

Acrodermatitis chronica atrophicans: various faces of the late form of Lyme borreliosis

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Abstract

Introduction: Acrodermatitis chronica atrophicans (ACA) is probably the most common late and chronic manifestation of the Lyme borreliosis seen in European patients.

Aim: To analyze epidemiological data, and to investigate the effects of treatment of patients with ACA.

Material and methods: Nine patients were included in the study. All patients had serological examinations (ELISA and Western blot) and histopathological examination of the skin lesions performed. Eight patients had PCR in the skin biopsy performed.

Results: The duration of symptoms ranged from 2 months to 2 years. In 7 patients, skin lesions were located on lower limbs, in 2 patients – in a non-typical body area – abdomen. In 1 patient, scleroderma and in 3 patients, diabetes mellitus was diagnosed. *Borrelia burgdorferi* DNA was detected in 25% of the skin biopsy specimens. IgG anti-*B. burgdorferi* specific antibodies were present in serum of all patients (confirmed by Western blot). In all cases, the diagnosis was confirmed by histopathological examination. The response to ceftriaxone therapy varied. In 5 cases, the lesions resolved completely, in others they faded.

Conclusions: Despite raising awareness of Lyme borreliosis, late forms of the disease such as ACA are still observed. Acrodermatitis chronica atrophicans skin lesions may be located in non-characteristic areas, e.g. abdominal skin. Symptoms are not irritating or painful, therefore patients do not seek medical help. The effect of antibiotic treatment varies.

Key words: acrodermatitis chronica atrophicans, Lyme borreliosis.

Introduction

Lyme borreliosis (LB) in Europe is caused by a genotype of the *Borrelia burgdorferi* sensu lato complex. There are three skin manifestations of LB: erythema migrans (EM), borrelial lymphocytoma (BL), and acrodermatitis chronica atrophicans (ACA) [1].

In Europe, LB with all its dermatologic manifestations occurs in almost all countries, predominantly in the central part of the continent. The annual incidence ranges from 9.4 cases per 100,000 population in France to 120 cases per 100,000 population in north-eastern Poland, 130 cases per 100,000 population in Austria and 155 cases per 100,000 population in Slovenia [2–4].

The overall prevalence of ACA in all European patients with LB is about 1–10%, depending on the region. For example, in Bulgaria, both BL and ACA account for

0.3% of LB cases [5]. In Norway, ACA accounts for 5% of all clinical cases of LB [6], and in northern Italy – 2.5% [7].

The diagnosis of ACA is much more difficult than that of EM or BL as the clinical manifestations of ACA may vary. Acrodermatitis chronica atrophicans is probably the most common late and chronic manifestation of the LB seen in European patients.

Aim

The objectives of the study were to verify human cases of ACA, to analyze their epidemiological data, and to investigate the effects of treatment of patients from the Podlaskie region of Poland, considered as endemic for tick-borne diseases.

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Material and methods

Nine patients (5 women, 4 men; mean age: 58.7 ±14.3 years-old, 4 (44%), inhabitants of cities) with ACA were included in the study. All patients were tested for anti-*B. burgdorferi* antibodies of the IgM and IgG class by ELISA (Borrelia recombinant IgG and IgM High Sensitivity, Biomedica, Austria). Results > 11 BBU/ml in the IgM and IgG classes were considered positive.

The studies have been approved by the ethics committee of the Medical University of Białystok, Poland.

In all cases, results were confirmed by Western blot testing (Biomedica, Austria). In all patients, the histopathological examination of skin samples was performed.

From 8 patients, skin biopsy samples of 3 mm in diameter were taken and examined for the presence of *B. burgdorferi* s.l. DNA by nPCR (nested PCR). After collection, skin biopsy samples were placed in aseptic round-bottom tubes and frozen or prepared fresh. All skin biopsies were cut into smaller parts with stainless steel knife-edge and covered with a maximum of 80 µl PBS buffer.

DNA extraction

DNA from skin biopsies was extracted by using a Qia-gen DNeasy Blood and Tissue Mini kit according to the manufacturer's instructions. Purified DNA (100 µl) was then frozen at -20°C before amplification.

PCR protocol for *Borrelia burgdorferi* s.l.

A fragment of the *fla* gene, the specific DNA sequence encoding flagellin was used for *B. burgdorferi* s.l. detection in "one tube" nested PCR. The *Borrelia burgdorferi* PCR kit (GeneProof, Czech Republic) for *in vitro* diagnostics was used for this purpose, minimizing non-specific reactions and maximizing sensitivity because of the "hot start" technology employed. Possibility of PCR inhibition is prevented by addition of internal control into the reaction mix. The risk of contamination is prevented by using uracil-DNA-glycosylase (UDG). 4 µl of the template DNA isolates was added to 36 µl of the MasterMix for final reaction mix volume of 40 µl. The course of the reaction in accordance with the manufacturer's instructions was performed on the SensoQuest LabCycler (SensoQuest, Germany) with authors' own modifications. Nested PCR was performed according to the following amplification program: UDG decontamination, initial denaturation at 96°C for 10 min, first amplification for 30 cycles (denaturation at 96°C for 20 s, annealing at 68°C for 20 s, extension at 72°C for 40 s), second amplification for 45 cycles (denaturation at 96°C for 20 s, annealing at 54°C for 20 s, extension at 72°C for 30 s) and final extension at 72°C for 2 min. The samples were cooled at +4°C.

The PCR products were separated on 2% agarose gel (Sigma-Aldrich, Germany) with the addition of ethidium

bromide (5 µg/ml; Syngen, USA) at 80 V for 80 min. The results of the PCR were viewed under UV light (UV to Gel Logic System 100 (Kodak Imaging System, Inc., USA). Probes with the PCR product of the size of 276 base pairs (bp) were regarded positive. The internal control had a size of 420 bp. For precise detection of *B. burgdorferi* s.l. *fla*, amplicons and internal control molecular weight marker (M100-500-Blirt S.A. Poland) was used.

Results

Eight (88%) of our patients remembered a tick bite. Five (55%) patients had been previously treated with antibiotics because of EM. In 5 (56%) cases, this was a job-related disease. The duration of symptoms ranged from 2 months to 2 years. In 7 (77%) patients, skin lesions were localized on the lower limbs. Two patients had co-existing skin lesions in a non-typical body area – abdomen (Figures 1–6). Six (66%) patients suffered from muscle and 6 (66%) from joint pain. In 1 patient, scleroderma and in 3 (33%) patients, diabetes mellitus was diagnosed as concomitant diseases.

In all patients, ELISA in the IgG class was positive (mean titer: 90.5 ±9.1 BBU/ml). All results were confirmed by Western blot. Histopathological examination revealed features typical of ACA: infiltration of lymphocytes, histiocytes and plasma cells, prominent vascular channels together with telangiectasia, atrophy of the dermis and subcutis, epidermal atrophy and loss of rete ridges, which confirmed the diagnosis.

Borrelia burgdorferi s.l. DNA was detected in 25% of the skin biopsy specimens. Detailed characteristics of patients is presented in Table 1.

Laboratory tests (blood morphology, aminotransferases activity, creatinine concentration, C-reactive protein (CRP) concentration) revealed no abnormalities.

All patients were treated with third-generation cephalosporin (ceftriaxone 2 g/day) for 28 days (according to Polish guidelines). The outcome of treatment varied. In 5 cases, the changes disappeared completely (after 1 to 6 months), in others faded, but skin thinning and discoloration of bluish pink remained (Table 1). No side effects of antibiotic therapy were observed.

Discussion

Acrodermatitis chronica atrophicans is a late and long-lasting form of LB, which may be present for many years. It is characterized by red or bluish-red lesions and leads to extensive flaccid atrophy of the skin, which becomes more and more prominent. Fibroid nodules may develop over bony prominences and sclerodermic lesions may develop in atrophic skin areas [8]. It may limit movement of upper and lower limb joints. ACA is most commonly located on extremities, although it may affect



Figure 1. Patient 2. Lesions typical of ACA on the left thigh



Figure 2. Patient 3. Lesions typical of ACA on the right palm



Figure 3. Patient 4. Lesions typical of ACA in the left knee area



Figure 4. Patient 7. Lesions typical of ACA on the left shank



Figure 5. Patient 8. Lesions typical of ACA on the whole right lower limb



Figure 6. Patient 9. ACA lesions on abdomen

other skin areas, such as the face [9]. In two of our patients, ACA was located in the abdominal area.

According to the literature, women are more predisposed to ACA (women are more than two thirds of patients) [7, 10]. This tendency was also observed in our study.

Table 1. Clinical characteristics and diagnostics tests results in patients with ACA

Parameter	Patient 1 Sept 2009	Patient 2 Feb 2010	Patient 3 June 2010	Patient 4 Oct 2010	Patient 5 March 2011	Patient 6 Dec 2012	Patient 7 Sept 2013	Patient 8 April 2014	Patient 9 August 2014
History									
Age	78	74	57	60	51	29	64	64	52
Sex	Male	Female	Female	Male	Male	Female	Female	Female	Male
Place of living	Town	Country	Country	Country	Country	Town	Country	Country	Country
Job-related	Yes	No	No	Yes	Yes	No	No	Yes	Yes
Time since tick bite [days]	NA	NA	NA	1800	3650	300	730	1800	360
Erythema migrans	1	1	0	0	0	1	1	1	0
Clinical presentation									
Localization	Abdomen	Left thigh	Right palm	Area around left knee joint	Left palm	Left ankle	Left shank	Right leg (from foot to thigh)	Abdomen and left shank
Photography	NA	Fig. 1	Fig. 2	Fig. 3	NA	NA	Fig. 4	Fig. 5	Fig. 6
Muscle pain	1	1	1	1	0	1	0	0	1
Joint pain	1	1	1	1	1	0	0	0	1
Diagnostic tests									
<i>B. burgdorferi</i> IgG [BBU/ml]	35	52	109	58	69	46	100	84	97
WB IgG	VlsE, p41, p18	P100, VlsE, p41, p18	VlsE, p39, p18, p100,	VlsE, p18,	VlsE, p100, p18	VlsE, p100, p41, p58, p39	VlsE, p100, p18	VlsE, p100, p18	VlsE, p18
PCR skin sample	Negative	Negative	Negative	Positive	Positive	Negative	NA	Negative	Negative
Histopathological examination	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive	Positive
Treatment									
Antibiotic	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin	III gen. cephalosporin
Duration [days]	28	28	28	28	28	28	28	28	28
Effect	Complete resolve	Partial resolve	Complete resolve	Complete resolve	Partial resolve	Partial resolve	Partial resolve	Complete resolve	Complete resolve

Acrodermatitis chronica atrophicans can occur in any age group but it is most common in adults, mainly those in their 40-ties or 50-ties and it occurs only rarely in children [11, 12].

Acrodermatitis chronica atrophicans may develop 6 months to 8 years after a tick bite [13]. In our study, the shortest time since the tick bite reported by a patient was 300 days, and the longest was 10 years.

Patients with ACA are usually in a good general condition, though they may experience rheumatologic or neurologic symptoms such as polyneuropathy (typically pain, paresthesia or both). According to the literature, neuropathy symptoms are evident in more than one half of the patients with ACA [13]. We have not observed any neurological symptoms, however 66% of our patients experienced joint pain and muscle pain.

According to the case definition by Stanek *et al.*, the diagnosis of ACA is based on a typical clinical picture, followed by serological tests (high level of specific IgG antibodies), and histological examination. Additionally, detection of *B. burgdorferi* by culture or PCR from the skin biopsy helps in diagnosis [4]. All our patients fulfilled the diagnostic criteria for ACA. Moreover, in 25% we detected DNA of *B. burgdorferi* in the skin biopsy.

The ACA lesion has a typical histological appearance with telangiectasias, patchy or band-like lymphocytic and plasma cell infiltrates. Various degrees of atrophy may be observed [4]. According to the recent research, cutaneous borreliosis can histopathologically manifest with a T cell-rich infiltrate mimicking cutaneous T-cell lymphoma [14, 15].

The differential diagnosis of ACA depends on the stage of the disease. ACA skin lesions on lower extremities are often misinterpreted as vascular insufficiency (e.g. chronic venous insufficiency, superficial thrombophlebitis, hypostatic eczema, arterial obliterative disease), acrocyanosis, livedo reticularis, lymphedema, a consequence of old age or chilblains. Fibrous nodules may be mistaken for rheumatoid nodules, gout or erythema nodosum [4].

A recent study by Brandt *et al.* has proved that PCR assays targeting *ospA* and *ospC* genes might be helpful in differential diagnosis as the main cause of ACA is *B. afzelii*, serotype 2, *osp C* groups Af5, Af2 and Af6 [15].

The standard treatment is based on antibiotic therapy with 1 of the following drugs: with amoxicillin 3 × 500–1000 mg *p.o.* for 14–28 days, doxycycline 2 × 100 mg or 1 × 200 mg *p.o.* for 14–28 days, ceftriaxone 1 × 2000 mg *i.v.* for 14–28 days, cefotaxime 3 × 2000 mg *i.v.* for 14–28 days, or Penicillin G 3–4 MU every 4 h *i.v.* for 14–28 days [16, 17]. As a rule, the outcome of treatment is good, especially if the acute inflammatory stage of ACA is treated adequately. The therapeutic outcome is difficult to assess in patients with the chronic atrophic phase, in which many changes are only partially reversible. All our patients were treated with third-generation cephalosporin. Response to 28 days third-generation cephalosporin therapy varied from partial dissolving of the lesion to complete fading.

Acrodermatitis chronica atrophicans may lead to ulcerations or bacterial superinfections [18]. It is also considered a risk factor for cancer development. We have not observed any complications in our patients.

Summing up, diagnosis of ACA is in most cases delayed as the patients do not report serious complaints and the disease usually develops many years after the tick bite. Causative treatment should be implemented as early as possible to prevent irreversible cutaneous damage.

Conclusions

Despite raising awareness of LB, late forms of the disease such as ACA are still observed. Skin lesions in ACA may be located in non-characteristic areas, e.g. abdominal skin and require serological and histopathological confirmation. As the symptoms are not irritating or painful, patients usually do not seek medical attention. The effect of antibiotic treatment varies.

Conflict of interest

The authors declare no conflict of interest.

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