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The Spirochetal Etiology of Acrodermatitis chronica atrophicans Herxheimer

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Spirochetes were recovered from the skin lesion of 1 out of 10 acrodermatitis chronica atrophicans patients (ACA). Spirochetes from this skin isolate and from *Ixodes (I.) ricinus* and *I. dammini spirochetes* were used as antigens in indirect immunofluorescence tests. All sera from 17 ACA patients showed high antibody titers to the three antigens. Seven of the 17 sera which had the highest titers had crossreactive antibodies to treponemal antigen detectable in the FTA-ABS test. The results indicate that spirochetes are of importance for ACA and probably the causative agent of this disease. The connection between ACA and tick bites and the relationship to erythema chronicum migrans Afzelius (ECMA) and Lyme disease are discussed. The results are consistent with the hypothesis that ECMA and ACA are different manifestations of the same spirochete, with ACA as a late manifestation. (Received December 21, 1983.)

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Acrodermatitis chronica atrophicans (ACA) was described before the turn of the century (1, 2) and was named by Herxheimer & Hartman in 1902 (3). Untreated ACA is a chronic progressive disease, that usually begins on the acral part of the extremities or at the knee or olecranon areas and which tends to spread on the extensor surfaces. The inflammatory phase usually continues for several years and is gradually replaced by atrophy. Early on neurological disturbances were described in case reports (4, 5) and then later reported by Hopf in a detailed investigation (6). In 1946 Svartz was the first to try penicillin treatment in 2 ACA patients because they had an elevated sedimentation rate (7). In 1949 Thyresson established ACA as an infectious disease in his report on the successful treatment with penicillin of 57 patients (8). Among other infectious agents spirochetes have been discussed (9), but the nature of the agent, however, remained unknown. In 1955 Götz showed that ACA could be transmitted from one human being to another by implantation of skin biopsies (10) and this was confirmed by Zmegac in 1966 (11). ACA is most often found in Northern, Central and Eastern Europe but seldom in the United States (12, 13, 14). Several authors have suggested that ACA may be transmitted by ticks (12, 13) and the geographical distribution of ACA in Europe corresponds to the spread of *Ixodes* (I.) *ricinus* (12, 13). There are case reports of erythema chronicum migrans Afzelius (ECMA) preceding ACA (12) and of co-existing ECMA and ACA (12, 15). With the Warthin-Starry stain Fritz et al. have described spirochetal structures in sections from both ECMA and ACA skin (16). A tickborne origin was early suggested for ECMA (17). We have been able to isolate spirochetes from an ECMA lesion and have recently shown that ECMA patients have significantly increased antispirochetal serum antibody titers as compared to a control group (18). Spirochetal etiology has of late also been found in cases of lymphocytic meningitis/meningoradiculitis in Sweden (19 and personal communication G. Stiernstedt).

Lyme disease (LD) was first recognized in the United States in 1975 (20). This disease may involve the skin, and give erythema chronicum migrans-like lesions, as well as the

joints, the heart and/or the nervous system. In 1982 a tickborne (*I. dammini*) spirochete was established as the causative agent of LD (21).

The aim of the present study was to investigate the hypothesis of spirochetal etiology in ACA by means of isolating the organism and by performing indirect immunofluorescence (IF) tests with different spirochetes as antigens and also to study the relationship between ACA and ECMA.

MATERIAL AND METHODS

Patients and controls

Since 1982 17 patients with untreated ACA have been investigated at the Department of Dermatology, Södersjukhuset, Stockholm, Sweden. All the patients had typical skin lesions on the extremities and the histopathological findings were in agreement with the ACA diagnosis. All the patients were carefully questioned concerning tickbites, the duration of the disease and a possible history of ECMA. Thirty-two age- and sexcorrelated humans visiting our Department were chosen as controls in the serologic tests.

Skin biopsies and cultures

Skin biopsies (4 mm punch) were taken from the clinically most active inflammatory area of the skin lesion from 10 patients. After removing the epidermis the skin specimens were each crushed in 1 ml of modified Kelly's medium (22) in a glass tissue homogenizer and examined under darkfield microscope. The homogenate was then transferred to a glass tube containing 9 ml of modified Kelly's medium for cultivation. A 30 μg neomycin disk (AB Biodisk, Solna, Sweden) was added. The culture tubes were incubated at 35°C and at different oxygen tensions. Some tubes were cultured in jars with low oxygen tension by using the GasPac 100 system (BBL Microbiology Systems, P.O. Box 243, Cockeysville, MD 21030, US) without catalyst and some were cultured anaerobically by using the GasPac 100 system and palladium catalyst. Tubes were also cultured without oxygen reduction. To culture tubes contaminated with *Staphylococcus epidermidis* a 30 μg rifampicin disk (AB Biodisk, Solna, Sweden) was added. The culture tubes were examined weekly for at least one month by darkfield microscopy.

Spirochetes from Ixodes ticks

Stock cultures of spirochetes from Swedish *I. ricinus* ticks and of strain B 31 isolated from *I. dammini* ticks in the US (21) are maintained in our laboratory in modified Kelly's medium as reported earlier (18). The strain of *I. ricinus* spirochetes was cultured in an anaerobic atmosphere and the strain of *I. dammini* spirochetes without oxygen reduction.

Serologic tests

The investigated sera from the 17 ACA patients were collected before penicillin treatment was started and the serum samples were stored at −70°C.

Indirect immunofluorescence (IF) tests with spirochetes isolated from ticks (I. dammini and I. ricinus) and from the skin of an ACA patient were performed on sera from the 17 ACA patients and the 32 controls. Each serum was tested simultaneously with the 3 different antigens and sera from patients and controls were tested at the same time. The indirect IF test was performed with a polyvalent conjugate (National Bacteriological Laboratory, Stockholm, Sweden) using the method previously described (18). The results are reported as reciprocal titers.

Serologic syphilis tests. The fluorescent treponemal antibody test with absorption with Reiter spirochetes (FTA-ABS) was performed as previously described (18). The *Treponema pallidum* immobilization test (TPI), the Wasserman reaction (WR) and the *Treponema pallidum* hemagglutination test (TPHA) (FujuZoki Laboratories, Tokyo, Japan) were also performed on all the patients.

RESULTS

Patients, tickbites and ECMA

The patient material consisted of 4 men and 13 women (76%), aged 30–85 years (median 65). The duration of the ACA varied from half a year to more than 5 years (median 2 years) at the first visit. Eight of the 17 patients knew they had received one or often several

Fig. 1. Cultured spirochetes from the skin of an ACA patient. Darkfield.

tickbites in the years prior to the ACA, but only 1 patient had suspected a connection between the tickbite and the ACA. This patient had a history of recurrent erythematous patches located on the arm near the tickbite, on which extremity a typical ACA developed 3 years later on the hand and olecranon area.

Five of the 17 ACA patients had typical histories of ECMA. Three of these 5 patients had had a spontaneously healing migrating erythema of some months duration and the erythemas had been located on the extremity on which symptoms of ACA started 2, 3 respectively 6 years later. Two of these 3 patients knew that the migrating erythema, which disappeared without treatment, was preceded by a tickbite. The fourth patient had suffered from an ACA on a foot for at least a year when he received a tickbite on the back followed by a migrating erythema, that healed without treatment after 3 months. The fifth patient showed up with an ACA on the left hand and arm which she had had for more than 2 years and a typical ECMA on the right leg with a duration of 6 months. The ECMA had started near the knee with a migrating erythema and the patient showed, at the examination, one faintly erythematous zone around the ankle and one around the thigh.

Isolation of spirochetes from skin biopsies

No spirochetes were seen in the examination of fluid from the crushed skin biopsies by darkfield microscopy. After 3 weeks of incubation one out of 10 of the skin biopsies yielded spirochetes (Fig. 1). The skin isolate was obtained from an ACA lesion on the left foot of a patient who had had symptoms for 2.5 years. The spirochetes were subcultured once or sometimes twice a week. In several passages rifampicin was added to the medium because of staphylococcal contamination. In the first passages the spirochetes grew poorly and aggregated, but after further passages and after cultivation at an atmosphere of 5 to

6% O_2, the spirochetes grew better. Initially the biopsy had been cultured without oxygen reduction. The strain was passaged for about 20 times in modified Kelly's medium before it was used as antigen in the serologic tests.

Serologic tests

Indirect IF tests with spirochete isolates from ticks and from the skin of an ACA patient. The results of the indirect IF test with the *I. ricinus* spirochete, the *I. dammini* spirochete and the human skin spirochete as antigens are shown in Table I. The sera from 16 of the ACA patients showed antibody titers of ≥160 with all 3 antigens and titers of ≥160 in all 17 sera with 2 antigens. All but one of the 32 control sera presented titers of ≤80. In both patients and controls the titers of each serum were the same, ±one titer step, irrespectively of which of the 3 antigens that was used. The 2 patients with the most extensive dermatitis had the highest titers (10240) with all 3 antigens. The patient from whom spirochetes were isolated had a titer of 320 with all 3 antigens.

Syphilis tests

The FTA-ABS test was positive in sera from 7 out of the 17 ACA patients with titers of 160–1280 (Table II). These 7 sera had the highest IF antibody titers (2560–10480) against the spirochetes from the ACA patient (Table II). The WR, the TPI and the TPHA tests were negative in all patients.

DISCUSSION

The isolation of spirochetes from a skin biopsy from a patient with ACA and the observations of high antibody titers in the indirect IF tests with spirochetes isolated from ticks in Sweden and the US and also from the skin of an ACA patient, indicate that spirochetes are of importance for ACA and that it is probably the causative agent of this disease. The histopathological findings of inflammatory infiltrates rich in plasma cells and spirochetal structures in the skin of ACA patients (16) also tally with the hypothesis of spirochetes being the infectious agent.

No positive serologic differences were found in the indirect IF tests between the 3 spirochetal antigens, indicating that the 3 strains of spirochetes are closely related. In the

Table I. *IF titers in sera from 17 ACA patients and 32 controls (C) with 3 different antigens: 1) I. dammini spirochete (IDS), 2) I. ricinus spirochete (IRS), and 3) the spirochete from a skin isolate of an ACA patient (ACAS)*

	IF-titers												
Antigen	<5	5	10	20	40	80	160	320	640	1 280	2 560	5 120	10 240
IDS													
ACA	–	–	–	–	–	1	4	2	1	2	2	2	3
C	3	3	5	9	9	2	1	–	–	–	–	–	–
IRS													
ACA	–	–	–	–	–	–	4	3	1	3	1	3	2
C	3	1	6	7	10	4	1	–	–	–	–	–	–
ACAS													
ACA	–	–	–	–	–	–	4	3	1	2	2	3	2
C	–	4	9	8	9	1	1	–	–	–	–	–	–

US the *I. dammini* spirochete has been linked to Lyme disease (21). There are many similarities between Lyme disease and the tick transmitted (*I. ricinus*) spirochetal manifestations seen in Europe, but there are also clinical differences, which may indicate that the spirochetes are not identical. There were differences concerning oxygen concentration for optimal growth between the strains (to be published), which may also indicate differences between the spirochetes. With protein analysis (SDS-PAGE) Barbour et al. have found minor distinctions between *I. dammini* spirochetes and *I. ricinus* spirochetes from Switzerland (23). Electron microscopical and protein characterizations of the Swedish *I. ricinus* and the human skin isolate spirochetes are in progress.

We have previously reported that sera from patients with uncomplicated ECMA have increased antibody titers to Ixodes spirochetes (18). Compared to those previously examined sera, sera from ACA patients usually showed a much higher antibody titer. Titers between 160–640 were found in sera from 4 patients with ECMA and neurological manifestations (unpublished data). The present material is too small to decide whether there are any titer differences between ACA patients with varying disease duration and between patients with localized or more extensive dermatitis. Although there is some overlapping of the results of the serology of sera from the patients with ACA and the controls, the indirect IF test will no dout be of diagnostic help in ACA. Serologic follow-up after treatment is in progress. Preliminary data indicate that the antibodies remain elevated for a considerable time.

In a previous paper (18) we have also reported on the results of the FTA-tests on sera from patients with uncomplicated ECMA, in an attempt to test for cross-reacting antibodies to treponemal antigens. The FTA-ABS test was negative in all the sera from the ECMA patients but in the present study 7/17 of the sera from the ACA patients showed positive titers. It should be noticed that the TPI test as well as the TPHA test turned out non-reactive in these 7 sera. This might indicate that different antigens of *Treponema pallidum* are involved in the FTA-ABS test and the TPHA/TPI tests. Already in 1952 Grüneberg reported positive "Pallida-reactions" with Reiter spirochetes in patients with ACA (9). The FTA-ABS test is routinely used in diagnosing syphilis in Sweden, and syphilis has previously been regarded as the only spirochetal infection acquired in Sweden, which may show a positive reaction in the FTA-ABS test. If FTA-ABS is the only verification test for syphilis, it is important to be aware of the occurrence of cross-reacting antibodies and thus a positive FTA-ABS in an ACA patient must not be mistaken for syphilis.

Discussion of the relationship between ACA and ECMA

ECMA was early suggested to be a tickborne disease (17). Because of the geographical distribution of ACA *I. ricinus* has been suspected of transmitting this disease too (12, 13).

Table II. *FTA-ABS titers and IF titers against the ACA spirochete (ACAS) in sera from 17 patients with ACA*

FTA-ABS titer	IF-titer ACAS						
	160	320	640	1 280	2 560	5 120	10 240
≤5	4	3	1	2	–	–	–
160	–	–	–	–	2	1	–
320	–	–	–	–	–	–	1
640	–	–	–	–	–	1	–
1 280	–	–	–	–	–	1	1

In the present study 8 of the 17 patients recalled tickbites before their ACA started and these results and the isolation of spirochetes from ticks and the serologic results with these spirochetes as antigens tally with the hypothesis that *I. ricinus* is the major vector in ACA.

It has previously been reported that ECMA and ACA may co-exist (12, 15) and this was also found in 2 cases in this study. The cases with active ACA and presumedly high serum spirochetal antibody titers, as symptoms of ECMA developed, indicate that the antibodies are not protective against an ECMA infection. In this respect a parallel may be drawn to syphilis, in which a reinfection may occur after treatment although the patient has positive serologic reactions and thus remaining antibodies.

Skin biopsies from ACA patients implanted into volunteers can produce erythema chronicum migrans-like eruptions (11). Hauser has reported about a patient with ECMA preceding ACA on the same extremity (12). In 3 of our patients symptoms of ECMA were also followed by an ACA on the same extremity after a period of latency, and these observations point to a connection between the two skin manifestations. The long intervening period is remarkable, however, but spirochetes may live in the organism for years, as was shown by the patient who had had symptoms for 2.5 years when we succeeded in isolating spirochetes. In this respect too, parallels can be drawn to syphilis, in which the *Treponema pallidum* spirochete can live latent in the body for many years before symptoms of tertiary syphilis develop. The usually much higher spirochetal antibody titers in sera from patients with ACA, compared to the titers in ECMA, may be explained by the generally more prolonged course and often pronounced inflammatory reaction in ACA. In a group of 161 investigated ECMA patients, with a median age of 53 years, we found a female predominance (69%) (unpublished data). This sex distribution is similar and the median age somewhat lower compared to the results found in the ACA patients in this study (76% female and median age 65 years). The results are consistent with the hypothesis that ECMA and ACA are different manifestations of the same spirochete, with ACA as a late manifestation, but it can still not be excluded that different but closely related spirochetes are involved.

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