

CLINICAL REPORT

Anetodermic Lupus Panniculitis and Antiphospholipid Antibodies: Report of Three Cases

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Anetoderma is a rare cutaneous disease characterized by a loss of normal elastic tissue that is presented clinically as localized areas of wrinkled or flaccid skin. This form may be associated with several immunological abnormalities, most notably lupus erythematosus and antiphospholipid antibodies with or without clinical manifestations of the antiphospholipid syndrome. A retrospective study was conducted with the aim of summarizing the clinical characteristics, course and laboratory findings in three women with anetoderma-associated lupus erythematosus panniculitis, an unusual variant of cutaneous lupus erythematosus. The 3 patients (of the 12 patients with lupus erythematosus panniculitis seen by us since 1990) were all at a young age at onset of panniculitis (median, 22 years). None of the patients developed severe systemic involvement up to 9 years (median, 5 years) from onset of the disease. The most noteworthy laboratory finding was the presence of antiphospholipid antibodies. Anetodermic lupus erythematosus panniculitis may be regarded as an uncommon variant of cutaneous lupus erythematosus mainly affecting young females and showing a favourable clinical course, although the patients should be followed and screened for the emergence of antiphospholipid syndrome. Antiphospholipid antibodies could play a role in the elastolytic process, leading to anetoderma. **Key words:** *anetoderma; antiphospholipid antibodies; lupus erythematosus; panniculitis.*

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Anetoderma is a rare cutaneous disease clinically characterized by localized areas of wrinkled or flaccid skin due to a loss of dermal elastic tissue (1–4). In its idiopathic form, termed primary anetoderma, both hormonal factors and infectious agents have been implicated, although the aetiopathogenesis of this form remains elusive. In contrast, secondary anetoderma may be associated with several immunological abnormalities, most notably lupus erythematosus (LE) and antiphospholipid syndrome (APS), raising the

possibility that immunological mechanisms could play a part in dermal elastolysis (5, 6). Within the clinicopathological spectrum of LE, lupus erythematosus panniculitis (LEP) represents an uncommon variant characterized by chronic inflammation and hyaline necrosis of subcutaneous tissue (7), which has only exceptionally been reported in association with anetoderma (8). We present here the clinical findings and course, and the laboratory characteristics of three female patients with anetoderma-associated LEP and antiphospholipid antibodies (APAs), and discuss the possible role of such autoantibodies in the elastolytic process.

PATIENTS AND METHODS

Twelve patients seen in our department from 1990 to 2002 were reviewed on the basis of exhibiting clinicopathological and immunological findings consistent with LEP. Three of them also presenting with anetoderma were selected. These female patients were evaluated for photosensitivity, systemic symptoms and signs associated with LE, such as Raynaud's phenomenon, arthralgias or arthritis, Sjögren's syndrome, presence of clinical discoid lupus erythematosus (DLE) changes on overlying skin or typical DLE lesions at other sites, and precipitating factors, particularly drug intake. Their medical records were reviewed for evolution and response to treatment, and histopathological and immunofluorescence findings of LEP lesions were evaluated. An Alcian blue (pH 2.5) preparation for mucin and Weigert-Van Gieson staining for elastic tissue were also performed. In addition, all patients underwent complete physical and routine laboratory examinations, including blood cell count, erythrocyte sedimentation rate, renal and hepatic function tests, protein electrophoresis and urinalysis. Triiodothyronine, thyroxine and thyroid stimulating hormone levels as well as immunoglobulin (Ig)G, IgA and IgM concentrations and C3 and C4 components of complement were also evaluated. Antinuclear antibodies (ANA), were detected by indirect immunofluorescence (IIF) on HEp-2 cells, anti-double-stranded-DNA (dsDNA) antibodies by IIF on *Crithidia luciliae*, antibodies to extractable nuclear antigens (SSA-Ro, SSB-La, Sm, Scl-70, PM-1, histidyl-tRNA synthetase [Jo-1] and ribonucleoprotein) by enzyme-linked immunosorbent assay (ELISA), anti-histone antibodies by immunoblot, anti-thyroglobulin, anti-thyroid microsomal, anti-mitochondrial and anti-smooth muscle antibodies by IIF. Rheumatoid factor and cryoglobulins were also assessed in serum as well as lupus anticoagulant (LAC), detected using various coagulation tests, and anticardiolipin antibodies, measured by ELISA and expressed as IgM phospholipid (MPL) units (normal limits, <10) and IgG phospholipid (GPL) units (normal limits,

<10), respectively. Anti- β 2-glycoprotein I antibodies could not be evaluated.

RESULTS

Clinical findings

The three patients with anetoderma-associated LEP were 24–29 years old (median 27 years) and median age at onset of LEP was 22 years (range 19–27 years). The duration of the disease ranged from 2 to 9 years. In all three patients, LEP started with an indurated, subcutaneous nodule over the affected site with an overlying erythema in cases 1 and 2. The involved sites were: upper limbs, most notably the lateral aspects of arms (all 3 patients); face (patients 1 and 2); neck (patient 1); back (patient 2); gluteal regions (patient 3). Only patient 1 had clinical evidence of DLE on the overlying skin (Fig. 1a). In all three patients, LEP lesions typically healed with lipoatrophy and scarring, producing large areas of skin contracture and depression (Fig. 1b). After up to 3 years, anetoderma changes developed on the previously involved skin or strictly close to the LEP lesions. Anetoderma was characterized by pink to reddish, oval, well-circumscribed and atrophic skin lesions, ranging from 1 to 4 cm in diameter (Fig. 1c). They protruded over the level of the surrounding skin, and their surface was flaccid and wrinkled, pressure with a finger revealing a characteristic herniation phenomenon.

Recurrent attacks of fever occurred in patient 1, who also complained of non-erosive arthritis involving some peripheral joints. On nail-fold capillaroscopy, this patient (who also suffered from Raynaud's phenomenon) showed elongation, tortuosity and aneurysmal dilatation of capillaries, thus fulfilling the American Rheumatism Association (ARA) criteria for diagnosis of systemic LE. No other systemic findings were observed, except in patient 2 who had arthralgias. The medical and surgical histories of all three patients were unremarkable, without any report of arterial or venous thrombosis; furthermore, none of the three had

pregnancies. The clinical course was recurrent over several years with relapses of new subcutaneous nodules that responded to antimalarial agents and/or systemic steroids, but without significant changes in anetoderma lesions. It is noteworthy that none of the three patients had taken any drugs other than those for LE and none had used oral contraceptives.

Laboratory findings

Patient 1 showed a low C3 (63 mg/dl; normal, 90–180) and slight proteinuria (216 mg/24 h; normal, <150 mg/24 h). The erythrocyte sedimentation rate was normal in all cases, while ANAs were present, up to 1/160 with homogeneous pattern, in all patients. Patient 3 had both anti-SSA-Ro and ribonucleoprotein antibodies. Prolonged activated partial thromboplastin time (APTT: 57.2 s in patient 1, 59.3 s in patient 2, and 60.1 s in patient 3, respectively; normal, 30–40) was demonstrated, and LAC was detected in all patients. Interestingly, anticardiolipin antibodies of both IgM and IgG type, were also found in all subjects: in patient 1 the titres were 18 MPL and 80 GPL (low positivity, 10–20; medium positivity, 20–80; high positivity, >80); in patient 2, 16 MPL and 182 GPL and in patient 3, 20 MPL and 131 GPL, respectively.

Immunofluorescence and histopathology

In all three patients, direct immunofluorescence demonstrated granular deposits of IgM and C3 along the dermo-epidermal junction in both LEP and anetoderma lesions.

All three cases showed similar changes in skin biopsy specimens of LEP lesions, namely the presence of infiltrates within the dermis and, more prominently, in the fat lobules and in the septa (Fig. 2a); the infiltrates were mostly composed of lymphocytes and histiocytes with a few plasma cells. Some lymphoid nodules with germinal centres were present within the adipose tissue lobules or in a paraseptal distribution (Fig. 2b). With

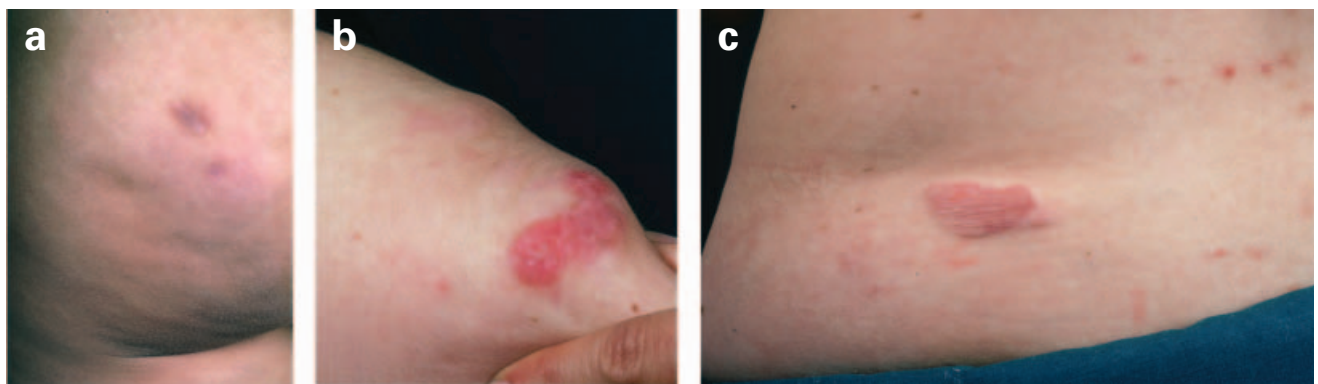


Fig. 1. Lipoatrophy and deep depressions associated with both DLE and anetoderma lesions: (a) over the lateral aspects of the arm (patient 1); (b) the oval anetoderma lesion on the back (patient 2); and (c) skin contracture and depression on the left gluteal region (patient 3).

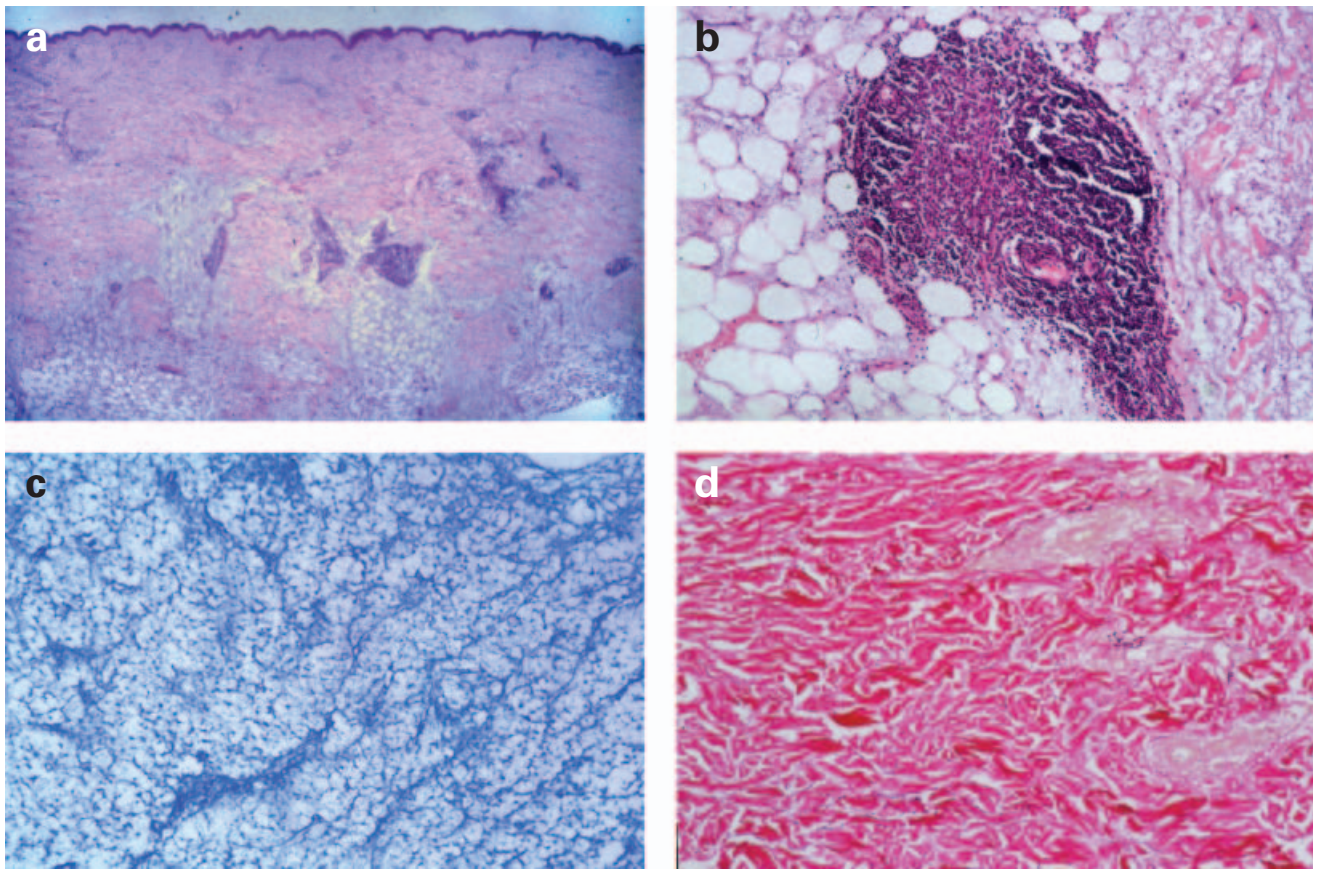


Fig. 2. (a) Inflammatory infiltrates within the dermis and, more prominently, within the fat lobules with hyaline fat necrosis (haematoxylin-eosin stain; original magnification $\times 100$; patient 2, back, subcutaneous nodule). (b) A lymphoid nodule with a germinal centre within an adipose tissue lobule ($\times 400$; patient 3, gluteal nodule). (c) Abundant mucin deposition throughout the dermis in case 3 (Alcian blue, $\times 400$; gluteal nodule). (d) Loss of elastic fibres in the dermis of an anetoderma lesion in patient 1 (Weigert-Van Gieson $\times 400$; lateral aspects of the arm).

Alcian blue stain at pH 2.5, abundant mucin deposition throughout the dermis was found in case 3 (Fig. 2c). Histological features diagnostic of DLE of the overlying epidermis and dermis were seen in case 1, and included epidermal atrophy, follicular plugging, hydropic degeneration of basal cells and superficial and deep perivascular lymphohistiocytic infiltrate. Histopathological examination of anetoderma lesions disclosed a slightly atrophic epidermis with a very discrete perivascular lymphocytic infiltrate in the dermis. Weigert-Van Gieson stain revealed a marked decrease in elastic fibres in the dermis and those remaining were thin, irregular and unstructured (Fig. 2d).

DISCUSSION

LE is one of the diseases that has traditionally been associated with anetoderma, including reports on 13 cases of SLE (5, 9), 14 cases of DLE (5, 10) and 3 cases of LEP (8). Despite this fact, a definitive relationship between LE and anetoderma has not been proven. However, the association between anetoderma and

APAs has been documented previously (5, 6, 11, 12), as well as a relationship between LE and APAs (5, 6, 11, 13, 14). Stephansson & Niemi (11), reviewing a group of SLE patients with and without APAs, observed that 15% of those with positive APAs developed anetoderma, while none of those without these antibodies developed this skin condition. On the basis of this study, a closer relationship of anetoderma with APAs than with LE itself has been suggested. As regards the pathophysiological role of APAs in anetoderma, some authors hypothesized that microthromboses in the dermal vessels could account for the development of local ischaemia, leading to degeneration of elastic tissue (11, 12, 15). Conversely, the destruction of elastic fibres may also be immunologically mediated: it has been suggested that APAs bind directly to the elastic fibres because of the presence of an antigen epitope that is phospholipid-related, possibly apolipoprotein H (12). We present in this report the clinical, histological and immunological findings of three patients with anetodermic LEP associated with APAs; to the best of our knowledge, such an association has not been reported

previously. Our three patients, who represented one-quarter of the total number of patients with LEP seen in our department since 1990, were all females with a young age at onset of LEP lesions (median 22 years). Similar to previous reports (16, 17), there was a predilection for the LEP skin lesions to appear on the upper limbs and face in our series. All three patients were alive and none developed severe systemic involvement after up to 2–9 years follow-up from onset of the disease. The clinical course was recurrent over several years with relapses of new LEP lesions that responded to antimalarial agents and/or systemic steroids. Thus, in spite of the fact that one of our patients fulfilled ARA criteria for the diagnosis of SLE, the prognosis in our series seems to be favourable, like the prognosis of LEP in general. Interestingly, after 1–3 years, anetoderma developed on the previously involved skin or close to the LEP lesions, suggesting a direct link between LEP and anetoderma, with APAs as possible triggering factors in the elastolytic process. The pathomechanisms triggering anetoderma in these patients remain unclear. Cutaneous inflammation of LEP as well as local non-inflammatory processes, such as microthromboses, or vasculitis induced by APAs might lead to anetoderma. However, histologically, we were not able to demonstrate vasculitis in LEP or anetoderma skin biopsy specimens from all of our patients, possibly because we have not been able to examine specimens at the time of onset of anetoderma lesions. On the other hand, the occurrence of vasculitis may be a possible explanation for the rather rapid development of anetoderma in case 3, as compared with the other two patients. It is noteworthy that all three patients exhibited LAC and anticardiolipin antibodies, the latter being a laboratory marker of the APS (18). APS may arise as a primary disease or may be associated with other diseases, most frequently SLE (19). On the other hand, considering that patients with APAs and anetoderma may develop APS (11), anetoderma is now regarded as one of the cutaneous manifestations of this syndrome. However, the revised international criteria for the diagnosis of APS (20), also comprising vascular thrombosis and/or complications of pregnancy, were not fulfilled in our cases and no specific treatment was prescribed.

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