

CASE REPORT

Nodular fasciitis, erythema migrans, and oligoarthritis: manifestations of Lyme borreliosis caused by *Borrelia afzelii*

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We describe a 35-year old patient with nodular fasciitis, erythema migrans, and gonarthrosis four months after a bite of a *Borrelia afzelii* infected tick. The *Borrelia afzelii* infection was identified by a polymerase chain reaction and direct sequencing of the amplification product. *Borrelia*-specific DNA was also detectable in nodular fasciitis tissue. We therefore conclude that *Borrelia afzelii* can be a causative agent of nodular fasciitis and Lyme arthritis in a highly endemic region of Northern Germany.

Key words: nodular fasciitis, *Borrelia afzelii*, Lyme arthritis

Nodular fasciitis (NF) was first described by Konwaler et al. in 1955 (1). It defines an inflammatory myofibroblastic tumor with some histological similarity to sarcomas. Therefore it can be subsumed under a group of tumor-like lesions called pseudosarcomas. Although it appears as a rapidly growing nodule it is not a neoplasm but an inflammatory process of unknown etiology, often preceded by trauma or infection. It typically occurs on the upper extremities of young adults but many other localisations have been described (2).

Lyme borreliosis (LB) is a tick borne infectious disease caused by the spirochete *Borrelia burgdorferi*, first described as an epidemic oligoarthritis in three Connecticut communities (3). Five years later a spirochete was identified as the etiologic pathogen (4). According to molecular studies *Borrelia burgdorferi sensu lato* (*Bbsl*) has been divided into several genospecies of which *B. burgdorferi sensu stricto* (*Bbss*), *B. afzelii* (*Ba*), and *B. garinii* (*Bg*) are known to be pathogenic for humans. While *Bbss* is the only pathogen causing LB in the United States, all three species are implicated in human disease in Europe. Direct molecular typing and determination of bacteria specific antibodies revealed a predominant association of *Ba* with acrodermatitis chronica atrophicans, of *Bg* with neurologic manifestations, and of *Bbss* with arthritis, whereas erythema migrans can be caused by all species (5–7). Besides the strain variability differences in the physicians' awareness might also

have an important influence on the variety of clinical characteristics described on different continents (8).

Case report

The patient, a 35-year-old man, discovered a tick bite in the left popliteal fossa 48 hours after gardening in Northern Germany in May 2000. The tick was still fixed to the skin and was completely removed by using a fine-toothed forceps. It was transferred to the rheumatology laboratory of Hannover Medical School and tested for *Bbsl* infection by PCR. DNA-extraction was performed by using Cetyltrimethylammoniumbromide (CTAB) and the QIAEX II gel extraction kit (Qiagen, Hilden, Germany) as described elsewhere (9). The nested PCR (10) targeted a *Bbsl*-specific 146 base-pair fragment of the outer surface protein A (*OspA*)-plasmid in two independent tests (Figure 1A). The PCR product was sequenced (MWG-Biotech AG, Germany) and the obtained sequences (106 base-pairs without oligonucleotide-primers: 5'-ATT GTC TTT ATC AGA AGT TCC TTT TAG CTC AAT CTT GTC TAC TGT TGC CTT TAG ACT GTA CTT ACC GTC TTT GTC TTT TTC TTT ACT TAC AAG AAC TTT CAT CTC A-3') were compared to known sequences using an internet based basic local alignment search tool (BLAST). The results were specific for *Borrelia afzelii* although the short PCR product could not be assigned to one single strain. The determination of *Borrelia*-specific antibodies by ELISA (RecomWell, Mikrogen GmbH, Germany) was negative at that time (IgM 6.07 U/ml, IgG 11.22 U/ml – normal range for IgM and IgG <20 U/ml). The patient decided not to take antibiotics as a prophylaxis according to widely accepted guidelines (11), but to watch carefully for any skin changes or other symptoms of

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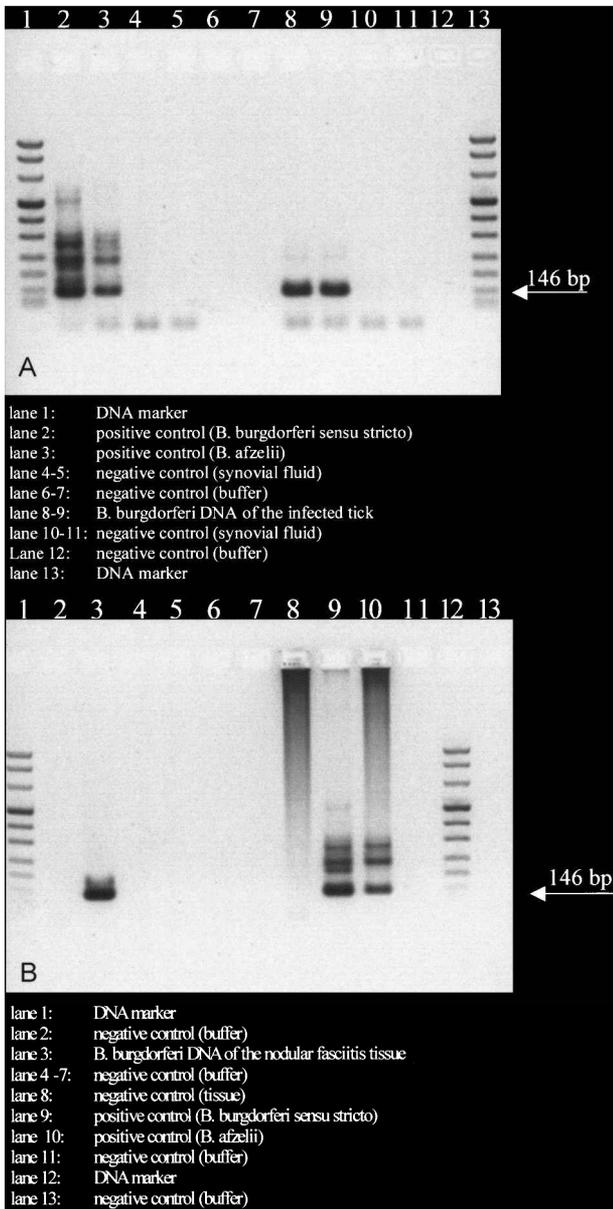


Fig. 1. *Borrelia burgdorferi sensu lato* nested PCR products after ethidium bromide stained agarose gel electrophoresis: A) infected tick; B) nodular fasciitis tissue.

infection. During the next 4 weeks he did not have any complaints.

Four months later he detected a tough subcutaneous nodule on the volar side of his left forearm. No trauma and no overt signs of infection had preceded. The nodule was rapidly growing, reaching 1.5 cm in diameter after 8 days. In ultrasonography it appeared to be a mixed hypoechogenic epifascial structure. At the same time the patient remembered his tick bite and recognized a typical erythema migrans of 25 cm in diameter at the left popliteal fossa. No other tick bites had occurred in the meantime. Erythrocyte sedimentation rate (ESR), blood count, and

c-reactive protein were still within normal ranges but *Borrelia*-specific IgG- and IgM- antibodies were elevated using the same ELISA test as before (IgM 43.91 U/ml, IgG 51.48 U/ml). Western blot analysis using recombinant proteins of the three genospecies *Bbss*, *Ba*, and *Bg* (RecomBlot, Mikrogen GmbH, Germany) showed IgM band "ospC" and IgG bands "p18" and "p41" which is a significant positive result according to the manufacturer's guidelines. The nodule at the forearm was removed in local anesthesia. The histology was typical for NF indicating fibroblastic proliferation with cystic spaces, micro-hemorrhages, and some multinucleated giant cells. Parts of the tissue were prepared for *Bbsl*-PCR using the same approach as for the tick. The *Bbsl*-PCR result was again positive in two independent tests (Figure 1B). After the excision of the nodule the patient was treated with oral doxycycline 200 mg daily for 30 days. Erythema migrans disappeared after 2 days of treatment. The patient had some days of myalgia and arthralgia at the initial treatment but was then feeling well. Fourteen days after the end of the antibiotic treatment the patient developed arthritis of both knees. As the patient was allergic to cephalosporines he was successfully treated with penicilline G (5 million units every 6 hours) for 14 days. *Borrelia* specific antibodies decreased to normal levels. The patient is free of complaints until now.

Discussion

NF is an inflammatory myofibroblastic process of unknown origin that has been found in relation to infection or trauma. While other inflammatory soft tissue disorders caused by *Borrelia* infections like myositis (12) or panniculitis (13) have been described, there is no published case of LB triggering NF. Hence, this relation was never systematically studied. In our case not only the chronological order of *Ba* infection and development of NF, but especially the presence of *Ba*-specific DNA in the NF-tissue refers to a causal connection between the two disorders. The detection of *Ba*-DNA does not prove the presence of viable bacteria so that only bacterial debris or antigens may have reached the NF-tissue. RNA-assays like reverse transcriptase (RT)-PCR could probably distinguish between dead and live bacteria, but these studies were not possible because the tissue was not previously prepared for RNA-analysis. Also humoral factors produced during the *Borrelia* infection could have been the trigger for development of NF but this seems to be less probable in presence of bacterial DNA. So far it remains open if, in the presented case, NF was caused by direct presence of viable bacteria, by presence of bacterial debris or,

less likely, just as a consequence of an “inflammatory milieu” characterized e.g. by special cytokine profiles.

According to antibody studies *Ba* is believed to cause mainly acrodermatitis chronica atrophicans. However, some European authors could identify *Ba* also as the causative agent of Lyme arthritis in single observations (14;15). In our case *Ba* caused a mild gonarthrititis with some joint effusion but without any elevation of inflammation parameters (ESR, c-reactive protein). A study of *Borrelia* infection in ticks in Lower Saxony (Northern Germany) revealed an infection rate of 9.3%. Fifty three percent were *Ba* infections (16). Therefore even rare clinical manifestations of *Ba*-infection, such as arthritis, are expected to occur more frequently in this region.

According to this case Lyme borreliosis may be one cause of nodular fasciitis. As this is the first published case it remains unclear if this is especially related to *B. afzelii* or also to other *Borrelia* genospecies.

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