Anetoderma Associated with Lyme Disease: A Case Report

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Accepted April 21, 2008.

Sir,

Anetoderma is a rare skin disease characterized by circumscribed areas of wrinkled, atrophic or slack skin due to the loss of elastic tissue in the dermis (1). Histologically, it is characterized by a decreased amount of dermal elastic tissue and variable levels of inflammatory infiltrate.

Currently, anetoderma is classified as either a primary or secondary form. The aetiopathogenesis of anetoderma is unknown. The frequent association of anetoderma with immune-mediated diseases and finding immunoglobulin at the anetodermic lesions suggests a possible immunological mechanism in the fragmentation and/or loss of elastic fibres (2).

CASE REPORT

A 42-year-old woman presented with a history of progressive, asymptomatic eruption that had developed over the last 10 years. Dermatological examination revealed multiple, oval, skin-coloured macules with a wrinkled surface, measuring about 1 cm or less in diameter. The macules were located on the lower abdomen, on the back and on the limbs (Fig. 1). Some small patches of vitiligo had also been present for more than 10 years on her trunk, armpits, lower limbs and hands.

The patient had a history of neurological disorders for at least 2 years, confirmed by neuropsychological examination. Cranial nuclear magnetic resonance (NMR) showed no cerebral abnormalities.

Recurrent arthralgia of the small joints of the hands, as well as diffuse myalgia, asthenia and, recently, subjective cardiac abnormalities were also described. From the general physical examination, muscle enzymes, electrocardiography and echocardiography were all found to be within normal limits.

A long history of iron-deficiency anaemia, Gilbert syndrome and allergic rhino-conjunctivitis was also reported. Full blood count, urinalysis, erythrocyte sedimentation rate, liver, renal and thyroid functional tests, were normal. IgM, IgG, IgA, IgE, C3 and C4 levels were normal. A slight iron-deficiency anaemia and hyperbilirubinaemia were detected. Antinuclear antibodies, human immunodeficiency virus antibodies, hepatitis B and C surface antigens were not detected.

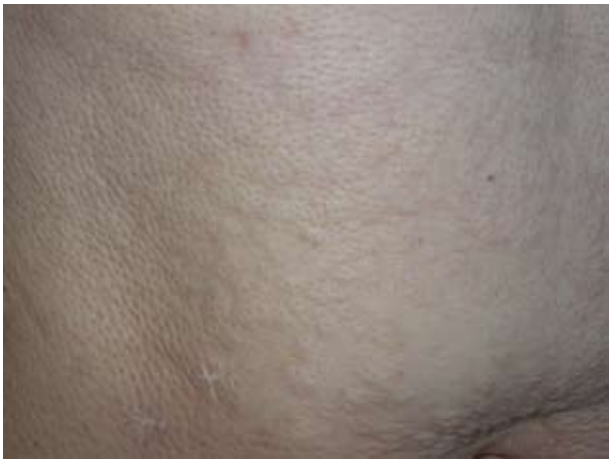

Fig. 1. Non-inflammatory macules on the lower abdomen.

Serology for *Borrelia* with enzyme-linked immunoassay (ELISA) test showed a slight increase in both IgG (44 U/ml; normal <20) and IgM (32 U/ml; normal <20).

Skin biopsy of the abdominal macules of slack skin confirmed the diagnosis of anetoderma. Weigert's stain revealed fragmentation and the decrease or total absence of the elastic fibres.

PCR analysis was performed in two distinct laboratories with different PCR techniques. In one case PCR analysis was performed on DNA obtained from blood and formalin-fixed paraffin-embedded skin biopsy, as previously reported (3).

Parallel, nested-PCR was performed for the detection of *B. burgdorferi* on DNA obtained from fresh specimens from skin lesions, blood and urine. A third cutaneous biopsy was inoculated in 7 ml of modified Barbour-Stoenner-Kelly (BSK) II medium under microaerophilic conditions at 34ºC in order to assay *Borrelia* growth. The culture medium was also analysed by nested-PCR after 3 days of incubation. DNA was extracted from 5 ml of *Borrelia* cultures using a High Pure Template Preparation Kit (Roche Diagnostics GmbH, Mannheim, Germany), according to the manufacturer's instructions. Five ml of fresh BSK medium were added to the remaining 2 ml of *Borrelia* culture, incubated for 2 weeks, and then observed every 3 days under dark-field microscopy. DNA was extracted from the different specimens as already described (4) and analysed using a primer set specific for a portion of the *ospA* gene (5, 6).

The *Borrelia* species was genotyped as previously reported (4).

One-step PCR analysis for flagellin was positive both for the blood and formalin-fixed skin biopsy (Fig. 2A). Nested-PCR was positive for DNA obtained from a fresh skin lesion, from peripheral blood and from the medium tissue culture, whereas the test performed on urine was negative (Fig. 2B). *B. burgdorferi* was cultured. *B. afzelii* genotype was identified from analysis of the nested-PCR products.

The diagnosis of Lyme disease was made on the basis of clinical and laboratory data. The patient underwent an antibiotic treatment with penicillin G 20 millions U/day i. v. divided in 4 doses daily for 14 days as well as a specific antidepressive therapy.

After 6 months, *Borrelia* could not be detected in serum samples. As neurological and myoarticular disorders persisted, a second antibiotic treatment with amoxicillin 1 g $\times$ 2/day *per os* for 21 days was given. During the following 6 months no new anetodermic lesions were observed. Myoarticular symptoms improved significantly, whereas the patient continued to complain of lack of concentration, memory deficit disorders and mood depression.

DISCUSSION

This report describes the coexistence in the same patient of anetoderma, vitiligo and Lyme disease. Lyme borreliosis is a multisystemic disease transmitted by

 ISSN 0001-5555
doi: 10.2340/00015555-0513

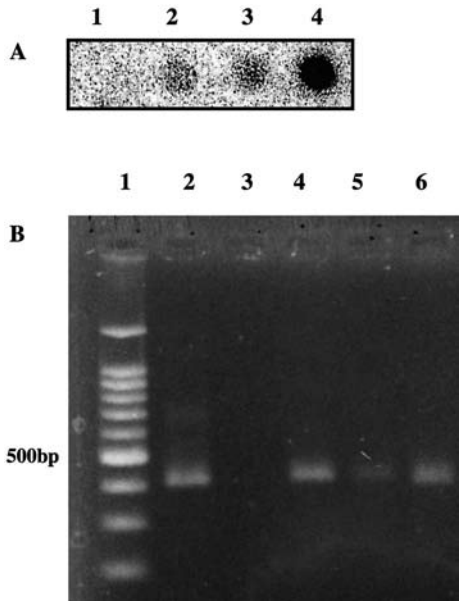

Fig. 2. (A) Autoradiography of the dot blot. 1: negative control; 2: PCR analysis on DNA obtained from formalin-fixed and paraffin-embedded skin biopsy; 3: PCR analysis on DNA obtained from peripheral blood; 4: positive control. (B) Agarose gel of the nested-PCR amplicons. 1: 100-base-pair ladder; 2: positive control; 3: nested-PCR on DNA obtained from urine; 4: nested-PCR on DNA obtained from peripheral blood; 5: nested-PCR on DNA obtained from fresh skin biopsy tissue; 6: nested-PCR obtained from the analysis of cell culture medium.

Ixodes ticks. Its aetiological agent is *B. burgdorferi*. The clinical picture and course of the disease can be highly variable. Dermatological manifestations include erythema migrans, borrelial lymphocytoma and acrodermatitis chronica atrophicans, but other types of sclerotic and atrophic lesions have also been reported (7). Anetoderma is a benign condition whose aetiopathogenesis remains unknown.

Laboratory and clinical data were consistent with the diagnosis of Lyme borreliosis. The patient had been living in a region endemic for Lyme disease until 1978, but she had not noticed any tick bites or migratory erythema during that period.

The diagnosis of anetoderma was made on the basis of clinical and histopathological features.

To our knowledge it is the first time that *Borrelia* has been isolated from anetoderma skin biopsy. Different studies have reported on the possible relationship between borrelial infection and anetoderma (8). In our case we detected borrelia DNA in both skin biopsy and blood using two distinct PCR assays, performed in different laboratories (Fig. 2). Moreover, we were able to identify the borrelia genotype. Serology demonstrated a slight increase in both IgG and IgM. Clinically the patient reported a 2-year history of myoarticular symptoms, which decreased after a specific antibiotic treatment for borrelial infection, whereas only a mild improvement of neurological symptoms was observed.

Vitiligo is a relatively common, acquired leukoderma in which endocrine and autoimmune disorders are observed with significant frequency (9). To our knowledge, there are no data supporting any correlation between vitiligo and borrelial infection.

The hypothesis of a pathogenetic relationship between anetoderma and Lyme disease is supported by some epidemiological and clinical findings. Anetoderma seems to be more frequent in Central Europe, as is acrodermatitis chronica atrophicans. Moreover, in some cases anetoderma has been reported with acrodermatitis chronica atrophicans, and an association between anetoderma and borreliosis has been described recently (8, 10).

Anetoderma is frequently associated with several autoimmune disorders (1). Phagocytosis of elastic fibres by macrophages has been observed in primary anetoderma (11). More recently Venencie et al. (12) found increased levels of pro-matrix metallo-proteinase-2 (pro-MMP-2), -9 (pro-MMP-9) and activated gelatinase A (MMP-2) in tissue cultures of anetodermic skin, suggesting their probable role in the destruction of cutaneous elastic fibres. An altered balance between metalloproteinases and their tissue inhibitors in anetodermic skin, has also been described (13). These findings suggest that the immune system may be involved in the elastolytic process within anetodermic lesion (13).

Several reports have demonstrated that *B. burgdorferi* is able to stimulate human monocytes, neutrophils, fibroblasts and keratinocytes in producing some matrix metalloproteinase. These proteases, by increasing bacterial penetration through the extracellular matrix component barriers, could explain the mechanism of bacterial migration in cutaneous lesions of patients with Lyme disease and allow the spirochetal dissemination to distant organs. Compartmentalization of the immune response at the skin, triggered by the persistence of *Borrelia* and the subsequent local production of some proteases, could represent the pathogenetic mechanism that has led to elastolysis in our case (14, 15).

Borrelia infection could play a significant part in anetoderma aetiopathogenesis. Hence, we suggest performing laboratory tests for *B. burgdorferi* and autoimmune disorders in any case of anetoderma. In cases positive for *Borrelia,* an appropriate antibiotic treatment could prevent progression of anetoderma lesions and could be effective for other possible manifestations of Lyme disease.

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