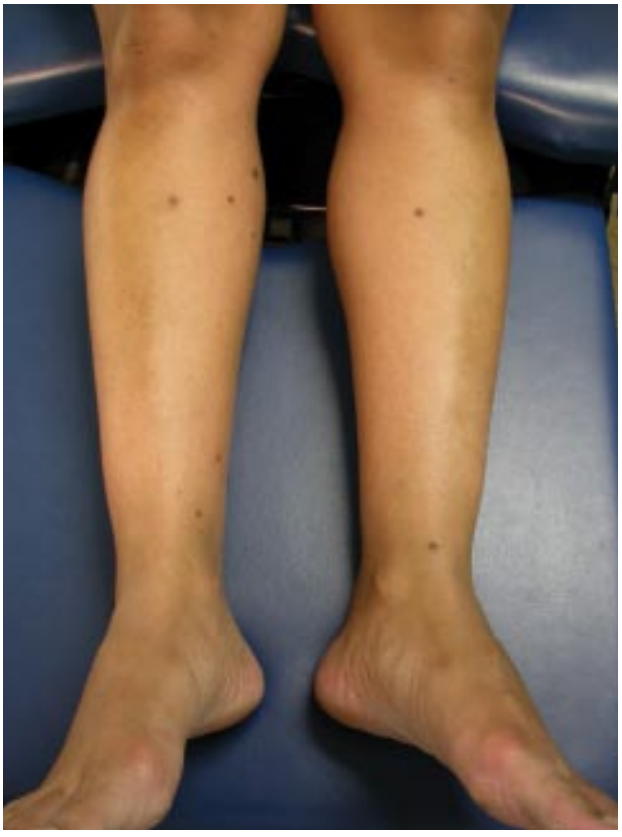
What Is Your Diagnosis?



A 43-year-old woman presented with 40 firm hyperpigmented papules on her legs, arms, and back. The lesions were mildly pruritic and cosmetically concerning. They had erupted slowly over the past 13 years. The patient had a history of type 1 diabetes mellitus, systemic lupus erythematosus, and pure red cell aplasia. Therapies included prednisone, mycophenolate mofetil, hydroxychloroquine sulfate, antithymocyte globulin, and more than 200 blood transfusions. The eruption was reported to be steady without relation to the clinical course of any of her diseases or therapies.

PLEASE TURN TO PAGE 317 FOR DISCUSSION

Thomas K. Barlow, DO; Joy C. Wu, DO; James W. Steger, MD; Elizabeth K. Satter, MD, MPH; all from the Department of Dermatology, Naval Medical Center, San Diego, California. Dr. Barlow currently is from Aviation Medicine, Naval Hospital, Oak Harbor, Washington. Dr. Wu currently is from 3rd Medical Group, Elmendorf Air Force Base, Alaska.
The authors report no conflict of interest.
The views expressed in this article are those of the authors and do not reflect the official policy or position of the US Department of the Navy, US Department of Defense, or the US Government.

The Diagnosis: Multiple Dermatofibromas

Dermatofibromas (DFs) are common benign tumors of the skin (Figure 1) that occur most often as solitary lesions on the lower extremities. They are usually darker than the surrounding skin and tethered to the underlying tissue, resulting in the classic dimple sign when compressed. The tumors are composed of fibrohistiocytic cells densely incorporated into a connective tissue matrix with thickened collagen bundles (Figure 2). The typical immunohistochemical signature of DFs includes positivity for factor XIIIa, $CD34^-$, and positivity for HMGA1 and HMGA2 (high mobility group AT-hook 1 and 2), which may help distinguish these lesions from dermatofibrosarcoma protuberans.[1] The etiology of DFs is not well understood, though local physical trauma, such as insect bites, has long been suspected as an inciting factor.

Widespread eruption of multiple DFs on the body is a rare clinical occurrence that has been reported in the setting of immunocompromise and autoimmune disease.[2] The individual lesions in this disorder have gross and histologic appearances identical to solitary DFs. Clinically, the syndrome of multiple DFs is set apart by the presence of many lesions, relatively quick eruption, and involvement of skin above the lower extremities. Two proposed definitions of multiple DFs are the presence of more than 15 lesions[3] and the development of 5 to 8 lesions within 4 months.[4]

Multiple DFs have been reported in association with a number of diseases, most commonly systemic lupus erythematosus (SLE), human immunodeficiency virus infection, and diabetes mellitus.[2] When associated with SLE, DFs have been observed before, at about the same time, and after diagnosis.[5] Dermatofibromas occur more often in females than males, which may be attributable to the higher incidence of SLE among females.[2]

There is a growing body of evidence suggesting that immune dysregulation plays a role in the pathogenesis of solitary and multiple DFs.[2,6,7] An immunologic role is implied by its frequent association with diseases of altered immunity and is further evidenced by the increased number of mast cells[8] and increased cytokine response in DFs. Reported cytokine changes include increased stimulatory potency of the serum of affected patients,[9] increased reactivity to IL-1,[10] and increased expression of receptors for transforming growth factor β types 1 and 2.[11] It also has been shown that the cytokine phorbol 12-myristate

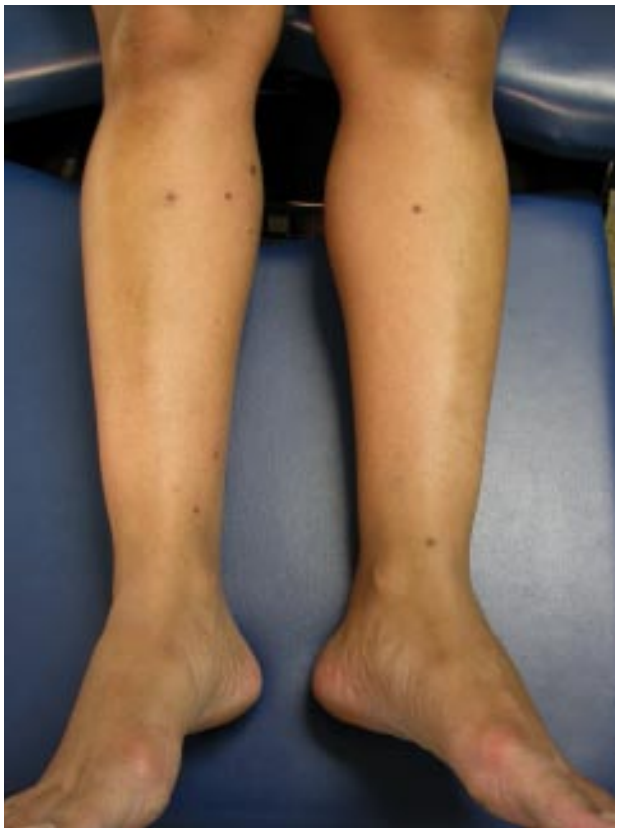


Figure 1. Multiple, darkly pigmented dermatofibromas on the legs of a patient with type 1 diabetes mellitus, systemic lupus erythematosus, and pure red cell aplasia.

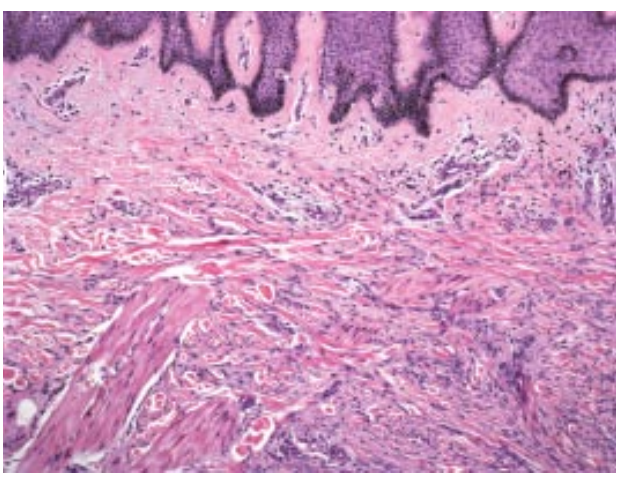


Figure 2. Biopsy of a lesion reveals proliferation of fibrohistiocytic cells in a dense connective tissue matrix consistent with dermatofibroma (H&E, original magnification ×100).

13-acetate can induce DF-like cells from monocyte-derived dendritic cells.[12] These findings suggest that DFs may be reactive tumors mediated by immune response to an unknown stimulus.

Dermatofibromas are difficult to treat. They may spontaneously regress or may persist throughout a patient's lifetime. Lesions can be excised, though recurrence is possible and the cosmetic outcome may be worse than the original lesion. A 600-nm pulsed dye laser has been shown to improve appearance and symptoms,[13] and a CO_2 laser has been successfully used for removal of bulky lesions.[14] In some cases, observation alone may be the best available therapy.

REFERENCES

1. Li N, McNiff J, Hui P, et al. Differential expression of HMGA1 and HMGA2 in dermatofibroma and dermatofibrosarcoma protuberans: potential diagnostic applications, and comparison with histologic findings, CD34, and factor XIIIa immunoreactivity. *Am J Dermatopathol.* 2004;26:267-272.
2. Niiyama S, Katsuoka K, Happle R, et al. Multiple eruptive dermatofibromas: a review of the literature. *Acta Derm Venereol.* 2002;82:241-244.
3. Baraf CS, Shapiro L. Multiple histiocytomas. report of a case. *Arch Dermatol.* 1970;101:588-590.
4. Ammirati CT, Mann C, Hornstra IK. Multiple eruptive dermatofibromas in three men with HIV infection. *Dermatology.* 1997;195:344-348.
5. Tsunemi Y, Tada Y, Saeki H, et al. Multiple dermatofibromas in a patient with systemic lupus erythematosus and Sjögren's syndrome. *Clin Exp Dermatol.* 2004;29:483-485.
6. Bhattacharjee P, Umar SA, Fatteh SM. Multiple eruptive dermatofibromas occurring in a patient with myelodysplastic syndrome. *Acta Derm Venereol.* 2005;85:270-271.
7. Chang SE, Choi JH, Sung KJ, et al. Multiple eruptive dermatofibromas occurring in a patient with acute myeloid leukaemia. *Br J Dermatol.* 2000;142:1062-1063.
8. Yamamoto T, Katayama I, Nishioka K. Role of mast cells in dermatofibroma: recent viewpoints into the pathogenesis. *Eur J Dermatol.* 2003;13:419-423.
9. Yamamoto T, Katayama I, Nishioka K. Involvement of basic fibroblast growth factor in fibroblast-stimulatory serum activity of a patient with systemic lupus erythematosus and multiple dermatofibromas. *Dermatology.* 1995;191:281-285.
10. Yamamoto T, Katayama I, Nishioka K. Possible involvement of interleukin-1 in the pathogenesis of dermatofibroma. *Acta Derm Venereol.* 1998;78:99-102.
11. Kubo M, Ihn H, Yamane K, et al. The expression levels and the differential expression of transforming growth factor-β receptors in dermatofibroma and dermatofibrosarcoma protuberans. *Br J Dermatol.* 2006;154:919-925.
12. Aiba S, Tagami H. Phorbol 12-myristate 13-acetate can transform monocyte-derived dendritic cells to different cell types similar to those found in dermatofibroma. a possible in vitro model of the histogenesis of dermatofibroma. *J Cutan Pathol.* 1998;25:65-71.
13. Wang SQ, Lee PK. Treatment of dermatofibroma with a 600 nm pulsed dye laser. *Dermatol Surg.* 2006;32:532-535.
14. Krupa Shankar DS, Kushalappa AA, Suma KS, et al. Multiple dermatofibromas on face treated with carbon dioxide laser. *Indian J Dermatol Venereol Leprol.* 2007;73:194-195.