

The Spirochetal Etiology of Lymphadenosis benigna cutis solitaria

ANDERS HOVMARK, EVA ÅSBRINK and INGEGERD OLSSON

Department of Dermatology, Södersjukhuset, Stockholm, Sweden

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Ten patients with a clinical diagnosis of lymphadenosis benigna cutis (LABC) solitaria were investigated. Four of the patients knew that they had received a tick bite during the year prior to the appearance of the LABC lesion. Five patients had had a migrating erythema, indicating a previous erythema chronicum migrans Afzelius, near the site where the LABC lesion had developed. In one patient meningitis and a facial palsy occurred. Elevated titers of antibodies against *Borrelia* spirochetes were found in sera from six of nine patients. Spirochetes were cultivated from one out of two biopsies from LABC lesions. The clinical findings, the results of the serologic tests and the successful cultivation of spirochetes show that *Ixodes ricinus*-transmitted *Borrelia* spirochetes can cause LABC solitaria. *Key words: Borrelia; Tick-borne.* (Received April 15, 1986.)

A. Hovmark, Department of Dermatology, Södersjukhuset, S-100 64 Stockholm, Sweden.

Spiegler in 1894 (1) and Fendt in 1900 (2) described cutaneous manifestations resembling sarcoma but with a benign course. The term lymphocytoma cutis was first used by Kaufmann-Wolf in 1921 (3). In 1943 Bäfverstedt classified the Spiegler-Fendt sarcoid as a lymphocytoma and coined the term lymphadenosis benigna cutis (LABC). He defined LABC as a benign, radiosensible disease characterized by a lymphoreticular proliferation in the dermis and/or subcutis (4). Clinically Bäfverstedt classified the disorder into two main forms, LABC solitaria and LABC dispersa. The former is the most common and occurs in both children and adults and predilection sites are the ear lobes and the nipples and areola mammae. The latter form, which may be entirely subcutaneous and very long-lasting (years to decades), is found in adults and has no predilection sites. A variety of patterns may be observed histologically. The presence of reaction centers in the dermis is a helpful diagnostic sign but not an obligatory finding in LABC. There are malignant disorders which may be difficult to differentiate from LABC both clinically and histopathologically. The histologic features may simulate malignant lymphoma and in particular a dense lymphocytic infiltrate without reaction centers may cause difficulties in the differentiation.

An association with tick bites has been found in some patients with LABC (5, 6, 7). Bianchi, in 1950, reported on the healing effect of penicillin (8). The occurrence of LABC together with erythema chronicum migrans Afzelius (ECMA) has been observed in several cases (4, 7, 9, 10). In 1957 and 1958 Paschoud succeeded in transferring circumscribed LABC from the ear lobe of one individual to another and he also observed transition into ECMA (11). LABC associated with polyradiculitis and cerebrospinal fluid disturbances has been described (6) and it has also been found that untreated LABC dispersa may be followed later by development of acrodermatitis chronica atrophicans (ACA) (12).

The findings of spirochete-like structures in mercury- (13) and silver- (14) stained sections of skin biopsies from patients with LABC and observations of increased serum titers of antibodies against *Borrelia* spirochetes in such patients (10, 15) have given support

to the hypothesis of a spirochetal etiology in this disease. However, there has hitherto been no report on spirochetal isolation from LABC lesions.

Spirochetes (*Borrelia burgdorferi*) have been cultivated from skin lesions of patients with Lyme disease in the United States (16). Similar, but probably not identical (10, 17), spirochetes have been isolated from Swedish patients with ECMA (18) and ACA (18, 19). The name *Borrelia Afzelius* or *Borrelia burgdorferi* var. *Afzelius* has been proposed for these spirochetes (17). ACA is a late (tertiary) manifestation of this spirochetosis, which during the early phases may cause conditions such as ECMA, meningitis/Bannwarth's syndrome/ facial palsy, and arthritis (10).

The purpose of the present investigation was to test the hypothesis that LABC is another cutaneous manifestation of *Ixodes ricinus* transmitted spirochetes.

MATERIAL AND METHODS

Patients

During 1984 and 1985 twelve consecutive patients with a clinical diagnosis of LABC solitaria were investigated at the Department of Dermatology, Södersjukhuset, Stockholm, Sweden. Two of the patients, one 6 months old and the other 3 years, with LABC solitaria were excluded from this study as neither serologic nor histopathologic tests had been performed on them. All patients were investigated personally by the authors.

Histopathologic and immunohistopathologic examinations

Biopsy specimens were taken for routine histology and stained with hematoxylin-eosin.

In two cases other biopsy specimens were frozen and cryostat sections were investigated with the use of an indirect immunoperoxidase technique for reactivity with a series of monoclonal antibodies, including Leu 2, 3 and 4 (Becton Dickinson, Sunnyvale, CA) for demonstration of T cells and Pan B and antisera against human IgM kappa and lambda light chains (Dakopatts, Denmark) for demonstration of B lymphocytes.

Serologic tests

The ELISA method described previously (20) was used to determine the titers of IgG antibodies against *Borrelia* spirochetes. A titer level in serum of >410 was considered as an increased titer, as 95% of the controls had lower titers. Spirochetes isolated from the skin of a patient with ACA (strain ACA 1) were used for the antigen preparation.

Spirochetal cultivation

In two cases attempts were made to cultivate spirochetes from skin biopsies taken from solitary LABC lesions. The method used for spirochetal cultivation has been described previously (18). A serum-less medium was used during the first passages.

Treatment

Our standard treatment for adult patients with uncomplicated LABC solitaria has been phenoxymethyl penicillin 2-3 g/day for 10 or 20 days.

RESULTS

The patient material consisted of 6 males and 4 females aged 2 to 71 years. Six of the patients were children, 2 to 8 years of age, with LABC located on an ear lobe. In three of the four older patients the LABC was located on the nipple and areola mammae and in the fourth patient on the helix of an ear.

Tick bites, ECMA and disease duration

Four of the patients knew that they had received a tick bite during the year prior to the appearance of the LABC lesion. At the time of the diagnosis the duration of the solitary LABC lesions varied from 2 to 8 months (median 4.5 months). Five patients had had a



Fig. 1. Lymphadenosis benigna cutis solitaria on the left nipple and areola mammae. Spirochetes have been cultivated from this lesion. (Photo Jonas Mardéll.)

migrating erythema, indicating a previous ECMA, near the site where the LABC lesion had developed. In one of these patients a discreet annular ECMA lesion still remained at the time of the LABC diagnosis. In four patients the erythema had been noted at the same time as or shortly before the LABC lesion was first observed. In the fifth patient the LABC was first noted 4 months after the disappearance of the migrating erythema. This was a 28-year-old man who remembered that he had removed a tick from the right side of his back during the summer of 1984. The bite was followed by a migrating erythema and about 6 months later the erythema had reached the right side of the chest, when it disappeared. In May, 1985, he first noticed swelling and pain in the right mamillary region. In September a malignancy was suspected and a puncture for cytologic investigation was performed. In November, 1985, a clinical and histopathologic diagnosis of LABC was made. Serologic tests showed a slightly increased antibody titer against *Borrelia spirochetes* (IgG ELISA titer 570).

The LABC lesion subsided or disappeared within 5 weeks after the start of antibiotic treatment in all cases.

Neurologic manifestations

One of the patients was a 38-year-old man, who had been referred to us from an otolaryngologic department, which he had visited because of a unilateral facial palsy on the left side. The facial palsy had occurred 8 days earlier. The patient had noticed a bluish-red swelling on the helix of his left ear for about two months. The results of clinical and histopathologic investigations were consistent with a diagnosis of LABC solitaria. Elevated serum antibody titers against *Borrelia spirochetes* were found (IgG ELISA titer 1260).

Examination of the cerebrospinal fluid also showed increased titers (IgG ELISA titer 184. Normal value <8) and a lymphocytic pleocytosis consistent with a diagnosis of a *Borrelia*-induced meningitis. Both the facial palsy and the LABC lesion disappeared after intravenous penicillin treatment.

Histopathologic and immunohistopathologic examinations

Histopathologic investigations were performed in seven of the patients. In all these cases a dense dermal lymphocytic infiltrate with an admixture of plasma cells, consistent with a diagnosis of LABC, was seen. Reaction centers were found in four of the biopsies.

At immunohistopathologic examination of a biopsy specimen from the areola mammae

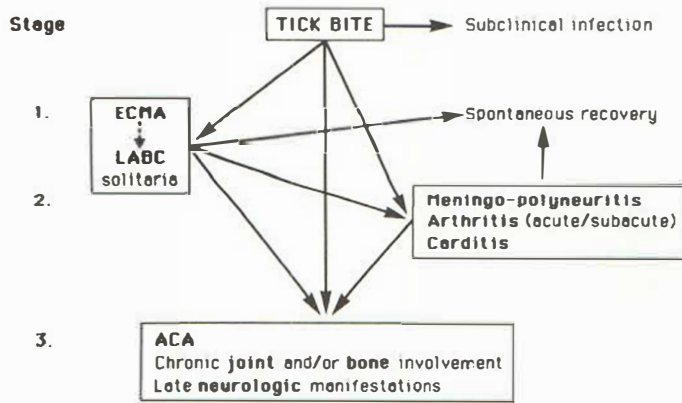


Fig. 2. Conceivable courses of *Ixodes ricinus*-transmitted *Borrelia* infection. ECMA = erythema chronicum migrans Afzelius, LABC = lymphadenosis benigna cutis, ACA = acrodermatitis chronica atrophicans.

of the patient, from whom spirochetes were cultivated (Fig. 1), it was found that the dermal infiltrate consisted of a mixture of B cells, helper T cells and suppressor T cells. In a biopsy specimen from the 28-year-old man, described above, the dermal infiltrate was dominated by polyclonal B cells.

Serologic tests

Serologic tests were performed in nine of the patients with LABC. The results of the serologic tests for IgG antibodies against *Borrelia* spirochetes are presented in Table 1, where they are compared with previously findings in 185 controls, in 88 patients with ECMA and in 41 patients with ACA (10,20). Elevated titers were found in sera from six of nine patients. Titers lower than 410 were noted in sera from three of the patients who had had their LABC lesion for less than 4.5 months.

Spirochetal cultivation

Spirochetes were cultivated from one of two biopsies from solitary LABC lesions. During the first passages the spirochetes grew poorly and aggregated, but after five passages the number of spirochetes increased more rapidly.

The patient, from whom spirochetes were cultivated, was a 71-year-old woman. Discoloration and swelling of the left nipple and areola mammae (Fig. 1) had started 2.5 months prior to the skin biopsy and the LABC diagnosis. As a malignancy was suspected she had undergone a mammography and cytologic punctures from the areola mammae and from an

Table 1. Serum antibody levels of IgG antibodies against *Borrelia* spirochetes, measured by the enzyme-linked immunosorbent assay, in nine patients with lymphadenosis benigna cutis (LABC), in 88 patients with uncomplicated erythema chronicum migrans Afzelius (ECMA), in 41 patients with acrodermatitis chronica atrophicans (ACA) and in 185 controls (C)

	<410	>410-1 000	>1 000-3 000	>3 000-10 000	>10 000
LABC	3	3	2	1	0
ECMA	72 (82%)	10	6	0	0
ACA	0	6	13	11	11
C	176 (95%)	9	0	0	0

enlarged lymph node in the left axillary region. At serologic tests an elevated titer of antibodies against *Borrelia spirochetes* was found (IgG ELISA titer 3400).

DISCUSSION

The present clinical findings, the course of the disease, the results of the serologic tests and the successful cultivation of spirochetes from an LABC lesion show that *Ixodes ricinus*-transmitted *Borrelia spirochetes* can cause LABC solitaria. Four of the patients had had ECMA, which is a primary stage manifestation of this infection, and one patient also showed secondary stage manifestations from the nervous system (meningitis with facial palsy). With the use of darkfield microscopy the spirochetes cultivated from the LABC solitaria lesion could not be differentiated from the *Borrelia spirochetes*, which we have previously cultivated from *Ixodes ricinus* ticks (21) or Swedish patients with ECMA or ACA (18, 19, 21). Electron microscopic and immunologic comparison between the different spirochete isolates may solve the question, whether the spirochetes causing LABC solitaria are identical to or differ from those causing ECMA and ACA. A diagnosis of LABC solitaria can sometimes be confirmed by the finding of increased serum titers of antibodies against *Borrelia spirochetes*. However, as is the case in the majority of patients with the early-stage manifestation ECMA, serologic testing may not always be of diagnostic help in LABC solitaria. Spirochetal cultivation is not a routine procedure and it may often be difficult to obtain sufficiently large skin biopsies for successful cultivation, particularly in children and when the lesion is located on the ear or face. Thus, in many cases the diagnosis of LABC has to be based on the clinical and histopathologic findings. Immunohistochemical investigations may be of good help in differentiating between benign and malignant lymphocytic infiltrates of the skin.

LABC solitaria can now be turned into the scheme of different clinical manifestations caused by *Ixodes ricinus*-borne *Borrelia spirochetes* (Fig. 2). Whether LABC dispersa, which may continue for years, is also a manifestation of *Borrelia spirochetes* remains to be investigated by means of spirochetal cultivation and serologic tests. Further clinical and histologic investigations of LABC solitaria are also needed in order to identify differences between this condition and lymphocytic skin infiltrates of other origins.

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REFERENCES

1. Spiegler E. Über die sogenannte Sarcomatosis cutis. Arch Derm Syph 1894; 27: 163.
2. Fendt H. Beiträge zur Kenntnis der sogenannten sarcoiden Geschwülste der Haut. Arch Derm Syph 1900; 53: 213.
3. Kaufmann-Wolf M. Über gutartige lymphocytäre Neubildungen der Scrotalhaut des Kindes. Arch Derm Syph 1921; 130: 425.
4. Bäfverstedt B. Über lymphadenosis benigna cutis. Eine klinische und pathologisch-anatomische Studie. Stockholm: P. A. Nordstedt & Söner, 1943.
5. Jordan P, Holtschmidt J. Traumatisches Zeckenbiss-Lymphocytom und Erythema chronicum migrans. Hautarzt 1951; 2: 397-401.
6. Paschoud JM. Lymphocytom nach Zeckenbiss. Dermatologica 1954; 108: 435-437.
7. Strandberg J. Regarding an unusual form of migratory erythema caused by tick bites. Acta Derm Venereol (Stockh) 1920; 1: 422-427.
8. Bianchi GE. Die Penicillinbehandlung der Lymphozytome. Dermatologica 1950; 100: 270-273.

9. Åsbrink E, Olsson I. Clinical manifestations of erythema chronicum migrans Afzelius in 161 patients. A comparison with Lyme disease. *Acta Derm Venereol (Stockh)* 1985; 65: 43-52.
10. Åsbrink E. Erythema chronicum migrans Afzelius and acrodermatitis chronica atrophicans. Early and late manifestations of Ixodes ricinus-borne Borrelia spirochetes. *Acta Derm Venereol (Stockh)* 1985. Suppl 118: 1-63.
11. Paschoud JM. Die Lymphadenosis benigna cutis als übertragbare Infektionskrankheit. IV Mitteilung. *Hautarzt* 1958; 9: 311-315.
12. Bäfverstedt B. Lymphadenosis benigna cutis (LABC)—its nature, course and prognosis. *Acta Derm Venereol (Stockh)* 1960; 40: 10-18.
13. Lennhoff C. Spirochetes in aetiologically obscure diseases. *Acta Derm Venereol (Stockh)* 1948; 28: 295-324.
14. Frithz A, Lagerholm B. Acrodermatitis chronica atrophicans, Erythema chronicum migrans and Lymphadenosis benigna cutis—spirochetal diseases? *Acta Derm Venereol (Stockh)* 1983; 63: 432-436.
15. Weber K, Schierz G, Wilske B, Preac-Mursic V. Das Lymphozytom—eine Borreliose? *Z Hautkr* 1985; 60: 1585-1598.
16. Steere AC, Grodzicki MS, Kornblatt AN, Craft JE, Barbour AG, Burgdorfer W, Schmid GP, Johnson E, Malawista SE. The spirochetal etiology of Lyme disease. *N Engl J Med* 1983; 308: 733-739.
17. Hovind-Hougen K, Åsbrink E, Stiernstedt G, Steere AC, Hovmark A. Ultrastructural differences among spirochetes isolated from patients with Lyme disease and related disorders and from Ixodes ricinus. *Zbl Bakt Microbiol Hyg*. In press.
18. Åsbrink E, Hovmark A. Successful cultivation of spirochetes from skin lesions of patients with erythema chronicum migrans Afzelius and acrodermatitis chronica atrophicans. *Acta Path Microbiol Immunol Scand [B]* 1985; 93: 161-163.
19. Åsbrink E, Hovmark A, Hederstedt B. The spirochetal etiology of acrodermatitis chronica atrophicans Herxheimer. *Acta Derm Venereol (Stockh)* 1984; 64: 506-512.
20. Åsbrink E, Hovmark A, Hederstedt B. Serologic studies of erythema chronicum migrans Afzelius and acrodermatitis chronica atrophicans with indirect immunofluorescence and enzyme-linked immunosorbent assays. *Acta Derm Venereol (Stockh)* 1985; 65: 509-514.
21. Åsbrink E, Hederstedt B, Hovmark A. The spirochetal etiology of erythema chronicum migrans Afzelius. *Acta Derm Venereol (Stockh)* 1984; 64: 291-295.