

Primary anetoderma and antiphospholipid antibodies

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Abstract

Primary anetoderma is a rare idiopathic disease of the skin, characterized by circumscribed areas of loose skin, and loss of elastic fibers upon histopathologic examination. It is occasionally observed in patients with systemic lupus erythematosus or other autoimmune diseases, but has been most consistently associated with antiphospholipid antibodies.

We report two cases of primary anetoderma, both with presence of anticardiolipin and anti- β 2-glycoprotein I antibodies, but only one with lupus anticoagulant. None of the patients fulfill diagnosis criteria for systemic lupus erythematosus or antiphospholipid syndrome. After reviewing the literature on the subject matter, we believe it is necessary to perform systematic screening for antiphospholipid antibodies in each primary anetoderma patient (Dermatol Argent 2008;14(5):372-378).

Key words: primary anetoderma; antiphospholipid antibodies; lupus erythematosus; antiphospholipid syndrome.

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Introduction

Anetoderma is an elastolytic skin process clinically characterized by circumscribed rounded areas of loose skin; and histologically, by loss of elastic dermal fibers. Two forms are traditionally distinguished, primary and secondary. The latter refers to an abnormal repair mechanism of preexisting skin lesions, where acne and varicella are the most frequent causes. In contrast, in the primary form lesions appear *de novo* on the previously healthy skin, and they have been related to a variety of pathologies, mainly autoimmune diseases.¹ Due to its low frequency, only isolated reports and series with few cases have been published. However, recently the strong link existing between dermatosis and the presence of antiphospholipid antibodies was established.

Firstly, we shall present the two cases we had the opportunity to study, and then we shall make some considerations on the subject matter.

Case 1

A 33-year-old male patient with recent diagnosis of membranous glomerulonephritis treated at the time of the consultation visit with the immunosuppressor mofetil mycophenolate 1.5g/day, and deltisone 40mg/day. Renal biopsy showed granular deposits of IgG, IgM, IgA, and C3 on the glomerular capillary wall, and the case had been construed as probably of lupus etiology. The patient was referred to our Dermatology Department for assessment of lesions on trunk and arms of a 4 years' evolution, asymptomatic, appearing without preexisting skin alterations. When examined, multiple round or oval

circumscribed lesions of 1 to 2cm diameter were observed, a little paler than the surrounding healthy skin, with smooth surface and atrophic appearance. Some adopted a saccular aspect, and all had reduced consistency at palpation (**Figure 1**). Skin biopsy with hematoxylin-eosin evidenced the presence of superficial and deep perivascular lymphocyte infiltrates (**Figure 2**). Elastolysis and elastorrhesis were found by elastic fibers stain, thus confirming diagnosis of anetoderma. Direct immunofluorescence of one of the lesions in the dermo-epidermal junction showed granular deposits of IgG, IgM, and C3; no deposits were found in the non-exposed healthy skin. Complete blood count, sedimentation rate, and blood and urine chemistry were normal. VDRL was reactive 1/8 with negative FTABs, and extended 55 second KPTT. Antiphospholipid antibodies were requested, and results were positive for lupus inhibitors, anticardiolipin IgM and anti-b2-glycoprotein I IgG and IgM antibodies. Anticardiolipin IgG antibodies were present in low titers. The study was completed with serum tests for ANA, rheumatoid factor and HIV, all with negative results.

In the second determination of antiphospholipid antibodies, after more than 12 weeks, lupus inhibitor and anticardiolipin IgG antibodies were positive. On this occasion, anticardiolipin IgM antibodies evidenced low titers. So far, no thrombotic event has ever occurred with the patient, and no other criterion was added for systemic lupus erythematosus. No new anetoderma lesions appeared either. Glomerulonephritis was controlled with lower doses of prednisone. Aspirin 100 mg/day was added to his usual medication.

Case 2

A 30-year-old patient with history of years of arthralgia, medicated with hydroxychloroquine 200 mg/day. She was referred to Dermatology to assess the presence of asymptomatic lesions on trunk and neck of an 8 years' evolution, appearing on previously healthy skin, and for the study of two facial plaques finally resulting in clinical and histological tumid lupus. The examination of superior back, anterior aspect of thorax and neck showed multiple round and oval lesions not greater than 2 cm diameter, well delimited, normal skin-colored or slightly lighter, a smooth surface, atrophic appearance and reduced consistency (**Figure 3**). Skin biopsy with hematoxylin-eosin evidenced the presence of superficial and deep perivascular lymphocyte infiltrates, and elastolysis plus elastorrhesis were found with elastic fiber stain (**Figures 4 and 5**). With diagnosis



Figure 1. Circumscribed, round lesions, slightly more clear than the surrounding skin, with reduced consistency on palpation (continuous arrows). Two lesions with saccular aspect are noted (discontinued arrows).

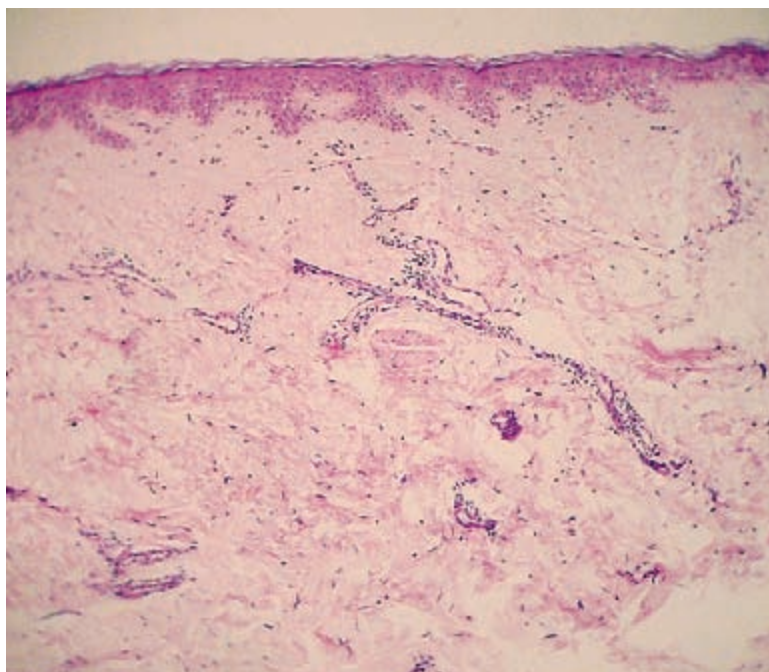


Figure 2. Slight mononuclear inflammatory dominantly superficial and deep perivascular infiltrate (H-E 10^x).

of primary anetoderma, direct immunofluorescence on one of the lesions and on non-exposed healthy skin was requested and no immunoglobulin or complement deposit was found in any of the samples. Complete blood count, and blood and urine chemistry were normal, and sedimentation rate was 33 mm in the first hour. La VDRL was non-reactive and coagulation tests were normal. Antiphospholipid antibodies were requested; lupus inhibitor was negative and anticardiolipin IgG and anti-b2-glycoprotein I IgG antibodies were positive. Rheumatoid factor and ANA were reactive, the latter with a 1/160 titer with spotted pattern, and positive results for anti-Ro and anti-La antibodies. The study was completed with HIV serology, with negative results.

Second determination of anti-b2-glycoprotein I IgG antibodies, after more than 12 weeks, was again positive. On this occasion anticardiolipin IgG and IgM antibodies were found in low concentrations.

So far, the patient has not shown thrombotic events, become pregnant, shown clinical signs of Sjögren's syndrome and, beyond photosensitivity and positive ANA, she has not added any other systemic lupus erythematosus criterion. No new anetoderma lesions have appeared either. She continues with hydroxychloroquine 400 mg/day and although tumid lupus lesions responded partially to topic tacrolimus and photoprotection, she may present intermittent exacerbations, which are controlled with topic and intralesional corticoids and brief periods of meprednisone 5 mg/day. Aspirin 100 mg/day was added to her usual medication.

Values of anticardiolipin and anti-b2-glycoprotein antibodies found in cases 1 and 2 are detailed in Table 1.

Discussion

Clinically, primary anetoderma lesions (PA) appear as circumscribed round or oval areas of skin with atrophic aspect and reduced consistency on palpation, which occasionally adopt a protruding saccular appearance. Most frequently, they localize on trunk, neck and arms, but there are reports of their appearing in other sites. No previous type of lesion precedes them on the location where they develop, but they appear *de novo*. The patient may be totally asymptomatic or refer pruritus and inflammation on the lesions, thus having an itching aspect at the onset or at any other time.¹ Due to these different presentation forms, traditionally two forms of anetoderma were described, the Jaddasohn-Pellizari-type and the Schweningen-Buzzi-type, according to the existence or not, respectively, of associated inflammation.¹ The classification has lost relevance, since no difference has been observed between the two entities as regards general prognosis or associated disease profile.² In addition, as discussed below, in practice there is always an inflammatory tissue component. Histologically, a superficial, and usually also deep, perivascular lymphocyte infiltrate is identified with hematoxylin and eosin. Although lymphocytes dominate, other inflammatory cells may be found. No epidermal or subcutaneous cell tissue alterations are observed.³ Occasionally, giant cells may be found in the dermis, including granuloma formation.^{3,4} It should be mentioned that in a minority of patients microthrombi of dermal vessels have been de-



Figure 3. Subtle, rounded lesions with fine superficial wrinkles. Reduced consistency on palpation.

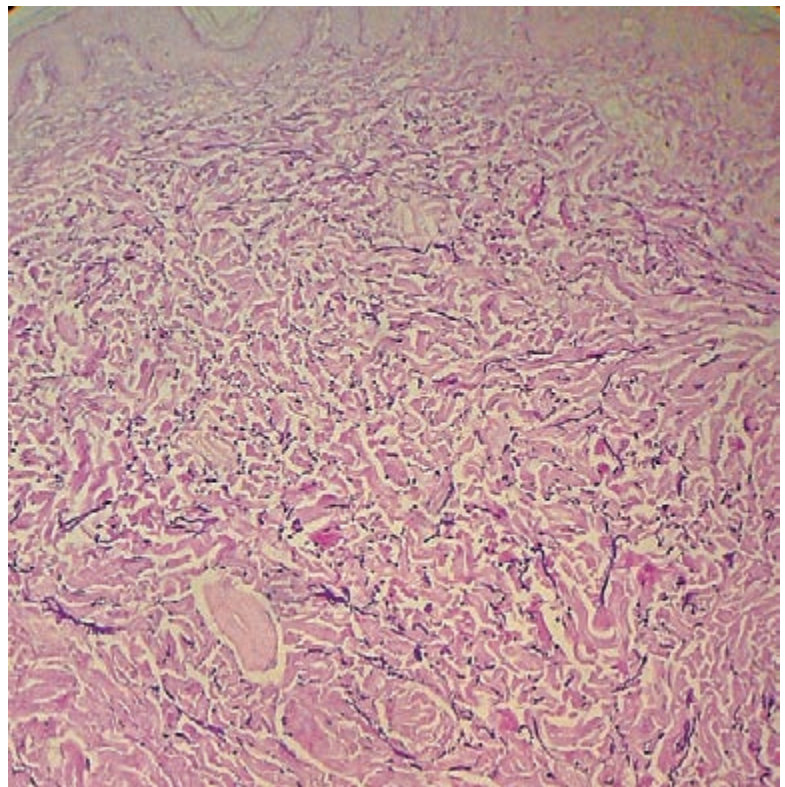


Figure 4. Absence of elastic fibers in the papillar dermis and their fragmentation at the reticular dermis level (resorcin-fuchsine 10').

scribed,⁵ and the possibility of the absence of this phenomenon being really a consequence of the opportunity of sample taking cannot be ruled out. The diagnosis of certainty of anetoderma is done upon a finding of elastolysis and elastorrhexis mainly affecting papillar and frequently reticular dermis by elastic fiber stain. The remaining fibers, in addition to be fragmented, adopt a characteristic tortuous and thinned-out aspect.³ The role played by direct immunofluorescence in the study of dermato-

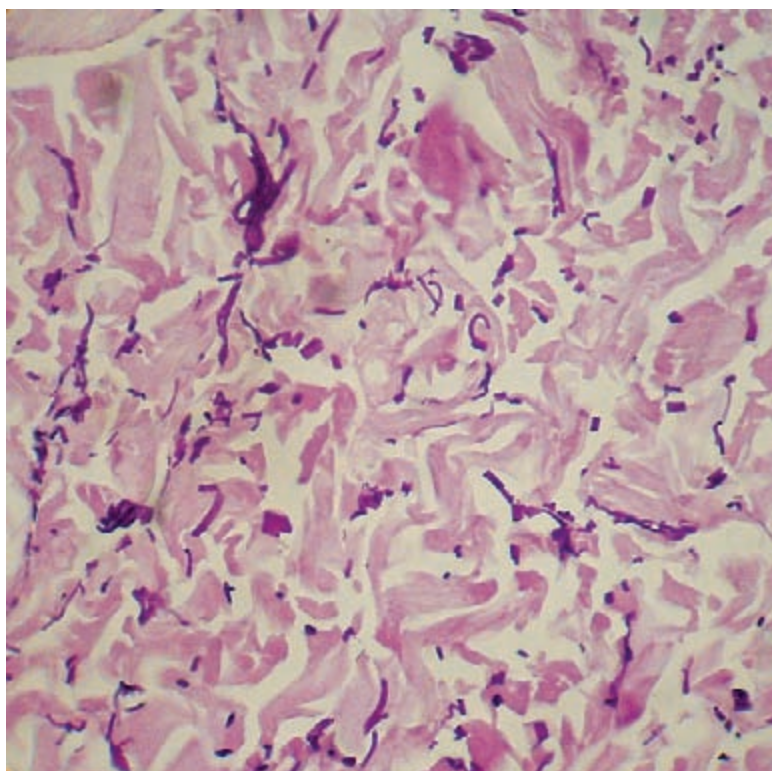


Figure 5. Fragmentation and thinning of elastic fibers in reticular dermis (resorcin-fuchsin 40').

TABLE 1. VALUES OF ACL AND A- β 2-GPI ANTIBODIES FOUND (IN UNITS)

	Case 1		Case 2	
	1st d	2nd d	1st d	2nd d
aCL IgG	32	98	61	32
aCL IgM	42	15	<2	8
a- β 2-GPI IgG	24	nd	12	22
a- β 2-GPI IgM	23	nd	19	16

aCL: anticardiolipin antibodies. a- β 2-GPI: anti- β 2-glycoprotein I.

1st d: first determination; 2nd d: second determination. Nd: not done.

Currently considered:

- positive titers (by definition intermediate-high) of anticardiolipin IgG or IgM antibodies, values exceeding 40 U.
- positive titers of anti- β 2-glycoprotein I IgG and IgM, values exceeding 10 and 20 units, respectively.

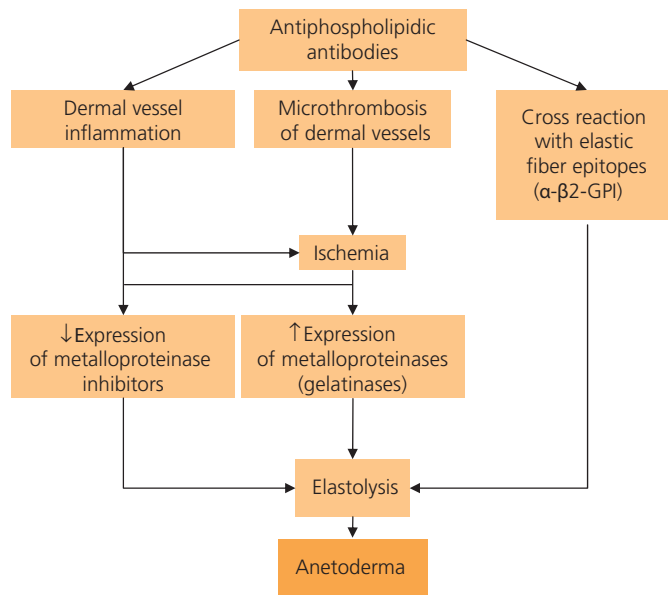
sis is not clear. Case series and isolated reports on said analysis performed show variable results, and as with our patients, fluorescent deposits may or may not be found.^{6,7} Morphology of the latter may be granular or linear. Several combinations of immunoglobulins (mainly IgM e IgG, occasionally IgA) and complement fractions (especially C3 and C1q) are possible. They may be found in the dermo-epidermal junction area, in the vascular walls or in the dermis, following disposition of elastic fibers.⁷⁻¹⁴ In many patients with positive immunofluorescence, deposits are usually found simultaneously on the junction area and the dermal vessels;^{7,12,13} sometimes, on the three sites mentioned above. Although seemingly less frequent, immune deposits may also be found in healthy skin, at the dermo-epidermal junction and the perivascular level.^{7,10} Although few publications count on the immunofluorescence test on undamaged skin, only a minority of patients with positive findings in this location had diagnosis of systemic lupus erythematosus (LES) or cutaneous lupus manifestations in general.^{7,10}

PA has been related to multiple diseases. For some time, its association with autoimmune pathologies has been highlighted, mainly LES and antiphospholipid antibodies syndrome (APS).^{15,16} Communications of diseases of this type include, among others, cutaneous varieties of lupus erythematosus,^{2,17} Graves' disease,¹¹ Hashimoto thyroiditis,¹⁵ systemic scleroderma,⁷ Addison's disease,² hemolytic anemia,^{7,9} autoimmune thrombocytopenia,¹ etc.

Likewise, serological tests usually accompanying said entities (antinuclear antibodies, rheumatoid factor, anti-thyroid antibodies, among others) have frequently been communicated coexisting with PA, even as separate laboratory findings. More recently, cases of PA have also been published in the HIV patient context.¹⁸ However, where work performing exhaustive and complete study is done on the presence of antiphospholipid antibodies, the most strong association of PA is with these antibodies. Although these antibodies may appear separately, they usually relate to autoimmune diseases or with infections, which may justify the heterogeneity of entities linked to dermatosis. Notoriously among LES patients, PA is only found in those with antiphospholipid antibodies.^{5,19,20} Stephansson et al. found PA lesions in 5 of 33 patients with LES plus antiphospholipid antibodies; these authors did not find the antibodies in the 37 lupus patients studied which did not have these antibodies.⁵ Likewise, Lindstrom et al. detected the presence of antiphospholipid antibodies in 7 of 8 HIV-positive patients with anetoderma, although the latter was secondary in most analyzed cases.¹⁸

Making a short revision of the literature on the subject matter, it is noteworthy that some publications of the midst of last century report cases associated to syphilis serology tests, but without cutaneous manifestations.² In one of the largest series on PA, Venecie and Winkelman determined VDRL (which has low sensibility and specificity as antiphospholipid antibodies detection method) in 14 patients and found only one false positive case.² Later, Hodak et al. performed VDRL and lupus inhibitor on six patients, but only one resulted positive for the latter, and no one was reactive for VDRL.⁷

However, in introducing anticardiolipin (aCL) IgG and IgM antibodies in PA patients, antiphospholipid antibodies detection sensitivity increases. In the above mentioned study by Stephansson et al., of the 5 patients with anetoderma and LES, 4 were positive for lupus inhibitor and 3 for aCL antibodies isotype IgG, M, and/or A. In spite of that, in a later work, the same author retrospectively studied the presence of lupus in-



Graph 1. Physiopathogenic mechanisms suggested for primary anetoderma.

hibitor and aCL antibodies isotypes IgG and IgM in 14 patients with PA (one of them with LES) and only found antiphospholipid antibodies in one case.²¹ However, as the antibody search is performed with higher sensibility and specificity methods, the ratio of cases evidencing the PA-antiphospholipid antibodies association increases. Publications completing the analysis anti-b2-glycoprotein I antibodies (a-b2-GPI) dosage show more definite data in this sense.²² Examples are the work by Disdier et al. and by Sparsa et al. In the first, the authors found the antibodies in the patients studied with anetoderma;¹⁶ in the second, in 8 of the 9 cases.²³ Where in addition to isotypes IgG and IgM, isotypes IgA of aCL and a-b2-GPI antibodies are determined, the results are even more conclusive. Thus, the last study by Hodak et al. detected presence of antiphospholipid antibodies in each of the 9 patients with PA analyzed. None of them had diagnosis of lupus erythematosus.¹⁵ Therefore, currently PA is recognized as a possible manifestation of the presence of antiphospholipid antibodies.^{15,24} These may be an isolated laboratory alteration, related to autoimmune diseases or HIV infections as mentioned above, or be a part of an APS.²⁵ It should be noted that almost half of patients studied in the most recent case series may be included in said syndrome, since in addition to the presence of the antibodies, these patients evidence some thrombotic event or obstetric complications.^{15,16,23} In some of them, these alterations developed years after occurrence of the anetodermic lesions, which constituted the first clinical signs of the syndrome.¹⁵ Physiopathogeny of PA is unknown. Many theories try to explain the elastolytic phenomenon. A possible mechanism may be the immunologic attack of elastic fibers, a product of cross-reaction between the b2-glycoprotein I and epitopes of these elastic fibers. This would be supported by the presence of immune deposits surrounding the elastic fibers in immunofluorescence of some patients.^{7,10,12} However, the current tendency considers the problem as a disequilibrium between metalloproteinases and their inhibitors. The antiphospholipid antibodies may trigger tissue ischemia and/or an inflammatory response, thus increasing the expression of gelatinases and reducing the expression of their inhibitors, causing elastolysis.^{26,27} The presence (in a minority of biopsies) of dermal vessel micro-thrombosis would suggest that

ischemia triggers the phenomenon,^{5,21} while the fluorescent perivascular immune deposits (found in many cases) would support inflammation as main responsible.^{7,12,13} **Graph 1** summarizes the physiopathogenic theories.

Conclusion

PA may be considered a cutaneous lesion highly suggesting the presence of antiphospholipid antibodies within or out of the context of a defined APS. Therefore, in every patient with said dermatosis, the exhaustive investigation of the presence of said antibodies is recommended, in addition to ruling out autoimmune diseases (especially LES) and HIV infection. In those patients with moderate-high titers of antiphospholipid antibodies and without history of thrombotic events, treatment with low doses of aspirin and primary preventive anticoagulant therapy is justified in surgeries requiring immobilization.²⁸ It is also important to prevent other prothrombotic factors such as obesity, smoking, oral contraceptives, etc. Since PA may be an early sign of diverse autoimmune diseases, long-term follow up of these groups of patients is mandatory, due to the possible appearance of a systemic disorder.

References

- Burgdorf W, Goltz R. Anetoderma y otras enfermedades atróficas de la piel. In: Fitzpatrick TB, Katz S et al. Dermatología en Medicina General. Buenos Aires: Edit. Médica Panamericana; 2001:1266-1269.
- Venencie PY, Winkelmann RK, Moore BA. Anetoderma. Clinical Findings, Associations, and Long-term Follow-up Evaluations. *Arch Dermatol* 1984; 120:1032-1039.
- Venencie PY, Winkelmann R. Histopathologic Findings in Anetoderma. *Arch Dermatol* 1984; 120:1040-1044.
- Ishida Y, Naitoh M, Yoneyama K, Shinkai H, et al. Coexistence of disseminated primary anetoderma and generalized granuloma annulare-like papules. *J Dermatol* 2007; 34:278-279.
- Stephansson EA, Niemi K, Jouhikainen T, Vaarala O, et al. Lupus Anticoagulant and the Skin. A Longterm Follow-up Study of SLE Patients with Special Reference to Histopathological Findings. *Acta Derm Venereol (Stockh)* 1991; 71:416-422.
- Disdier P, Harlé JR, Andrac L, Verrot D, et al. Primary anetoderma associated with the antiphospholipid syndrome. *J Am Acad Dermatol* 1994; 30:133-134.
- Hodak E, Shamai-Lubovitz O, David M, Hazaz B, et al. Immunologic Abnormalities Associated with Primary Anetoderma. *Arch Dermatol* 1992; 128:799-803.
- Kossard S, Kronman KR, Dicken CH, Scroeter AL. Inflammatory macular atrophy: immunofluorescent and ultrastructural findings. *J Am Acad Dermatol* 1979; 1:325-334.
- Walshe MM. Anetoderma. *Br J Dermatol* 1980; 103(Suppl):56-57.

10. Bergman R, Friedman-Birnbaum R, Hazaz B, Cohen E, et al. An Immunofluorescence study of primary anetoderma. *Clin Exp Dermatol* 1990; 15:124-130.
11. Hodak E, Shamai-Lubovitz O, David M, Hazaz B, Lahav M, et al. Primary Anetoderma associated with a wide spectrum of autoimmune abnormalities. *J Am Acad Dermatol* 1991; 25:415-418.
12. Roberts NM, Farrell A, Woodrow D, Leibowitch M, et al. Anetoderma of Jadassohn-Pellizzari. *J Royal Soc Med* 1995; 88:599-600.
13. Fernández-Galar M, España A, Lloret P. Systemic lupus erythematosus-associated anetoderma and anti-phospholipid antibodies. *Clin Exp Dermatol* 2003; 28:39-42.
14. Macedo de Souza E, Christofolletti Dalton PE, Cintra ML. Anetoderma associated with primary antiphospholipid syndrome. *J Am Acad Dermatol* 2007; 56:881-882.
15. Hodak E, Feuerman H, Molad Y, Monselise Y, et al. Primary anetoderma: a cutaneous sign of antiphospholipid antibodies. *Lupus* 2003; 12: 564-568.
16. Disdier P, Christides C, Andrac-Meyer L, Rojat-Habib Mc, et al. L'Anétodermie au cours du syndrome des antiphospholipides. Trois cas. *Ann Dermatol Venerol* 1996; 123:800-803.
17. Hassan ML, Konopka H, Schroh R. Anetodermia y Lupus Eritematoso. *Med Cut ILA* 1987; 15:341-349.
18. Lindstrom J, Smith KJ, Skelton HG, Redfield R, et al. Increased anticardiolipin antibodies associated with the development of anetoderma in HIV-1 disease. *Int J Dermatol* 1995; 34:408-415.
19. Montilla C, Alarcón-Segovia D. Anetoderma in systemic lupus erythematosus: relationship to antiphospholipid antibodies. *Lupus* 2000; 9:545-547.
20. Sabio JM, Tercedor J, Massare E, Jiménez-Alonso J. Anetoderma associated with systemic lupus erythematosus and antiphospholipid antibodies. *Lupus* 2004; 13:826-827.
21. Stephansson E, Niemi K. Antiphospholipid antibodies and anetoderma: are they associated? *Dermatology* 1995; 191:204-209.
22. Romaní J, Pérez F, Llobet M, Planagumá M, et al. Anetoderma associated with antiphospholipid antibodies: case report and review of the literature. *J Eur Acad Dermatol Veneorol* 2001; 15:175-178.
23. Sparza A, Piette JC, Wechsler Bertrand, Amoura Z, et al. Anetoderma and its prothrombotic abnormalities. *J Am Acad Dermatol* 2003; 49:1008-1012.
24. Gibson GE, Su D, Pittelkow M. Antiphospholipid syndrome and the skin. *J Am Acad Dermatol* 1997; 36:970-982.
25. Miyakis S, Lockshin MD, Atsumi T, Branch DW, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4:295-306.
26. Venencie PY, Bonnefoy A, Gogly B, Gruolt N, et al. Increased expression of gelatinases A and B by skin explants from patients with anetoderma. *Br J Dermatol* 1997; 137:517-525.
27. Ghomrasseni S, Dridi M, Bruno G, Bonnefoix M, et al. Anetoderma. An altered balance between metalloproteinases and tissue inhibitors of metalloproteinases. *Am J Dermatopathol* 2002; 24:118-129.
28. Samaritano LR. Antiphospholipid Syndrome: Review. *South Med J* 2005; 98:617-625.