

Letter to the Editor

Linear scleroderma ‘en coup de sabre’ associated with facial atrophy in a patient seropositive for *Borrelia burgdorferi*: a true case of molecular mimicry?

Sir,

Borrelia burgdorferi has been linked to the pathogenesis of localized scleroderma (LSc) and lichen sclerosus et atrophicus. However, considerable controversy still exists as to the actual role. We describe a peculiar presentation of linear scleroderma ‘en coup de sabre’ associated with facial atrophy in a patient seropositive for *B. burgdorferi*, raising the possibility that this spirochete might trigger the clinical appearance of this disease. Infectious agents may act as triggers of autoimmune skin diseases via direct damage or molecular mimicry, because of homologies between microbiologic proteins and skin. Increasing clinical and experimental evidences suggest, in fact, the possible association of infectious agents with autoimmune diseases, and cross-reactivity between host self-antigens and microbial determinants was also observed. Infecting pathogens express peptides that are similar in structure or sequence to particular self-components, and this may induce autoimmune responses (1, 2).

Case report

A 10-yr-old girl presented with band-like sclerotic lesion on the right frontoparietal region, mild facial palsy, eyelid ptosis, nose-labial furrow smoothing, deviation of the mouth to the left and chewing muscles spasms. One year before, her parents had noticed a hyperpigmented spot on the right side of her forehead, which gradually began to spread upward to the scalp and downward to the nose. The lesion was asymptomatic and not preceded by trauma; no history of tick bite or typical symptoms of Lyme disease were reported. Clinical examination revealed an

atrophic, shiny, brownish-yellow plaque situated on the forehead and frontal area, extending from the parietal region downward to the bridge of the nose, in the paramedian area, and to the chin. In this area, a remarkable atrophy and sclerosis of skin and underlying tissues was present (Fig. 1a). Moreover, a deep subcutaneous cleft above the right eyebrow with rarefaction of the eyebrow was also visible (Fig. 1b). The overlying skin was smooth, shiny and fixed to the underlying structures with no perilesional erythema. The tongue, gingiva and palate were not involved.

The parents of the child refused to allow skin biopsy, being apprehensive of more damage to her face. Routine blood chemistry and urinalysis were normal; search for a number of serum autoantibodies (antinuclear, anti-ENA, anti-JO1, and anti-Scl70) was negative. Instead, high titers of serum antibodies against *B. burgdorferi* were detected by both enzyme immunoassay [immunoglobulin M (IgM) > 160 IU/ml and IgG > 75 IU/ml] and enzyme-linked fluorescent immunoassay for the detection of total IgG and IgM (VIDAS Lyme IgG and IgM, BioMérieux, Marcy-l’Etoile, France; test value, 1.66, negative, <0.75). To confirm these suggestive positive findings, we evaluated the presence of *Borrelia* proteins in the serum of our patient with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) immunoblotting. The result showed the presence of 39, 41, 22 and 31 kDa bands (Fig. 2).

Electroencephalography, electrocardiography, abdominal sonography, axial computed tomography and cranial magnetic resonance imaging did not yield abnormalities. Electromyography brought into evidence a reduced conduction speed of right facial muscles.

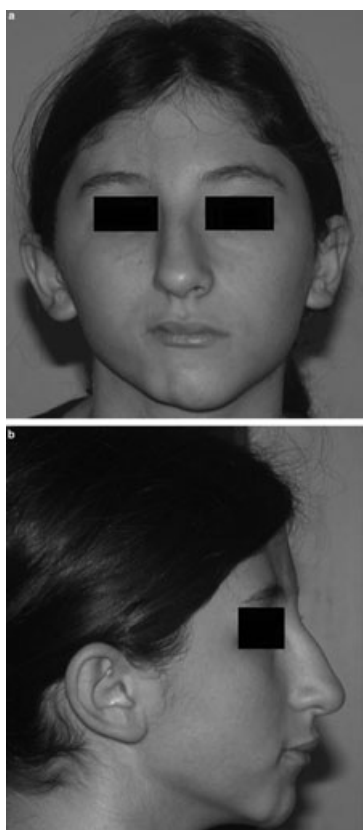


Fig. 1. (a) The 10-yr-old girl with mild facial palsy, ptosis and marked atrophy of subcutaneous structures on the right upper side of the face; (b) note the deep subcutaneous cleft above the right eyebrow.

Localized scleroderma is a chronic inflammatory disease of the connective tissue, clinically presenting as a band of sclerotic, hyperpigmented, and hypopigmented skin. Its prevalence is higher in children and adolescents, particularly in females. It usually involves the skin and subcutaneous tissue only; however, neurologic, ophthalmologic and skeletal abnormalities, as well as facial atrophy, are not infrequently observed. Association with systemic manifestations or other autoimmune diseases is, instead, rare.

In the last few years, a close relationship between LSc and *B. burgdorferi*, the etiologic agent of Lyme disease, has been hypothesized (3, 4). Lyme disease is, in fact, a multisystem illness, and in its course are sometimes present cutaneous manifestations clinically and histopathologically similar to sclerotic lesions (5). However, the actual role of *B. burgdorferi* in the development of LSc is still debated (6–10).

Molecular mimicry has been proposed as a possible mechanism in the pathogenesis of autoimmune and inflammatory skin diseases (11, 12).

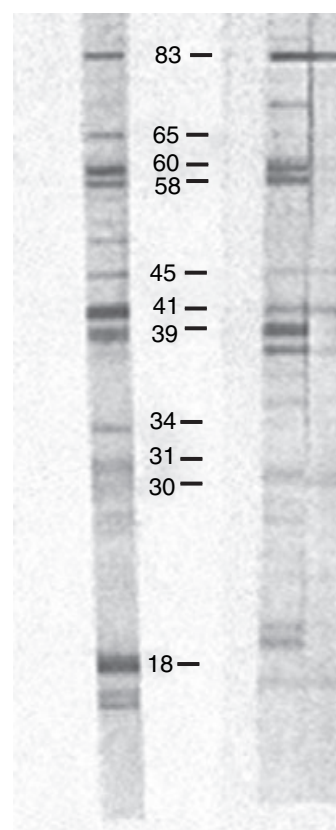


Fig. 2. Immunoblotting showing the presence of 39, 41, 22 and 31 kDa bands.

Increasing epidemiologic and clinical observations suggest the association between infections and autoimmune diseases, and experimental evidences of epitopes shared by microbial and human molecules strengthen this hypothesis. Infectious agents may act as triggers of skin reactive diseases via either direct damage or molecular mimicry (because of amino acid sequence homologies between microbiologic and cutaneous proteins), with subsequent activation of autoreactive T-lymphocytes.

In LSc, elevated serum levels of Th₁ type cytokines [interleukin (IL)-1 α , IL-1 β , IL-2, interferon (IFN)- γ] were found (may be consequential to an abnormal response to excessive production of IL-1), suggesting their involvement in the pathogenesis of the disease by Th₁/Th₂ imbalance (13–15).

Infectious agents can up-regulate Th₁ cytokines, thereby increasing selected expression of molecules such as major histocompatibility complex glycoproteins, as well as activation and co-stimulatory molecules, leading to imbalance in the immune response (1). Moreover, previous studies indicate that *B. burgdorferi* selectively induces human T cells with a Th₁-like cytokine

secretion profile (5, 16). These events were observed in several studies on the etiopathogenesis of LSc (13–15), suggesting that infections may be associated with the development of sclerotic lesions.

Some authors recently reported that a T-cell epitope (amino acids 165–173) of *B. burgdorferi* outer surface protein A (OspA) has significant homology with a fragment of human LFA-1 α (leukocyte function-associated antigen 1 α) (amino acids 332–340), and hypothesized that this could lead, through molecular mimicry, to an inappropriately prolonged production of inflammatory mediators even after complete elimination of the spirochete (17). The likelihood of this hypothesis has been confirmed by Trollmo et al., who showed that OspA-specific T cells significantly respond to stimulation with the above-mentioned fragment of human LFA-1 α (18). Moreover, other authors showed that expression of LFA-1 and ICAM-1 (intercellular adhesion molecule 1) is increased in the course of LSc, and significantly correlated with disease severity (13, 15), strengthening the idea that 'cross-reactivity' between OspA and LFA-1 α could play a role in perpetuating the chronic inflammatory process, contributing to the pathogenesis of fibrosclerotic lesions.

In conclusion, although it is likely that genetically predisposed subjects can develop abnormal immune response because of an antigen mimicking a self-protein, clear evidence that molecular mimicry is a mechanism for the induction of autoimmunity is, to date, available only for a limited number of diseases. The progress in the identification of microbial peptides, together with a better understanding of the epidemiology of infectious agents and of autoimmunity, will allow a better comprehension of the molecular mechanisms triggering autoimmune diseases.

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