal and subcutaneous nodular and diffuse inflammatory cell infiltrate composed predominantly of lymphocytes and numerous eosinophils forming eosinophilic abscesses focally. The infiltrate comprised scattered lymphoid follicles with germinal centers and was associated with dermal fibrosis and increased small blood vessels with flat endothelial cells. Epidermotropism and folliculotropism were not seen. Immunoperoxidase studies revealed the lymphoid follicles to be composed of CD20-positive cells and to stain with both Igκ and Igλ. The surrounding infiltrate was CD45RO positive and was composed of CD4-positive and to lesser extent CD8-positive cells (Fig. 3).

Another 6-mm punch biopsy was obtained from one of the digitate patches and revealed mild spongiosis, numerous atypical lymphocytes with large cerebriform nuclei at and above the dermo-epidermal junction, and a mild to moderate superficial perivascular lymphocytic infiltrate with coarse papillary dermal fibrosis (Fig. 2B). Immunoperoxidase studies revealed the epidermotropic lymphocytes to be positive for CD3 and CD4 and negative for CD20 and CD7. The dermal infiltrate stained positively with CD3 and was composed predominantly of CD8-positive and to a lesser extent CD4-positive T cells.

T-cell receptor (TCR) gene and immunoglobulin gene rearrangement studies were performed on DNA extracted both from a fresh biopsy specimen and paraffin-embedded sections. BIOMED-2

multiplex primer sets were used in this study to evaluate TCR-β, TCR-γ, TCR-δ,⁵ and IgH clonality. Each sample was tested by 2 different techniques for confirmation of results: polymerase chain reaction heteroduplex analysis with polyacrylamide gel detection (American University of Beirut Medical Center) and GeneScan fragment analysis for fluorescence detection using ABI 3130xl instrument (Baylor University Medical Center). Both clonality assays were performed using the same primers but different detection systems. The heteroduplex and GeneScan analysis resulted in polyclonal smear and Gaussian curves, respectively, indicating the presence of polyclonal lymphoid cells in both the infiltrated plaques and the digitate patches.

Based on the chronic indolent course of the subcutaneous nodules/plaques, their histological findings, and the association with persistent eosinophilia and high serum IgE levels, the diagnosis of KD was made. The diagnosis on the digitate patches was patch-stage MF and was made based on the clinical, histological, and immunoperoxidase findings and despite the negative molecular findings of T-cell clonality.⁶

Because the patient was not bothered by the MF lesions and because she refused treatment of KD lesions with radiation, surgery, or the conventional immunosuppressive medications, a decision was reached to attempt treatment with rituximab 375 mg/m² weekly for 4 weeks. While on therapy, she experienced a mild transient increase in the number of her MF lesions, whereas the KD lesions remained stable. Follow-up at 3 and 6 months after the end of treatment revealed significant and sustained improvement of the MF lesions. As for the KD lesions, they were noted to be of the same size but significantly softer and less nodular upon palpation. At 6-month follow-up, serum IgE level dropped to 222 IU/L. A repeat biopsy from the same left lower back KD lesion revealed a dense pandermal and subcutaneous nodular lymphocytic infiltrate with numerous eosinophils and a marked small blood vessel proliferation. Immunoperoxidase studies revealed the infiltrate to be composed predominantly of CD3- and CD4- and to a lesser extent CD8-positive cells. Only rare CD20-positive B cells were noted. In comparison with the first biopsy, there was absence of germinal centers and the B-cell component was markedly decreased (Fig. 4).

DISCUSSION

The etiopathogenesis of KD is still not clear. Based on the associated peripheral eosinophilia and increased serum IgE levels, some consider it as a reactive immunologic response to

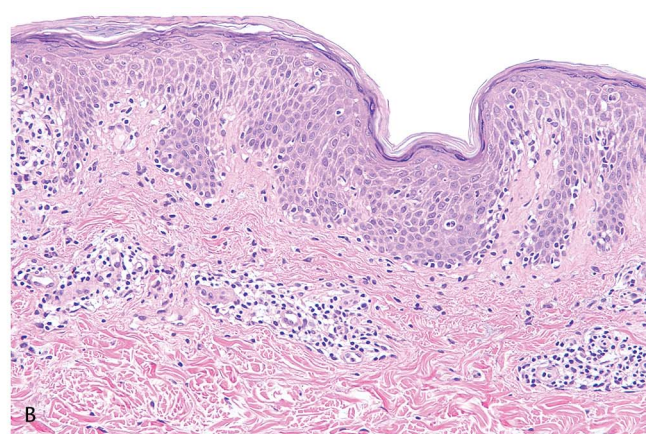


FIGURE 2. A, Digitate lesions of MF. B, Histology revealed mild spongiosis, numerous atypical lymphocytes at and above the dermoepidermal junction, and a mild to moderate superficial perivascular and interstitial lymphocytic infiltrate.

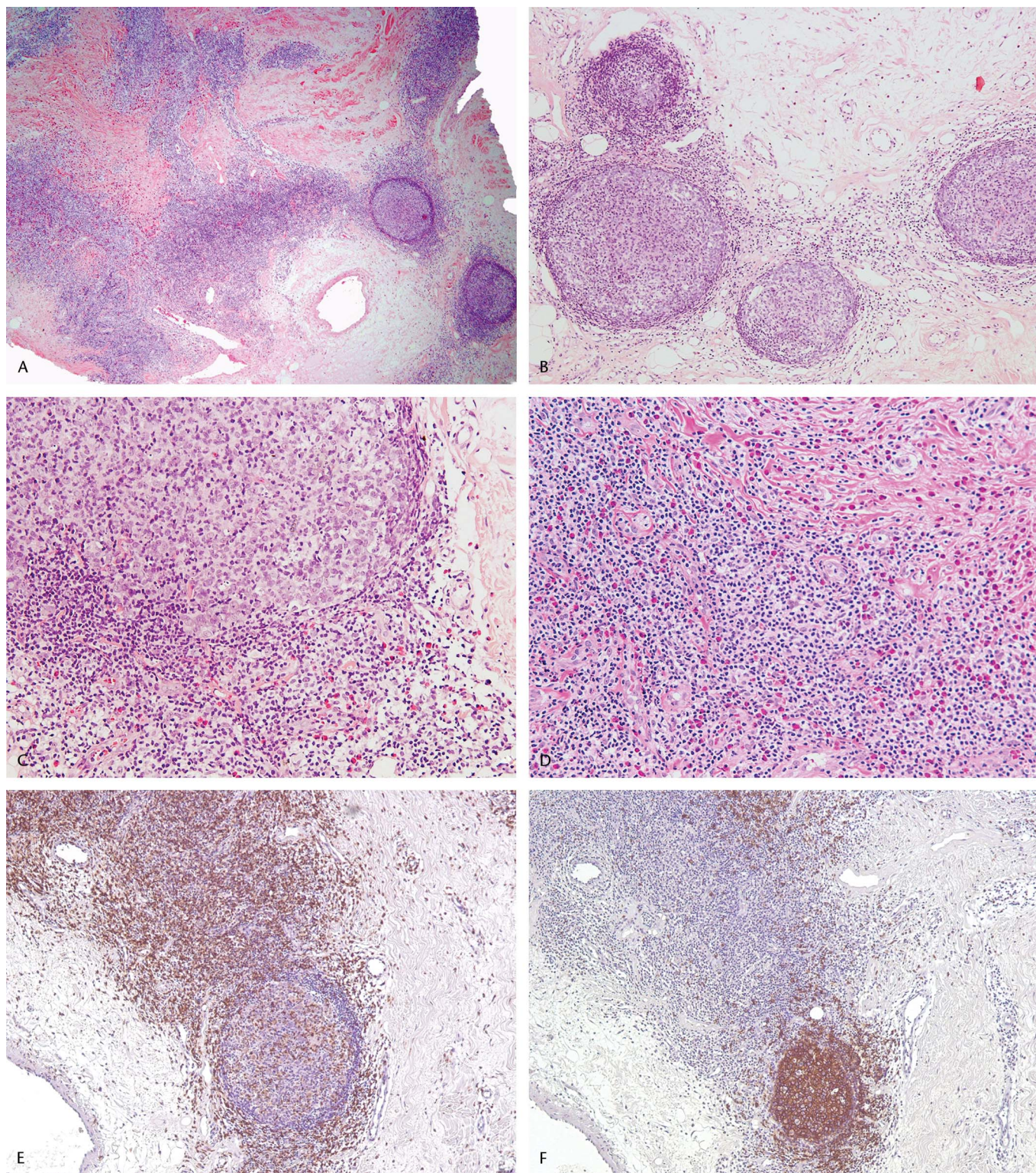


FIGURE 3. Histology of lower back KD lesion before treatment with rituximab. There are dense deep dermal and subcutaneous lymphoid aggregates comprising scattered lymphoid follicles with germinal centers (A) and (B). C, The lymphoid follicles were surrounded by a lymphocytic infiltrate lacking atypia and comprising numerous eosinophils. D, Note both the dense lymphoid infiltrate with numerous eosinophils and the small blood vessel proliferation in the fibrotic stroma. Immunoperoxidase studies revealed the germinal centers to be CD20 positive (E) and the surrounding infiltrate to be CD45RO positive (F).

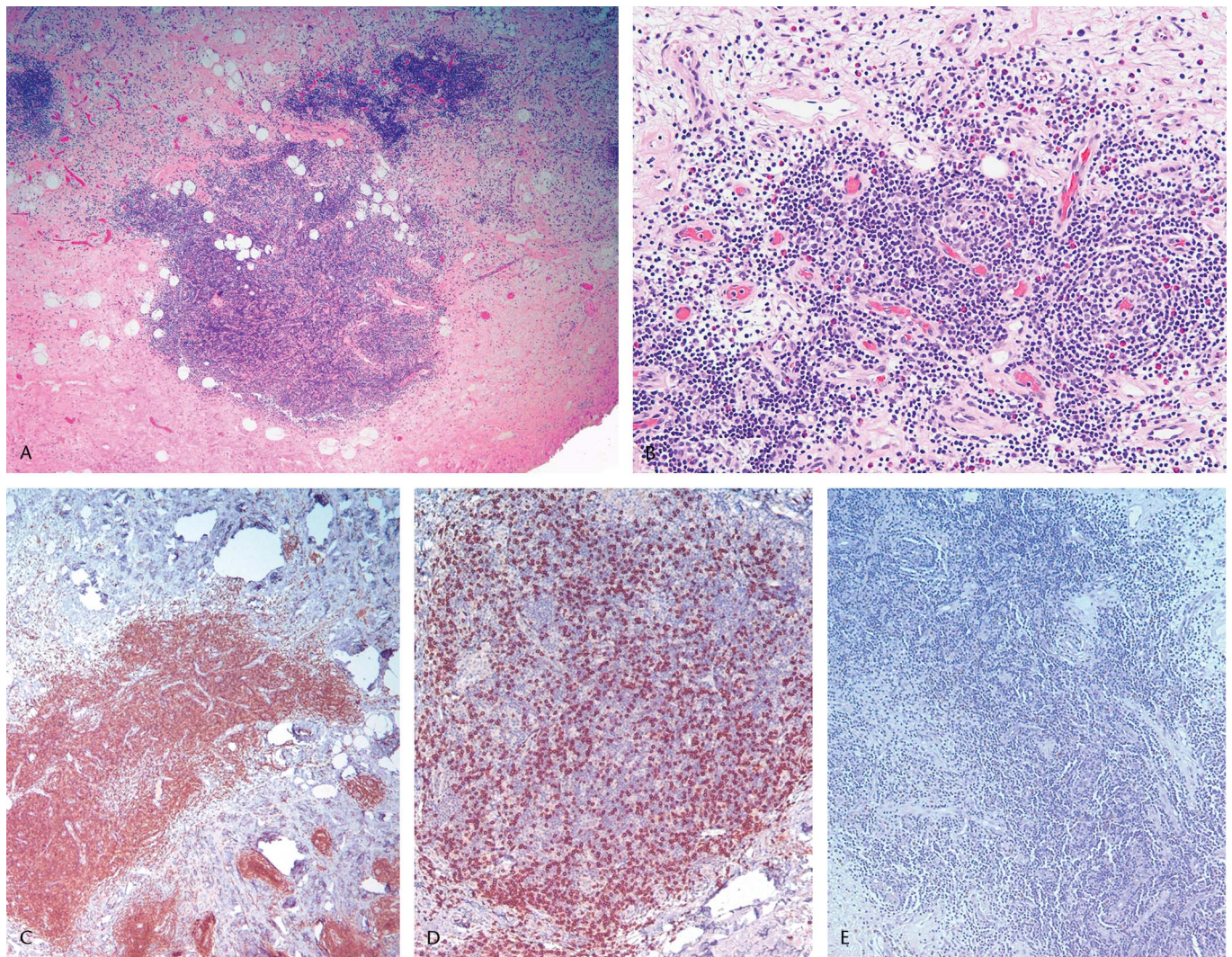


FIGURE 4. Histology of lower back KD lesion after treatment with rituximab. There is a dense deep dermal/subcutaneous infiltrate. A, Note the absence of the germinal centers. B, The infiltrate is predominantly lymphocytic and comprises numerous eosinophils and admixed small blood vessels. Immunoperoxidase staining with CD4 (C), CD8 (D), and CD20 (E). Note the negative immunostaining with the latter stain, as expected with rituximab therapy.

some stimuli, although underlying allergic, viral, or parasitic etiologies have been only rarely identified.^{2-4,7-9} On the other hand, there is now evidence that mast cells and T cells do play an important role in the pathogenesis of KD through increased production of T_H2 -type cytokines.^{5,10,11} Furthermore, clonal rearrangement of the TCR- δ gene, as in the case of angiolymphoid hyperplasia with eosinophilia,¹² has been demonstrated in a KD neck lesion and in a subsequent groin lymph node from the same patient. The presence of identical T-cell clones in different sites and at different times suggested that a clonal T-cell population might have contributed to the pathogenesis of KD in this particular case.⁵ Other studies have failed to demonstrate clonal lymphoid proliferation in KD.^{1,11} Jang et al¹³ reported positive results for polymerase chain reaction (PCR) analysis of TCR in 2 of 7 cases of angiolymphoid hyperplasia with eosinophilia and in 2 of 2 cases of KD. These same cases, however, were negative for

heteroduplex polymerase chain reaction, a more specific assay for clonality. Several explanations for these findings are suggested. First, clonality in KD may be a sporadic finding. Second, KD may be a heterogeneous disease, with some cases being associated with T-cell clonality. These T-cell clones, however, may not be detectable by the available PCR assays, which may not cover all possible rearrangements of the TCR chains.¹¹

The clinical course of KD is benign but often progressive, and the main problem with all treatment modalities including surgical excision, radiotherapy, systemic corticosteroids, and other immunosuppressive therapies is the high rate of recurrence.^{2,3} Although surgery remains the mainstay of therapy, disadvantages may include disfigurement. Local radiation is used conservatively because affected patients are usually young.^{14,15} Other treatment modalities including cyclosporine, pranlukast, pentoxifylline, cetirizine,

and all-*trans* retinoic acid, used alone or in combination with prednisone, have been shown to be effective in sporadic reports.^{16–19}

Our case exhibited many interesting features. The patient was a Lebanese middle-aged woman who presented with multiple KD lesions over the abdomen and back since the age of 17 years. Only rare reports described KD over the trunk (particularly the back) and in non-Asian patients such as whites, blacks, Hispanics, Arabs, and Westerns.^{2,3} In addition, the simultaneous occurrence of MF, a cutaneous T-cell lymphoma, and KD has never been reported in the literature and sets forth support to the hypothesis that KD may be a T-cell-driven entity. The association between these 2 uncommon conditions is unlikely to be due to chance alone. Although PCR studies in the current case failed to demonstrate clonality in both KD and MF lesions, the possibility of one common T-cell clone accounting for both conditions cannot be excluded and this may be partly related to the sensitivity of these assays.^{20,21} The possibility of a common viral etiology can also be entertained especially that viruses such as human T-cell lymphotropic virus type 1 and Epstein–Barr virus have been sporadically/inconsistently linked to MF and KD.^{7,22,23}

The differential diagnosis of KD in this case included follicular center cell lymphoma. However, the latter was ruled out based on many reasons. Clinically, the lesions started at the age of 17 years and remained stable over the following 20 years. The patient had associated elevated serum IgE and eosinophilia. Histologically, the infiltrate was mixed in nature being composed of reactive lymphoid follicles with surrounding T lymphocytes and numerous eosinophils and was associated with a small blood vessel proliferation. Immunoperoxidase studies revealed the lymphoid follicles to stain with both Igκ and Igλ stains. Additionally, the IgH clonality assay did not detect any clonal B-cell population in the samples.

In addition, this case describes the first attempt at treating both KD and MF with rituximab. Due to the presence on histology of lymphoid follicles and the persistent high serum IgE levels, we elected to attempt this modality of treatment. After rituximab therapy, KD lesions became less nodular and histology revealed absence of germinal centers and marked decrease in the B-cell component. In addition, serum IgE level significantly decreased. This is consistent with the mechanism of action that rituximab treatment is expected to elicit. The failure to clear completely may support the hypothesis that the B-cell component is reactive rather than essential in the pathogenesis of KD. Finally, the sustained improvement of MF to rituximab in this patient is hard to explain especially in view of the absence of aberrant CD20 coexpression by neoplastic T cells, a finding that has been rarely reported in primary cutaneous T-cell lymphomas.²⁴

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