Multiple Eruptive Dermatofibromas in a Patient with Systemic Lupus Erythematosus, Lupus Nephritis and Receiving Immunosuppressive Drugs: A Case Report

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ABSTRACT:

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Multiple eruptive dermatofibromas (MEDFs) are a rare condition, found in only less than 0.3% of all dermatofibromas. The occurrence of more than 5 lesions within the period of 4 months or the presence of more than 15 lesions in any period is the current definition of MEDFs. This variant of the disease has been thought to be related to immune dysregulation. Inhibiting down-regulatory T cells may contribute to the development of MEDFs in immunodeficient states; otherwise, dermatofibromas may arise in response to a potential pathogen that the immune system is unable to eradicate. In this report, we describe a 32-year-old woman with underlying systemic lupus erythematosus, lupus nephritis, and received oral prednisolone,

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cyclosporine and azathioprine. She presented with multiple small brownish nodules approximately 12 lesions over a period of 3 months on both lower extremities.

Key words: Multiple eruptive dermatofibromas, SLE, lupus nephritis, immunosuppression

Introduction

Dermatofibroma (DF) is an asymptomatic benign fibrohistiocytic tumor that is commonly found in the lower extremities[1]. The patient usually manifests with solitary or few brownish nodules. Multiple eruptive dermatofibromas (MEDFs), a rare presentation of the disease, have been reported to be associated with several autoimmune diseases, immunosuppressive agents, HIV infection, solid organ, and hematologic malignancies[1]. Herein, we report a case of MEDFs in a middle-aged woman with systemic lupus erythematosus (SLE) and lupus nephritis (LN) receiving multiple immunosuppressive drugs.

Case report

A 32-year-old Thai woman presented in early 2018 with lower limb edema, malaise, and discoid skin lesions. Laboratory results revealed positive antinuclear antibodies (ANA) at 1:320 in a homogeneous pattern, positive anti-dsDNA, low levels of C3 and C4. Finally, SLE with LN class IV was diagnosed. The patient was initially treated with intravenous methylprednisolone and intravenous cyclophosphamide. Then, she received oral prednisolone 40 mg daily and hydroxychloroquine 200 mg daily as maintenance therapy. In September 2018, cyclosporine was initiated during prednisolone tapering. Two years after, in September 2020, azathioprine was introduced during the time of dosage reduction of cyclosporine.

In December 2020, while she was receiving prednisolone 7.5 mg daily, cyclosporine 100 mg daily, and azathioprine 50 mg daily, she was referred to our department. Her chief complaint was the appearance of multiple brownish nodules developed on her legs over a period of 3 months. Physical examination revealed multiple firm, round, brownish nodules, approximately 12 lesions measuring 3 to 8 mm in diameter, on both legs (Figure 1). The lateral digital pressure of the lesion presented a positive dimple sign. A biopsy specimen taken from the right thigh showed a dermal nodular proliferation underneath the hyperplastic epidermis with elongated rete ridges and increased basal layer pigmentation (Figure 2A). In the entire dermis, fibrohistiocytic spindle cells aggregated in a storiform pattern were demonstrated (Figure 2B). All of these histological findings were consistent with dermatofibroma.

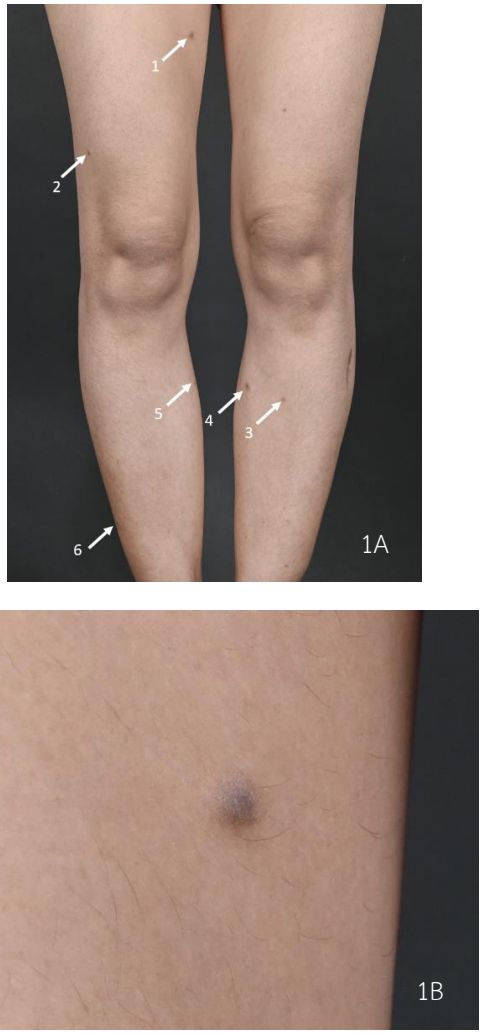

Figure 1 A) Multiple small brownish nodules on both lower extremities
B) A dermatofibroma on the right thigh

Discussion

DF is a common benign fibrohistiocytic tumor. It frequently occurs as a solitary firm nodule seen in an otherwise healthy person. MEDFs, however, are uncommon presentation and were first reported in 1970 as 'multiple histiocytomas' by Baraf and Shapiro[2]. The current term 'MEDFs' were accepted to be used since 1973 to name the occurrence of DF over 15 lesions or the development of more than 5 DF lesions in less than 4 months[1,3-4]. From previous studies, approximately 70% of MEDFs had an underlying disease[1,5]. Of these, more than 80% were related to immune dysregulation conditions including autoimmune diseases with or without immunosuppressive drugs (SLE, Sjogren's disease, pemphigus vulgaris with ulcerative colitis, and myasthenia gravis), HIV infection, malignancies (acute myeloid leukemia, mycosis fungoides, T-cell lymphoma, multiple myeloma, breast cancer, and thymoma) and kidney transplantation[1,5]. However, other systemic diseases can be occasionally found in MEDFs patients such as hypertriglyceridemia, hydronephrosis, atopic dermatitis, pregnancy, and pulmonary hypertension[5].

Niiyama et al. noted that MEDFs patients associated with SLE accounted for nearly half of those with underlying conditions[6]. The lesions can appear before the SLE diagnosis, during the time from diagnosis to treatment, or after the initiation of immunosuppressive drugs[7]. However, most SLE patients usually developed MEDFs after receiving or increasing the dosage of immunosuppressive agents, which simultaneously happened following disease exacerbation[6-7]. Therefore, it is difficult to

conclude that the occurrence of MEDFs is caused by SLE itself or immunosuppressive therapies.

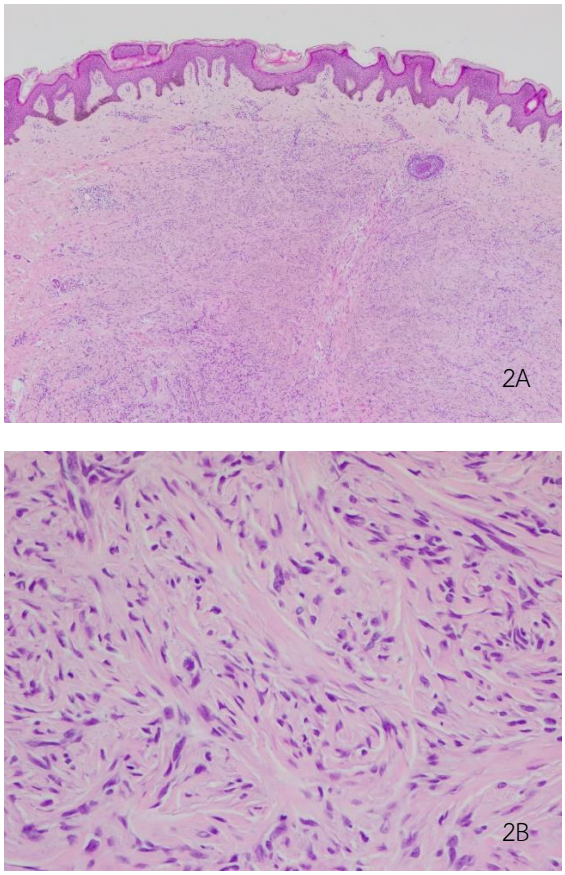

Figure 2 A) Histology of a nodular lesion revealed hyperplasia of the epidermis, increased basal layer pigmentation, and proliferation of spindle cells with peripheral entrapment of collagen bundles in the dermis (H&E, X4)
B) Spindle cells showed fibrohisticytic appearance with prominent storiform pattern (H&E, X40)

Our case emphasizes that immunosuppressive drugs also play an important role in the pathogenesis of DFs. Because her lesions developed promptly after taking azathioprine, which was initiated during cyclosporin and prednisolone tapering without disease aggravation. Until now, there was no study that concluded the most common immunosuppressive drugs or dosage related to the development of MEDFs. However, the concurrent use of systemic corticosteroids seems to be prevalent in the reported cases during the emergence of DFs[5-6]. Moreover, a previous report by Lin et al. revealed the increase and reduction in the number of DFs related to the dosage of corticosteroids[8].

Currently, the exact etiology of DF remains unclear. However, several hypotheses of DFs development have been proposed. The lesion was suggested to occur as a reactive process after various stimuli, such as local trauma, insect bites, and infectious agent[7]. Moreover, the prior study suggested that DF is an abortive immune mechanism initiated by dermal dendritic cells[9]. Otherwise, DFs could develop as an immune response to a putative pathogen that could not be eliminated by the suppressed immune system[4]. In our case, no triggering factor was noted before the appearance of MEDFs.

In addition, Yamamoto et al. mentioned the relationship between growth factors and the development of MEDFs. They found various growth factors including platelet-derived growth factor and basic fibroblast growth factor in the

serum from SLE patients with MEDFs[10]. Accordingly, mast cells, which are believed to secrete growth factors, were evidenced in the DF section. The number of mast cells was also correlated to the age of lesion[10].

In conclusion, we report MEDFs occurred two years after the diagnosis of SLE. They manifested in abrupt onset while azathioprine was initiated. MEDFs are currently recognized as a sign of immune dysregulation. Thus, the patient who presented with MEDFs should be evaluated for underlying conditions that altered immune status.

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