H. R. Bruckbauer, V. Preac Mursic, P. Herzer, H. Hofmann

Sudeck's Atrophy in Lyme Borreliosis

Summary: A patient with disseminated Lyme borreliosis is reported. The patient suffered from erythema migrans and radicular pain. Serologic tests routinely performed (IFT, ELISA, Western blots with different strains and *Borrelia*-LTT) were negative. However, *Borrelia burgdorferi* (genotype *Borrelia afzelii*) was cultivated from a skin biopsy. Western blot with the patient's isolate and sera showed strong reactivity only with the 60 kDa protein. In spite of immediate diagnosis and intravenous antibiotic treatment according to current recommendations he developed pain in the right ankle, which was resistant to further antibiotic and anti-inflammatory therapy. Sudeck's atrophy was diagnosed by X-ray. Treatment with calcitonin brought immediate relief from pain and led to radiographically demonstrable recalcification.

Introduction

Lyme borreliosis is a multisystem disease, involving skin, joints, nervous system and the heart. The causative agent is *Borrelia burgdorferi sensu lato*. The diagnosis of Lyme borreliosis usually is established by history, clinical and serological findings, and ideally by direct demonstration of *B. burgdorferi* in histological sections, or by cultivation of the organism in the MKP-medium (a modified Kelly medium) [1]. Antibody detection depends on the course of the infection and the applied test system. While antibodies can be detected in 50–80% of the early infections (i.e. erythema migrans), serological tests are nearly 100% reactive in the later course (i.e. acrodermatitis chronica atrophicans) [2, 3]. Usually history and clinical picture lead to the diagnosis of Lyme borreliosis. Serological findings support the clinical diagnosis [4]. As erythema migrans is usually the first indicator for Lyme disease, it is necessary to recognize it in order to begin immediate treatment and avoid late manifestations and chronic disease. The diagnosis was established by the typical clinical picture of erythema migrans and radiculitis in the case presented. Serological analysis of serum and cerebrospinal fluid revealed no antibodies at any time of the disease. However, *B. burgdorferi* was cultivated from a skin biopsy. In spite of immediate therapy, the patient subsequently developed Sudeck's atrophy as a hitherto rarely described complication [5, 6].

Case Report

The patient, a 72-year-old man, presented in early September 1992 with a 20 × 30 cm sharply margined, red-violaceous erythema localized in the dermatomes Th10 to Th12 on the left side. The margin of the erythema was accentuated; the center of the lesion showed a papulous violaceous reaction. At this time the patient suffered from radicular pain in the left lower trunk and left leg. He reported the bite of an unknown insect on the left side of his waist 6 weeks earlier. The skin lesion appeared 1 week after the insect bite and was accompanied by itching. Subsequently generalized arthralgias, constitutional symptoms and headache appeared. The radicular pain had occurred 4 weeks after the appearance of the skin lesion. After the diagnosis of lumbago he was previously treated with diclofenac (50 mg/die) without much success. According to the history and clinical findings we diagnosed an erythema migrans and suspected neurological involvement.

Laboratory findings: Histology: Histological examination of a skin biopsy from the margin of the erythema migrans showed a normal epidermis. In the corium there was a dense perivascular lympho-histiocytic and plasmacellular infiltration. The histological pattern was concordant with the diagnosis of erythema migrans.

Tissue culture: B. burgdorferi was cultivated from the skin specimen in modified Kelly's medium MKP [1]. The isolate was characterized as *Borrelia afzelii* strain (*R. Wallich*, Deutsches Krebsforschungszentrum, Heidelberg).

Serological tests: All serological tests for Lyme borreliosis performed revealed no significant elevation of antibodies to *B. burgdorferi* or specific bands in Western blot, respectively, at any time of the investigation. Ten different commercially available tests were performed: *B. burgdorferi*-IgG-IFT-abs (Fresenius), an immunofluorescent assay against whole borreliae (strain B31, serum was absorbed with FTA-absorbent [Behring]) flagellum ELISA (DAKO), an IgM and IgG immunoassay against purified flagellum antigen; μ-capture ELISA (DAKO) with flagellum antigen for IgM antibodies; *B. burgdorferi*-ELISA (Behring), an IgM and IgG immunoassay against extracted antigens of *B. burgdorferi*, strain PKo (Behring), Western blot with strain B31 as antigen (Cambridge Bio); and Western blot with recombinant antigens of *B. burgdorferi* (p100, p41, p31 [OspA], p22 [OspC] and p14 [p41-fragment]) [3] (Recomblot®, Microgen).

The assays were performed and interpreted according to the manufacturers' instructions.

T-cell proliferation test: In vitro lymphocyte stimulation with *B. burgdorferi* (*Borrelia*-LTT) (Prof. *Burmester*, Institute for Clinical Immunology and Rheumatology, Erlangen, Germany)

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Dr. med. *H. R. Bruckbauer*, PD Dr. med., Dr. med. habil. *Heidelore Hofmann*, Klinik u. Poliklinik für Dermatologie u. Allergologie am Biederstein, Technische Universität München, Biedersteiner Str. 29, D-80802 München; Prof. Dr. rer. nat. *Vera Preac Mursic*, Max von Pettenkofer-Institut, Pettenkoferstr. 9a, D-80336 München; Prof. Dr. med. *P. Herzer*, Tal 6, D-80331 München, Germany.

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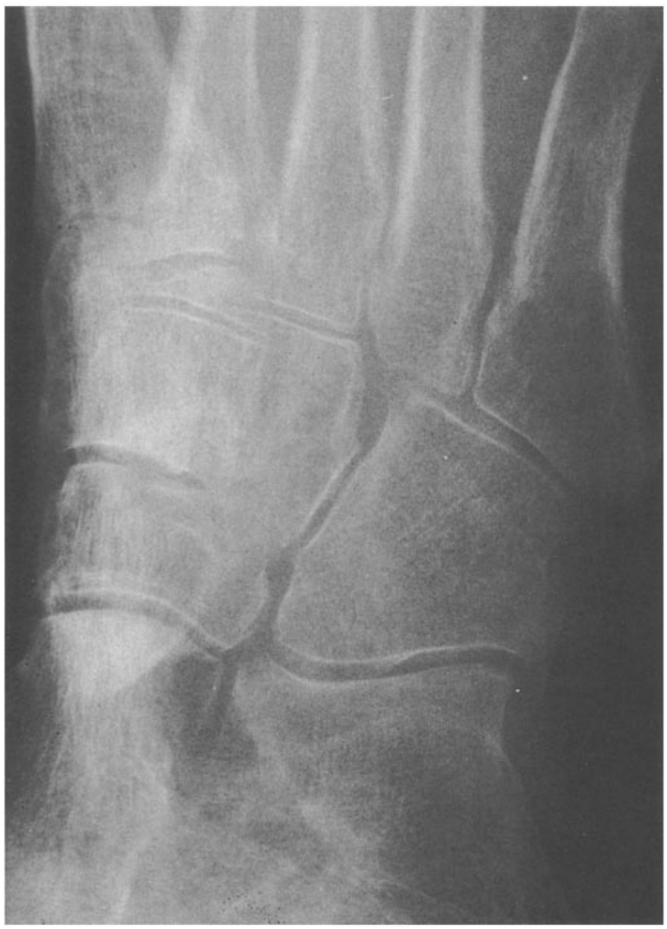

Figure 1: Patchy osteoporosis and demineralization of the right foot.

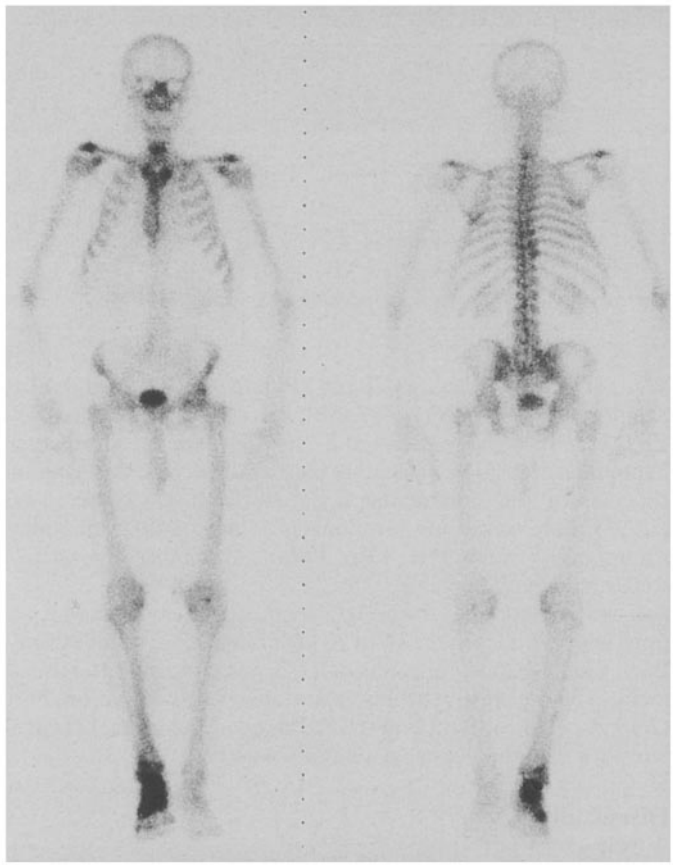

Figure 2: Increased perfusion and bone metabolism in the right tarsus. (Nuklearmedizinische Klinik und Poliklinik der Technischen Universität München)

showed no increased proliferation of T-cells after stimulation (Δ cpm = 10,000, normal range: Δ cpm < 20,000).

CSF results: The cerebrospinal fluid showed an elevated total cell count (31 per µl). Proteins and immunoglobulins were within normal limits. *B. burgdorferi* ELISA in the CSF was negative.

All routine blood parameters performed were within normal range, ESR 7 mm/h.

Clinical Course: The patient was treated with ceftriaxone (2 g/d) intravenously for 14 days. Within 4 days relief from radicular pain and regression of skin symptoms could be noticed.

One month after the end of antibiotic therapy the patient developed edematous swelling and pain in the right ankle and lower leg. The skin of the right lower leg was slightly violaceous, reddened and warmer than on the other side. Sensitivity in the right foot was impaired. A skin biopsy from the right ankle after therapy showed no histologic abnormality; *B. burgdorferi* was not cultivated. The serological tests for Lyme borreliosis were still negative. Nonsteroidal anti-inflammatory drugs were given and repeated antibiotic treatments were performed (doxycycline 200 mg daily, orally for 2 weeks, ceftriaxone 2 g daily for 2 weeks) without significant improvement. The right foot and the distal part of the right lower leg were still swollen, warm and still showed diffuse red-violaceous discoloration 5 months after onset of the disease. Movement in the right ankle was slightly restricted. Deep vein thrombosis could be excluded by venography. The neurological examination showed impaired sensitivity in the right foot and toes, as far as vibrations and discriminative sensations were concerned. The CSF at that time was without pathological findings.

The X-ray of the right foot showed patchy osteoporosis (Figure 1). The 99m-Tc-scintigraphy revealed increased perfusion and bone metabolism in the right tarsus (Figure 2).

These radiographic findings were considered to be compatible with Sudeck's atrophy. The patient was therefore treated with calcitonin (Cibacalcin® 100 U/d subcutaneously) for 5 weeks. Two days later an impressive relief from pain could already be observed.

The patient was without pain 10 months later. However, reflecting the clinical picture of Sudeck's atrophy, the right lower leg was still discolored and the right ankle was still swollen. At that time, an X-ray showed recalcification (Figure 3); a scintigram showed normal findings. All serological parameters for Lyme borreliosis (IFT, ELISA and Western blot) were still negative.

Western blot with different strains of B. burgdorferi: To analyze the patient's sera with different genospecies and OspA-serotypes of *B. burgdorferi*, we performed additional Western blots. The test strains are described in Table 1. *Borrelia* strains were cultivated in BSK-Medium (Sigma) supplemented with 7% rabbit serum at 32°C and prepared as described [7]. Gel electrophoresis on 17% one dimensional SDS-polyacrylamide gels and Western blotting on nitrocellulose sheets were performed as described [7, 8]. Serum dilutions: 1:1,000 for IgG and 1:500 for IgM, respectively. The sera before treatment (September 1992: 9/92) and after treatment (December 1993: 12/93) were analyzed for IgM and IgG antibodies with Western blot. The pattern in the polyacrylamide gel is demonstrated in Figure 4.

Table 1: Characterization of test strains (according to *Wallich* [8]).

Isolate	Origin	Geographic region	OspA serotype	Genospecies
B31	Tick	USA	I	*Borrelia sensu strictu*
ZS7	Tick	Germany	I	*Borrelia sensu strictu*
ZQ1	Tick	Germany	II	*Borrelia garinii*
ACA-1	Skin (ACA)	Sweden	IV	*Borrelia afzelii*
PKo	Skin (ECM)	Germany	IV	*Borrelia afzelii*
PMe	Skin of presented patient (EM)	Germany	Unknown	*Borrelia afzelii*

Western blot results: IgM-Blots (Figure 5): IgM antibodies against p41 (strains ZQ1, ZS7, B31, PKo, PMe) and p34 (strains ZS7, B31, PKo) were detected in the pretreatment serum from September 1992 (9/92). All other pale bands were assessed as unspecific. In the posttreatment serum from December 1993 (12/93) there were only low concentrations of IgM antibodies against p41 (strains B31, PKo, PMe). Antibodies against p34 were no longer detectable.

IgG-blots (Figure 6): In the IgG blots, both sera showed reactions with proteins in the 60 to 70 kDa range in all tested strains. Each of the bands appeared paler or disappeared after treatment. The weakest reactions were observed with strain ZQ1 (*Borrelia garinii*). Both sera stained an eye-catching 60 kDa protein with the homologous patient's isolate PMe.

Discussion

The patient described here showed typical signs of Lyme borreliosis: erythema migrans and radicular pain. The clinical diagnosis was supported by cultivation of *B. burgdorferi* from a skin biopsy. The strain was characterized as *B. afzelii*. After antibiotic therapy, the patient developed symptoms and signs of Sudeck's atrophy in the ankle joint contralateral to the primary erythema migrans and radicular pain. The patient did not develop an adequate humoral or cellular immune response to *B. burgdorferi* at any time during the course of the disease.

IgM and/or IgG antibodies can be detected in 50–80% of patients with erythema migrans; in later stages of the infection antibodies are detected in 65 to 100%, depending on the method used [2]. Antibody reaction may be abrogated by early antibiotic treatment [9]. Cellular response to *B. burgdorferi* can be measured by T-cell proliferative assay.

To assess whether our patient was infected by a *Borrelia* strain that shows antigenic determinants different from the known strains, we performed a SDS-PAGE analysis and Western blots with the patient's own isolate and different *B. burgdorferi* strains. Sera from the time before and after therapy were tested.

Except with the patient's own isolate, Western blots with *B. burgdorferi* strains belonging to different genospecies

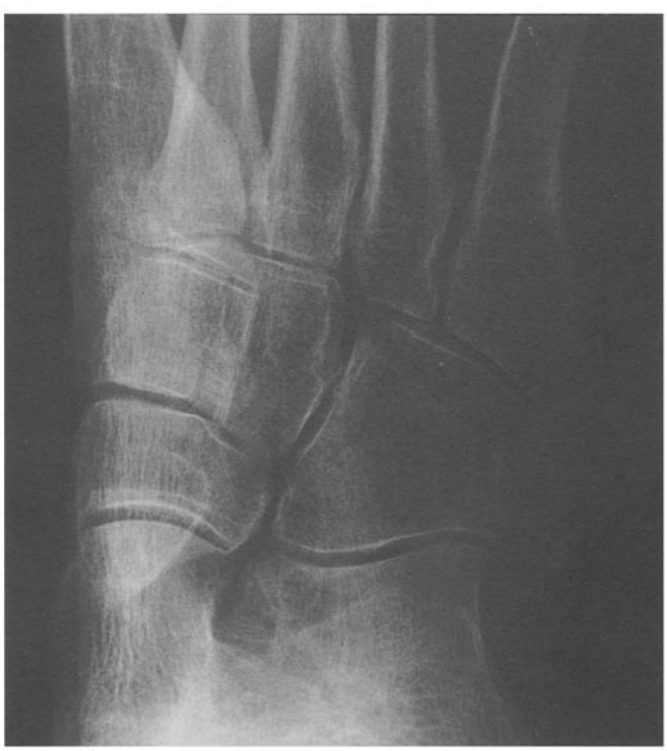

Figure 3: The control X-ray of the right foot 10 months after calcitonin therapy shows recalcification.

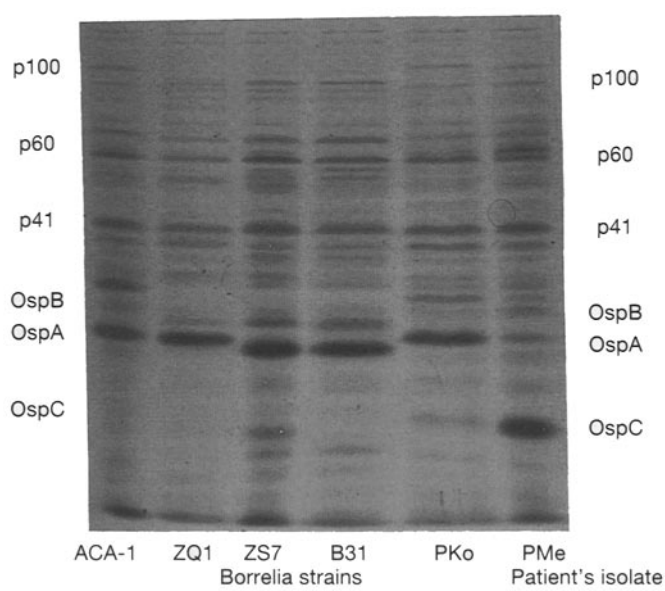

Figure 4: SDS-PAGE of the different *Borrelia burgdorferi* strains used as antigen for Western blot.

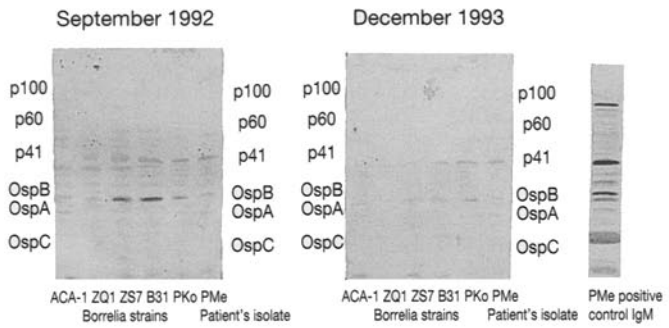

Figure 5: IgM-patterns of two different sera in Western blot against the different test antigens.

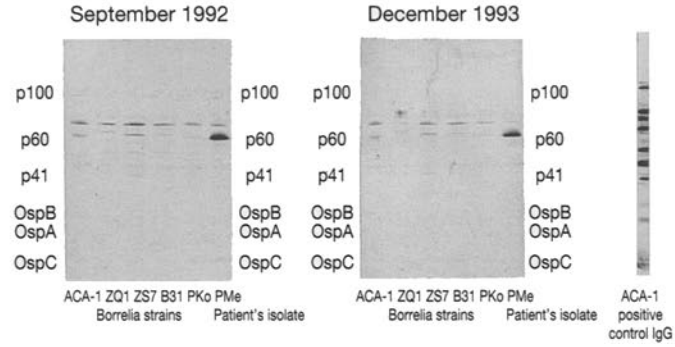

Figure 6: IgG-patterns of two different sera in Western blot against the different test antigens.

revealed no significantly different patterns. The Western blot results were consistent with the results obtained by other serological methods. We mainly found reactions in the 60 to 70 kDa range where several authors described highly conserved "heat shock proteins" [10, 11]. Antibodies against these proteins have repeatedly been described as being unspecific [7, 12]. The Western blot with the patient's own strain showed a strong reaction to a 60 kDa protein which was described as a common antigen by *Hansen* et al. [12].

The protracted course of the disease in this patient may have been caused by an impaired immune reaction. With the exception of a strong reaction to a 60 kDa protein, we were not able to detect a humoral or cellular immune response. On the other hand, the strong reaction against the 60 kDa protein may initiate autoimmune reactions to cross-reactive epitopes in the macro-organism and hence subsequently cause arthralgias [11, 13] and Sudeck's atrophy. Sudeck's atrophy may also be result of neurovegetative affection or radicular symptoms, though it was on the contralateral side. Heterogeneous factors for Sudeck's atrophy have been discussed: injuries, preceding arthritis, immobilization and neurovegetative dystonia [14]. So far, Sudeck's atrophy was rarely described as a possible complication of Lyme borreliosis. *Neumann* et al. [5] described an association between Sudeck's atrophy and *B. burgdorferi* in four patients. Three of them suffered from dermatological manifestations: acrodermatitis chronica atrophicans (two patients) and morphea (one patient). All four had increased antibody titers against *B. burgdorferi*. *Kohler* et al. [6] examined 42 patients with neuroborreliosis and painful meningopolyneuritis and found Sudeck's atrophy in three cases. All of them had elevated IgG antibody titers in the serum, one of them also had elevated IgG in the CSF.

It was not possible to prevent Sudeck's atrophy in our patient in spite of antibiotic treatment consistent with current therapy schedules. Four mechanisms can be considered as possible pathogenetic mechanisms for sympathetic reflex dystrophy: 1) chronic spirochetal infection caused by persistence of spirochetes in sequestered sites, 2) post-arthritic sympathetic dystrophy, 3) post-neuritic sympathetic atrophy after meningopolyneuritis, including affection of the autonomic nervous system, 4) an unknown cause, independent from the observed *B. burgdorferi* infection.

In contrast to the observations of *Kohler* et al. [6], our patient did not recover after repeated excessive antibiotic treatment. Hypothesis 1 hence seems unlikely. We did not have an indication for monarthritis (hypothesis 2). That leaves hypotheses 3 and 4. The temporal connection favours hypothesis 3, but the pathogenetic mechanisms are still unclear. Unknown, nonspecific immune phenomena (e.g. local cytokine production, molecular mimicry, autoimmune mechanisms) continuing for months or several years after the apparent eradication of live spirochetes have been repeatedly discussed [15, 16].

The patient described showed two unusual characteristics: seronegativity and Sudeck's atrophy after confirmed Lyme borreliosis.

In patients with Lyme borreliosis who develop joint pain after adequate antibiotic therapy, the differential diagnosis between reactive arthritis and Sudeck's atrophy should be considered, especially when non-steroidal anti-inflammatory drugs are ineffective. Trophically altered skin with a glossy surface may be indicative. An X-ray typically shows patchy osteoporosis with emphasized cortical borders; scintigraphy reveals increased perfusion and bone metabolism. In such cases treatment with calcitonin is helpful and causes fast pain relief and recalcification [17].

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