Case report

ERYTHEMA MIGRANS FOLLOWING ACRODERMATITIS CHRONICA ATROPHICANS - FURTHER EVIDENCE FOR POSSIBLE REINFECTION WITH BORRELIA BURGDORFERI

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ABSTRACT

A 57-year-old woman, living in an area endemic for Lyme borreliosis (LB), presented with erythema migrans (EM) that developed four weeks after a tick bite on the left thigh. The serum ELISA IgG antibody titre against Borrelia burgdorferi (Bb) was highly positive. The patient was treated with minocyclin (200 mg/day, 14 days). Upon completion of therapy, the EM had cleared completely. Two years earlier, however, a diagnosis of acrodermatitis chronica atrophicans (ACA) on the left forearm and hand had been made on clinical as well as histopathological grounds. The serum ELISA IgG antibody titre against Bb was highly positive at that time also. A course of treatment with peroral amoxicillin (500 mg) and clavulanic acid (125 mg) three times a day (three weeks) led to marked improvement of the ACA skin changes. No more signs of this inflammation were found when the patient presented with EM. Many questions concerning molecular and immunologic aspects of LB remain open, especially the extent to which Bb antibodies protect against reinfection. The occurrence of EM in a patient who has previously had ACA may be explained by reinfection with Bb. Thus, the presented case substantiates the hitherto held suspicion that infection with Bb does not necessarily lead to protective immunity.

KEY WORDS

Lyme borreliosis, acrodermatitis chronica atrophicans, erythema migrans, reinfection, immunity

INTRODUCTION

Lyme borreliosis (LB) is caused by the spirochete Borrelia burgdorferi (Bb), of which at least three subtypes have been described (Bb sensu stricto, Borrelia garinii, Bb group VS 461) (1,2). LB can be subdivided into three stages, and nearly all organs may be affected. Skin manifestations are seen most frequently, and may occur during all stages of the disease. Erythema migrans (EM) is the hallmark of the early stage of LB, developing at the site of inoculation of Bb. Acrodermatitis chronica atrophicans (ACA) is a late, chronic skin manifestation of LB, arising months to years after infection with Bb. According to current knowledge, it appears that the human immune response to Bb infection does not necessarily lead to protection against renewed Bb infection (3). Simultaneous or subsequent occurrence of EM and ACA, due either to superinfection or reinfection, have been reported (4,5,6,7). Superinfection is possible by transmission of two different subtypes of Bb (5). Reinfection may be explained by the lack of protective immunity resulting from Bp infection (3). This report considers a 57-year-old woman, living in an area endemic for LB, who presented with EM on her left thigh, and had a history of ACA two years previously. This situation may be explained by reinfection with Bp.

CASE REPORT

In December 1991, a then 55-year-old woman was seen at the Department of Dermatology in Graz, Austria. She presented with an one year history of a diffuse red swelling together with signs of skin atrophy on the ulnar aspect of her distal left forearm and hand, consistent with the clinical diagnosis of ACA (Fig. 1). The serum ELISA IgG antibody titre against Bb was highly positive; no IgM antibodies were found. Histopathologic examination of a punch biopsy, taken from the left forearm, confirmed the clinical diagnosis. Said examination revealed a perivascular and interstitial inflammatory infiltrate within the dermis, cytomorphologically characterized by a predominance of lymphocytes and plasma cells (Fig. 2). Peroral treatment with amoxicillin (500 mg) and clavulanic acid (125 mg) three times a day was given for three weeks, which led to marked improvement of the skin changes. Two years later, the patient was seen again, this time with a ring-shaped, sharply demarcated erythematous skin lesion of 30 cm diameter on the left thigh, clinically consistent with EM (Fig. 3). The erythema first occurred 6 weeks before admission, and expanded centrifugally during this time. Four weeks before the onset of EM, the patient was bitten on the left thigh by a tick in a geographic region endemic for LB. Inguinal lymph nodes were swollen, and the patient complained of malaise. A punch biopsy from the border of the erythematous lesion was taken. Histopathologic examination revealed a moderately dense, superficial and deep, perivascular infiltrate of lymphocytes, histiocytes and plasma cells, thus supporting the clinical diagnosis of EM (Fig. 4). The left forearm and hand, previously affected by ACA, displayed skin which was wrinkled, but no sign of inflammation. The serum ELISA IgG antibody titre against Bb was highly positive, the IgM titre was negative. Blood chemistry was within normal limits, only the BSR was slightly elevated. An ECG and echogram of the heart, a neurologic examination, and electromyography (upper and lower extremities) disclosed no pathologic findings. Treatment

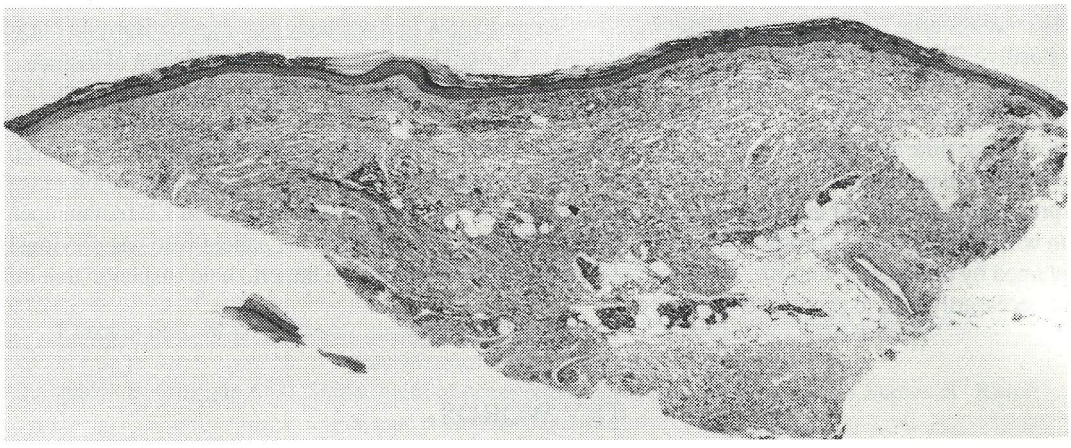

Figure 2: Histopathology of acrodermatitis chronica atrophicans. Epidermal atrophy, bandlike inflammatory infiltrate composed of lymphocytes and plasma cells, and telangiectatic blood vessels in the upper dermis; reduction of the breadth of the dermis. H&E, scanning magnification.

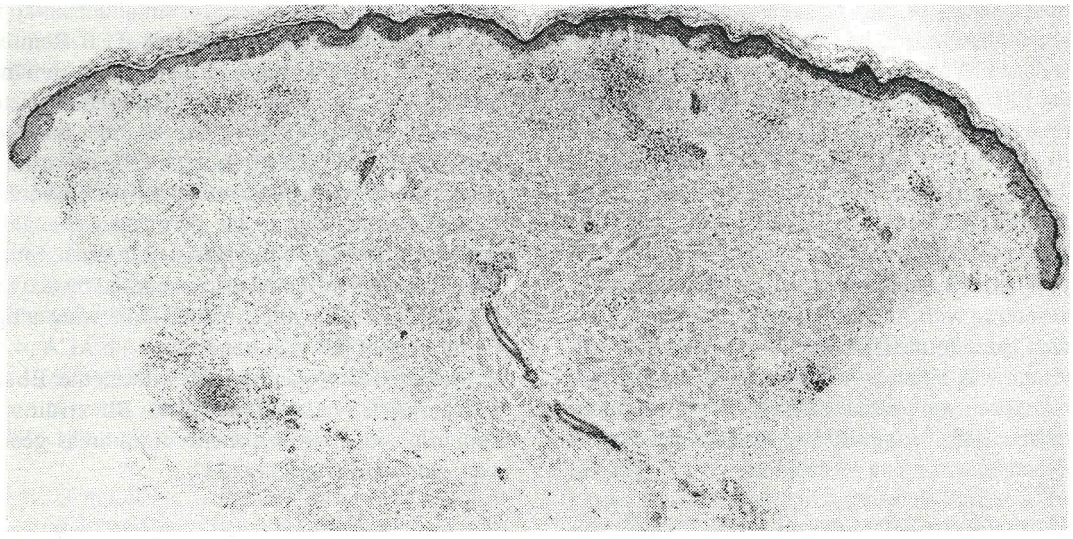

Figure 4: The histopathological features from a biopsy specimen of the left thigh are consistent with erythema migrans. H&E, scanning magnification.

with minocycline (2 x 100 mg daily, 14 days) was instituted. By the end of therapy, the EM had cleared completely. The IgG antibody titre against Bb remained highly positive, the IgM titre was still negative.

DISCUSSION

EM is the typical manifestation of early LB, arising at the inoculation site of Bb, days to months after a tick or insect bite. Initially, a homogeneous red or bluish-red lesion occurs. Later, a bright red, expanding ring with a fading centre develops in most cases. Serology is not very helpful in diagnosis, because positive antibody titres against Bb are only found in 20 - 50 % of the cases (8). Histopathology is nonspecific, but some features - as found in the EM specimen of the patient described - may support the diagnosis, namely a superficial and deep perivascular infiltrate, composed of lymphocytes and plasma cells. EM usually disappears within a few months, even without therapy. Nevertheless, early treatment with oral antibiotics is necessary to prevent complications.

ACA is a late skin manifestation of LB with a chronic, and usually progressive course. It begins months to years after Bb infection with an acute inflammatory stage. The predilection sites are the acral body parts. It predominates in women and in the later decades of life. The skin lesions gradually develop into the chronic atrophic stage. The diagnosis of ACA is primarily based on clinical criteria. The histopathologic features, as observed in our patient, are characteristic, and confirm the diagnosis of ACA. Elevated IgG antibody titres against Bb are found in nearly all patients with ACA (9). On the other hand, seroprevalence in Europe ranks between 3 % and more than 40 % (10, 11).

In our patient, IgG antibodies against Bb were highly positive in 1991, a well known finding in patients with ACA (9). It is not possible to determine the extent to which EM has influenced the still highly positive IgG antibody titre in 1993.

Many immunologic issues in LB remain unclear. An essential point concerns the question, whether or not Bb antibodies protect against a repeat infection, and if so, for how long. Animal experiments have demonstrated the capability of Bb antibodies in defence against infection. However, spirochetes already residing in the tissue cannot be effectively attacked by these antibodies (12, 13). Moreover, the protective effect of these antibodies seems to be limited (14). From human medicine, it is known that specific antibodies and T-cells develop in LB (15, 16). However, it is unlikely that these mechanisms provide truly a protective immunity (3). Reports of the subsequent occurrence of the same or different manifestations of LB support the possibility of reinfection due to a lack of such protective immunity. As early as 1955, Hauser described EM preceding ACA in a few patients (17). In the recent literature, a preceding EM has been found in about one fifth of a Swedish study group of 50

patients with ACA (6). In a German study, 2 out of 21 patients with ACA had a history of EM (7). Furthermore, Weber and co-workers have observed reappearence of EM in two patients. These secondary EM usually developed more than one year after the first EM in another part of the body (18). Possible reinfection has also been described by Pfister and co-workers in 1986 (19). There are also reports about EM arising in patients already suffering from ACA, possibly due to superinfection. (4, 20).

Recently, Wienecke and co-workers published the case of a patient presenting with ACA following a tick bite 4 years before he first came to medical attention (5). Three weeks later, the patient was bitten by another tick, and developed EM at this site. Biopsies were taken, and a Bb-specific gene segment was successfully amplified by PCR from both ACA and EM. Molecular subtyping revealed the VS 461 group of Bb in the ACA lesion. Bb sensu stricto and Borrelia garinii were identified within the EM. Thus, the case of Wienecke and co-workers may be interpreted as a superinfection by two borrelia subtypes during persistent infection with a third one. The authors conclude that an infection with one Bb subtype does not lead to immunity against infection with other subtypes.

Considering the presented literature, various interpretations are possible of the subsequent or simultaneous appearence of the same or different manifestations of LB. Reinfection (6, 7, 17, 18, 19) might be due to an insufficient immune response to one of the three subtypes of Bb (Bb sensu stricto, Borrelia garinii, Bb group VS 461). On the other hand, reinfection could be caused by a Bb subtype different from the one in primary infection, against which no specific antibodies have been produced. Due to the permanent change in surface proteins of Bb after it has persisted in tissue for a long time (21), "reinfection" could also be caused by activation of Bb (e.g. during another infection (22)) following antigenic shift. Occurrence of EM simultaneously with ACA (4, 5, 20) may be explained by a superinfection with another Bb subtype (5). Furthermore, heterogeneity of Bb strains has been demonstrated, even in patients from areas geographically very close to one another (23).

In conclusion, this case report of a patient who developed EM two years after having had ACA lends further weight to the concept of reinfection with Bb. Our observation further emphasizes that protective immunity does not necessarily develop in patients with LB.

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