Anetoderma: A Case Report and Review of the Literature

Donald P. Kineston, MD; Yang Xia, MD; George W. Turiansky, MD

Anetoderma is a rare benign dermatosis caused by a loss of mid-dermal elastic tissue resulting in well-circumscribed areas of pouchlike herniations of flaccid skin. Anetoderma is classically categorized as either primary (idiopathic) or secondary (following an inflammatory dermatosis in the same location). We report a case of primary anetoderma (PA) occurring in a human immunodeficiency virus 1 (HIV-1)–infected man. We review the clinical presentation, possible etiologies, associated conditions, and limited treatment options of this disease.

Cutis. 2008;81:501-506.

Case Report

In June 2004, a 25-year-old man with a 2-year history of human immunodeficiency virus 1 (HIV-1) infection, a CD4 lymphocyte count of 176 cells/μL (reference range, 500–1500 cells/μL), and a viral load of 15,897 copies/mL (high viral load, 5000–10,000 copies/mL) was placed on a highly active antiretroviral therapy (HAART) consisting of lamivudine, zidovudine, and efavirenz. In February 2006, he presented with multiple cutaneous lesions on the trunk.

The patient was not compliant with his HAART regimen. He noted that the first lesion appeared in September 2005 on the left lateral flank. The last known CD4 lymphocyte count was 177 cells/μL, with a viral load of 50 copies/mL one year earlier (September 2004). The other lesions gradually appeared on the rest of the trunk and back within the next several months. The patient denied any symptoms associated with the lesions and did not recall if there was associated erythema prior to the appearance of the lesions. He had not developed any new lesions after the CD4 lymphocyte count increased to 277 cells/μL, with an undetectable viral load in January 2006 after taking his HAART medications more consistently. His medication history included co-trimoxazole and pravastatin, and he denied ever using penicillamine.

Results of a physical examination revealed multiple 4- to 10-mm flesh-colored to light pink oval papules and plaques that were easily compressible and located diffusely over the abdomen and back (Figure 1A). In addition, a single, firm, 1-cm, flesh-colored to whitish plaque was located above the umbilicus with a nearby flesh-colored soft papule on the lateral abdomen (Figure 1B). The patient denied any systemic symptoms and had no history of cardiovascular disease. In addition, he denied a history of varicella, recent insect bites, prurigo nodularis, Lyme disease, or molluscum contagiosum. There was a childhood history of acne vulgaris, predominantly involving the face.

Laboratory evaluations at presentation revealed a positive rapid plasma reagin (RPR) test result with a titer of 1:2 and a negative fluorescent treponemal antibody absorption test result. Complete blood count and comprehensive metabolic panel were within reference range. Results of antinuclear antibody testing were negative.

Routine histologic examination of the firm plaque above the umbilicus revealed no difference compared with a biopsy specimen of healthy skin 8 mm from the lesional skin (Figure 2). However, elastic tissue stain results showed a substantial loss of elastic fibers in the reticular dermis of lesional skin compared with healthy skin (Figure 3).

The patient was referred to an infectious disease service for evaluation of the positive RPR test result. A second set of RPR and fluorescent treponemal antibody absorption serologies was performed and

Accepted for publication March 8, 2007.

Dr. Kineston is from Regional Support Organization, Norfolk, Virginia. Drs. Xia and Turiansky are from Walter Reed Army Medical Center, Washington, DC.

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 of the US Department of the Army, US Department of the Navy, US Department of Defense, or US Government.

Correspondence: Yang Xia, MD, 6900 Georgia Ave NW, Washington, DC 20307 (yang.xia@amedd.army.mil).

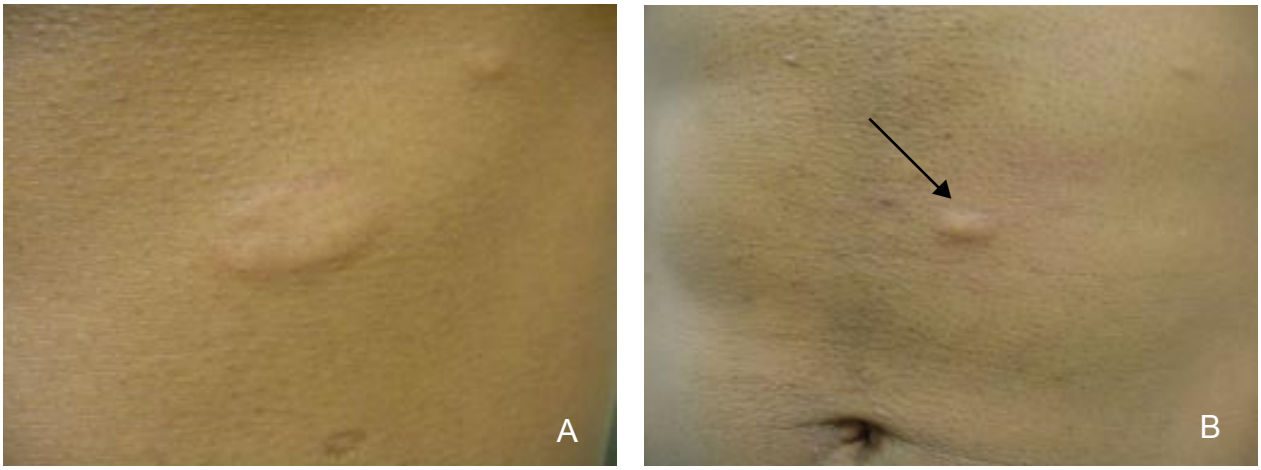

Figure 1. Flesh-colored to light pink protuberant papule and plaque on the trunk (A). Flesh-colored to whitish firm plaque above the umbilicus (arrow) with a nearby flesh-colored soft papule on the lateral abdomen (B).

had negative results. The patient was subsequently lost to follow-up. The diagnosis was Schweninger-Buzzi type of primary anetoderma (PA).

Comment

The term *anetoderma* is derived from the Greek words *anetos* (relaxed) and *derma* (skin). Anetoderma was first described in 1892 by Jadassohn[1] as erythematous macules on the elbows of a 23-year-old woman that progressed into the characteristic atrophic-appearing wrinkled patches of skin. Anetoderma was subsequently reported in the English language literature as macular atrophy.

Anetoderma typically is characterized by well-circumscribed areas of atrophic-appearing macules or patches. The lesions may be depressed or slightly pouchlike with a distinct inward herniation on palpation that is limited by a surrounding rim of healthy skin. The color of the lesions can vary from flesh colored to white, blue, or brownish gray, and the size of the lesions can range from a few millimeters to centimeters. The trunk and proximal extremities are the most commonly involved sites, with the face and neck being less common. The distal extremities, palms, soles, scalp, and mucous membranes are rarely involved.[2]

The prevalence of anetoderma is unknown. Most reported cases occur in patients aged 20 to 40 years, but the range of affected patients spans from infants to the elderly.[3] The disease appears to have a female predominance and does not have a racial predilection.

Anetoderma is classified into the following 5 groups: primary (PA), secondary anetoderma (SA) or postinflammatory anetoderma, drug-induced anetoderma,[4] familial anetoderma, and anetoderma in association with prematurity or congenital anetoderma[5] (Table 1).

Primary anetoderma is not associated with a known preexisting skin disease. Primary anetoderma traditionally has been further subdivided into the Jadassohn-Pellizzari type, with preceding clinical inflammation or urticaria, and the Schweninger-Buzzi type, which arises in previously healthy-appearing skin.[2] Although both subtypes of PA have some degree of histologic inflammation, there is no difference in the clinical course. Therefore, this differentiation is considered to be of historic interest only.[6]

Secondary anetoderma develops at the site of a previous dermatosis. Dermatoses reported in association with this type of anetoderma include acne vulgaris,[7] varicella,[7] syphilis,[8] insect bites,[9] prurigo nodularis,[10] pilomatrixoma,[9,11] Lyme disease,[12] B-cell lymphoproliferative disorders,[13,14] primary cutaneous immunocytoma,[15] Hansen disease,[16] juvenile xanthogranuloma,[17] urticaria pigmentosa,[18] post–hepatitis B vaccination,[19] generalized granuloma annulare,[20] hamartomatous congenital melanocytic nevi,[21] application of leeches,[22] molluscum contagiosum,[23] myxofibrosarcoma,[24] nodular amyloidosis,[2] and tuberculosis[2] (Table 2).

Primary anetoderma and/or SA also have been reported to occur in HIV-1 infection in conjunction with autoimmune diseases[25,26] such as systemic lupus erythematosus (SLE),[27-29] Grave disease,[30] Addison disease,[2] antiphospholipid syndrome,[31-33] primary Sjögren syndrome,[34] and hemolytic anemia[30] (Table 2).

The use of penicillamine has been the only reported medication linked to the development of anetoderma lesions.[4]

Additional forms of anetoderma include a familial form, which has an autosomal dominant inheritance pattern,[35,36] and anetoderma of prematurity, which is seen exclusively in premature neonates with a gestational age of 24 to 29 weeks following

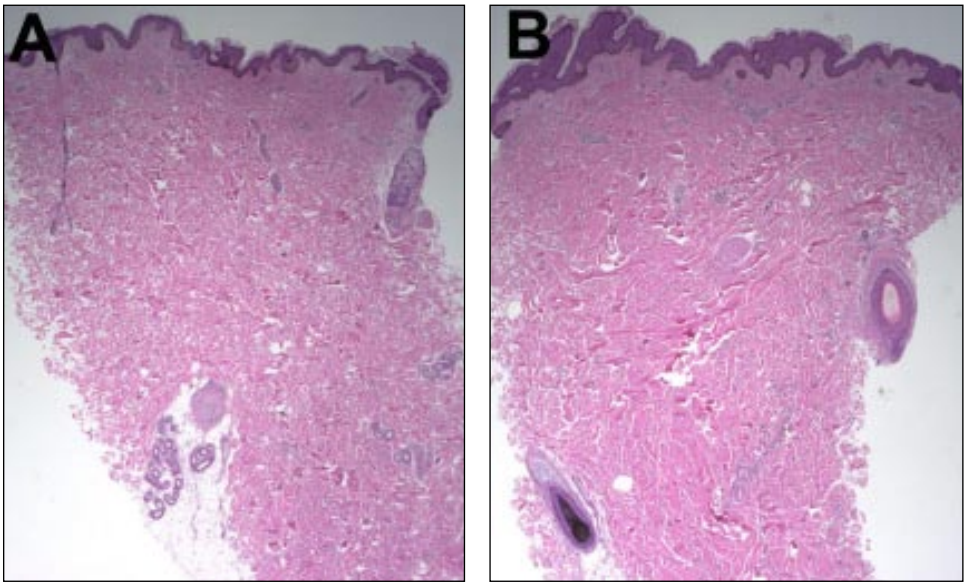

Figure 2. Lesional skin with a healthy-appearing dermis (A) compared to healthy skin (B)(H&E, original magnification ×5 for both).

extended periods of monitoring in the neonatal intensive care unit.[5] Lesions in these patients have been hypothesized to arise secondary to local tissue ischemia from a prior placement of monitoring leads or to be associated with adhesives for a monitoring device applied at the affected sites.

Although the pathogenesis of PA remains unclear, the decrease in elastic tissue may be due to either a decrease in elastin production or increased degradation by elastolytic enzymes. Elastolysis may be a result of increased production of elastolytic enzymes, a decrease in elastolytic enzyme inhibitors, or an increase in phagocytic activity. Zaki et al[37] has demonstrated active phagocytosis of elastic fibers by macrophages on electron microscopy in patients with PA. Venencie and Winkelmann[38] noted a lymphohistiocytic infiltrate with a predominance of $CD4^+$ lymphocytes in biopsy specimens of patients with PA, which suggested a possible immune-mediated inflammatory response. It has yet to be determined if the actual degradation of dermal elastic fibers seen in PA is triggered by inflammatory mediators provoking a cell-mediated immune reaction or by the presence of immune complexes or antibodies in the affected dermis provoking elastophagocytosis. Another hypothesis is that there is an increase in the elastolytic enzyme activity related to anoxic cell events such as compression or microthrombi, which creates a subsequent imbalance between elastolytic enzymes and their inhibitors that results in elastic fiber breakdown.

Kossard et al[39] were the first in the English language literature to suggest a potential autoimmune role in PA. One patient demonstrated IgM and C3 deposits in direct immunofluorescence (DIF) of lesional skin in a granular pattern at the dermoepidermal junction as well as IgM in a granular and fibrillar pattern between the dermal collagen fibers

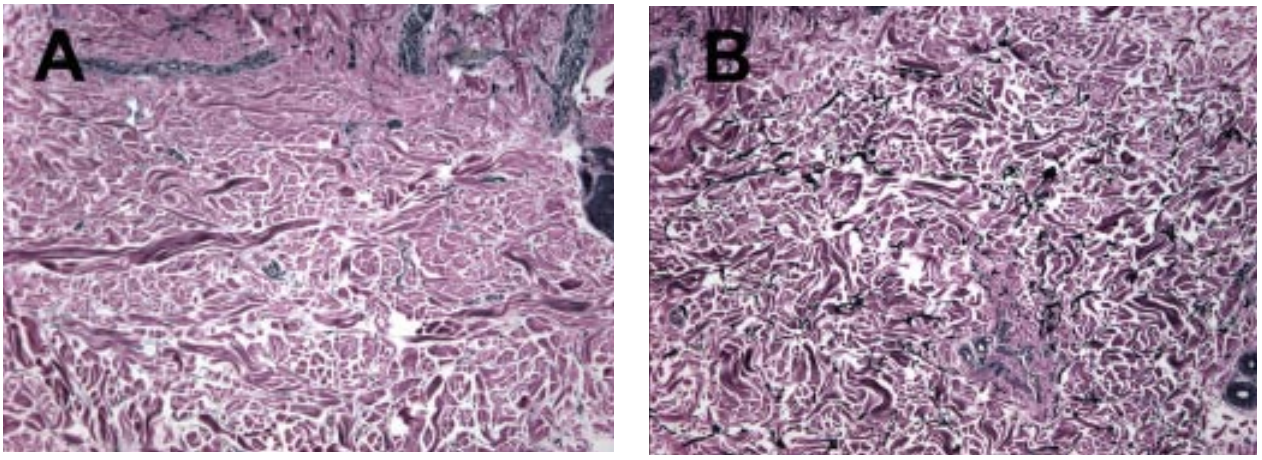

Figure 3. Elastic tissue stain of lesional skin showed a substantial loss of elastic fibers in the reticular dermis (A) as compared to the average number of elastic fibers in healthy skin (B)(Verhoeff, original magnification ×10 for both).

Table 1.

Classification of Anetoderma

Primary
Jadassohn-Pellizzari type (precedent clinical inflammation)
Schweninger-Buzzi type (arises in previously healthy-appearing skin)
Secondary
Preceding dermatosis
Drug Induced
Penicillamine
Familial
Autosomal dominant inheritance pattern
Prematurity
Neonates

and C3 deposition on the elastic fibers. Hodak et al[30] reported several patients with PA with varied immunoreactants on DIF including granular deposits of IgM, C3, C1q, IgA, and IgG at the dermoepidermal junction, and IgM and C3 within the dermal blood vessel walls of both the affected and unaffected skin. However, the above DIF findings are relatively nonspecific and can be commonly seen in skin biopsy results in patients with SLE.

Several case reports and series have reported patients with PA that were found to have SLE and/or the presence of antiphospholipid antibodies (aPLs) on laboratory evaluation.[27,31-33] Patients with a positive aPL test result also had elevated titers of anticardiolipin antibodies, anti–β2 glycoprotein I, and lupus anticoagulant.[31] In addition, Lindstrom et al[26] reported moderately elevated anticardiolipin antibody levels in 7 of 8 HIV-1–positive patients with anetoderma but only borderline levels in 4 HIV-1–positive patients without anetoderma. This finding suggested that immune dysregulation, including the presence of aPL, may predispose patients to develop PA.[26]

Secondary anetoderma often occurs after the resolution of a primary inflammatory lesion. However, the pathophysiology of SA is not well-understood.

The use of penicillamine has been reported in association with the formation of anetoderma lesions. At the biochemical level, elastic fibers are unable to develop normally through the inhibition of aldol cross-linking.[40] This mechanism occurs in a similar manner by which penicillamine inhibits collagen cross-linking.

Local tissue ischemia, presumably from the placement of monitor leads and adhesives, has been proposed as a mechanism for anetoderma of prematurity.[5] Tissue hypoxia/reoxygenation in the area of the electrode placement has been shown to stimulate matrix metalloproteinases, which are involved in the degradation of specific extracellular matrix components, including elastin.[41,42] Specifically, an increase in expression of matrix metalloproteinase-2 (gelatinase A) and a decrease in the production of its inhibitor, tissue inhibitor of metalloproteinase-2, were noted in patients with anetoderma.[43]

Other entities to consider in the differential diagnosis of anetoderma include localized acquired cutis laxa, mid-dermal elastolysis, atrophic scars, connective tissue nevus, perifollicular atrophoderma, focal dermal hypoplasia, nevus lipomatosus cutaneous superficialis, granulomatous slack skin, B-cell lymphoma, morphea, lichen sclerosus et atrophicus, atrophia maculosa varioliformis cutis, atrophoderma of Pasini and Pierini, atrophoderma vermiculata, striae distensae, and neurofibromas.[2,3,14]

Histologically, anetoderma shows a near complete loss of elastic fibers in the papillary and reticular dermis. A periadnexal and perivascular lymphocytic dermal infiltrate, including plasma cells and histiocytes, can be present in lesional skin.[38] Rarely, histologic examination may reveal cutaneous plasmacytoma or benign cutaneous lymphoid hyperplasia.[44] On electron microscopy, residual fine and fragmented elastic microfibrils may be seen, as can elastophagocytosis.[6,37] The concentration of elastin can be further verified by measuring the desmosine content in the affected skin, which in the case of anetoderma is markedly reduced.[45] DIF of lesional skin may demonstrate nonspecific immunoreactant deposition.[30,39]

There is no known effective treatment of established anetoderma lesions. The various treatment modalities reported to date have included cryotherapy, intralesional steroids, colchicine, hydroxychloroquine, vitamin E, oral penicillin G, epsilon-aminocaproic acid, aspirin, niacin, dapsone, and phenytoin.[3,7] Colchicine has been reported to be effective in preventing the onset of new PA lesions.[46] In addition, control of underlying dermatoses may prevent the formation of new SA lesions.

Table 2.

Secondary Anetoderma–Associated Conditions

Autoimmune Conditions
Addison disease
Antiphospholipid syndrome
Discoid lupus
Grave disease
Hemolytic anemia
Primary Sjögren syndrome
Systemic lupus erythematosus
Infectious Conditions
Hansen disease
Human immunodeficiency virus infection
Lyme disease
Molluscum contagiosum
Syphilis
Tuberculosis
Varicella
Inflammatory Conditions
Acne vulgaris
Application of leeches
Generalized granuloma annulare
Insect bites
Juvenile xanthogranuloma
Post–hepatitis B vaccination
Prurigo nodularis
Urticaria pigmentosa
Tumor/Deposition Conditions
B-cell lymphoproliferative disorders
Hamartomatous congenital melanocytic nevi
Myxofibrosarcoma
Nodular amyloidosis
Pilomatrixoma
Primary cutaneous immunocytoma

Excision is the only definitive treatment of established lesions. Primary anetoderma lesions can evolve slowly over a period of weeks after initial presentation and can remain unchanged thereafter for life.[2] Although the appearance of new lesions over many years is common, there have been no reports of the spontaneous regression of the lesions.

Clinical associations with several ocular, bony, cardiac, and endocrine abnormalities have been reported with anetoderma.[2] Although no causality has been proven, a thorough physical examination may be indicated in any newly diagnosed patient with anetoderma because of the possibility of the above observed associations. Similarly, the frequent association with autoimmune disorders, HIV-1 infection, syphilis, and borreliosis should prompt laboratory evaluations.

Conclusion

Anetoderma is a rare benign entity with poorly defined pathogenesis and numerous clinical associations, which necessitates a careful clinical evaluation for all newly diagnosed patients.

REFERENCES

1. Jadassohn J. Ueber eire eigenartige form von 'Atrophia maculosa cutis.' *Arch Dermatol Syph.* 1892;11(suppl 1): 342-358.
2. Venencie PY, Winkelmann RK, Moore BA. Anetoderma. clinical findings, associations, and long-term follow-up evaluations. *Arch Dermatol.* 1984;120:1032-1039.
3. Aghaei S, Sodaifi M, Aslani FS, et al. An unusual presentation of anetoderma: a case report. *BMC Dermatol.* 2004;4:9.
4. Davis W. Wilson's disease and penicillamine-induced anetoderma, abstracted. *Arch Dermatol.* 1977;113:976.
5. Prizant TL, Lucky AW, Frieden IJ, et al. Spontaneous atrophic patches in extremely premature infants: anetoderma of prematurity. *Arch Dermatol.* 1996;132: 671-674.
6. Venencie PY, Winkelmann RK. Histopathologic findings in anetoderma. *Arch Dermatol.* 1984;120:1040-1044.
7. Lewis KG, Bercovitch L, Dill SW, et al. Acquired disorders of elastic tissue: part II. decreased elastic tissue. *J Am Acad Dermatol.* 2004;51:165-185.
8. Clement M, du Vivier A. Anetoderma secondary to syphilis. *J R Soc Med.* 1983;76:223-224.
9. Shames BS, Nassif A, Bailey CS, et al. Secondary anetoderma involving a pilomatricoma. *Am J Dermatopathol.* 1994;16:557-560.
10. Hirschel-Scholz S, Salomon D, Merot Y, et al. Anetodermic prurigo nodularis (with Pautrier's neuroma) responsive to arotinoid acid. *J Am Acad Dermatol.* 1991;25 (2, pt 2):437-442.

11. Kelly SE, Humphreys F, Aldridge RD. The phenomenon of anetoderma occurring over pilomatricomas. *J Am Acad Dermatol.* 1993;28:511.
12. Bauer J. Anetoderma: another facet of Lyme disease? *J Am Acad Dermatol.* 2003;48(suppl 5):S86-S88.
13. Kasper RC, Wood GS, Nihal M, et al. Anetoderma arising in cutaneous B-cell lymphoproliferative disease. *Am J Dermatopathol.* 2001;23:124-132.
14. Segurado MA, Guerra-Tapia A, Zarco C, et al. Anetoderma secondary to cutaneous B-cell lymphoma. *Clin Exp Dermatol.* 2006;31:130-131.
15. Child FJ, Woollons A, Price ML, et al. Multiple cutaneous immunocytoma with secondary anetoderma: a report of two cases. *Br J Dermatol.* 2000;143:165-170.
16. Khandpur S, Agarwal S, Reddy BS. Anetoderma secondary to lepromatous leprosy. *Indian J Lepr.* 2001;73:51-54.
17. Gamo R. Anetoderma developing in juvenile xanthogranuloma. *Int J Dermatol.* 2005;44:503-506.
18. Gebauer KA, Navaratnam TE, Holgate C. Pruritic pigmented papules posing permanent problems. urticaria pigmentosa (UP) with secondary anetoderma. *Arch Dermatol.* 1992;128:107-110.
19. Daoud MS, Dicken CH. Anetoderma after hepatitis B immunization in two siblings. *J Am Acad Dermatol.* 1997;36:779-780.
20. Ozkan S, Fetil E, Izler F, et al. Anetoderma secondary to generalized granuloma annulare. *J Am Acad Dermatol.* 2000;42:335-338.
21. Cockayne SE, Gawkrodger DJ. Hamartomatous congenital melanocytic nevi showing secondary anetoderma-like changes. *J Am Acad Dermatol.* 1998;39:843-845.
22. Siragusa M, Batolo D, Schepis C. Anetoderma secondary to the application of leeches. *Int J Dermatol.* 1996;35:226-227.
23. Shalders K, Ilchyshyn A, Walzman M. Secondary anetoderma following molluscum contagiosum infection. *Acta Derm Venereol.* 2003;83:461-462.
24. Chaby G, Viseux V, Chatelain D, et al. Myxofibrosarcoma associated with anetoderma [in French]. *Ann Dermatol Venereol.* 2006;133:35-37.
25. Mastrolorenzo A, Tiradritti L, Vichi F, et al. Primary anetoderma and HIV infection: a case report. *AIDS Read.* 2006;16:92-96.
26. Lindstrom J, Smith KJ, Skelton HG, et al. Increased cardiolipin antibodies associated with the development of anetoderma in HIV-1 disease. Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). *Int J Dermatol.* 1995;34:408-415.
27. Sparsa A, Piette JC, Wechsler B, et al. Anetoderma and its prothrombotic abnormalities. *J Am Acad Dermatol.* 2003;49:1008-1012.
28. Fernandez-Galar M, Espana A, Lloret P. Systemic lupus erythematosus–associated anetoderma and antiphospholipid antibodies. *Clin Exp Dermatol.* 2003;28:39-42.
29. Stephansson EA, Niemi KM, Jouhikainen T, et al. Lupus anticoagulant and the skin. a longterm follow-up study of SLE patients with special reference to histopathological findings. *Acta Derm Venereol.* 1991;71:416-422.
30. Hodak E, Shamai-Lubovitz O, David M, et al. Immunologic abnormalities associated with primary anetoderma. *Arch Dermatol.* 1992;128:799-803.
31. Hodak E, Feuerman H, Molad Y, et al. Primary anetoderma: a cutaneous sign of antiphospholipid antibodies. *Lupus.* 2003;12:564-568.
32. Bilen N, Bayramgurler D, Sikar A, et al. Anetoderma associated with antiphospholipid syndrome and systemic lupus erythematosus. *Lupus.* 2003;12:714-716.
33. Stephansson EA, Niemi KM. Antiphospholipid antibodies and anetoderma: are they associated? *Dermatology.* 1995;191:204-209.
34. Herrero-Gonzalez JE, Herrero-Mateu C. Primary anetoderma associated with primary Sjögren's syndrome. *Lupus.* 2002;11:124-126.
35. Thomas JE, Mehregan DR, Holland J, et al. Familial anetoderma. *Int J Dermatol.* 2003;42:75-77.
36. Peterman A, Scheel M, Sams WM, et al. Hereditary anetoderma. *J Am Acad Dermatol.* 1996;35:999-1000.
37. Zaki I, Scerri L, Nelson H. Primary anetoderma: phagocytosis of elastic fibres by macrophages. *Clin Exp Dermatol.* 1994;19:388-390.
38. Venencie PY, Winkelmann RK. Monoclonal antibody studies in the skin lesions of patients with anetoderma. *Arch Dermatol.* 1985;121:747-749.
39. Kossard S, Kronman KR, Dicken CH, et al. Inflammatory macular atrophy: immunofluorescent and ultrastructural findings. *J Am Acad Dermatol.* 1979;1:325-334.
40. Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol.* 1996;35:732-742.
41. Ben-Yosef Y, Lahat N, Shapiro S, et al. Regulation of endothelial matrix metalloproteinase-2 by hypoxia/reoxygenation. *Circ Res.* 2002;90:784-791.
42. Patroi I, Annessi G, Girolomoni G. Mid-dermal elastolysis: a clinical, histologic, and immunohistochemical study of 11 patients. *J Am Acad Dermatol.* 2003;48:846-851.
43. Ghomrasseni S, Dridi M, Gogly B, et al. Anetoderma: an altered balance between metalloproteinases and tissue inhibitors of metalloproteinases. *Am J Dermatopathol.* 2002;24:118-129.
44. Jubert C, Cosnes A, Wechsler J, et al. Anetoderma may reveal cutaneous plasmacytoma and benign cutaneous lymphoid hyperplasia. *Arch Dermatol.* 1995;131:365-366.
45. Oikarinen AI, Palatsi R, Adomian GE, et al. Anetoderma: biochemical and ultrastructural demonstration of an elastin defect in the skin of three patients. *J Am Acad Dermatol.* 1984;11:64-72.
46. Braun RP, Borradori L, Chavaz P, et al. Treatment of primary anetoderma with colchicine. *J Am Acad Dermatol.* 1998;38:1002-1003.