Lymphadenosis benigna cutis resulting from *Borrelia* infection (*Borrelia* lymphocytoma)

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Swelling and erythema of the right pinna developed in a 7-year-old girl. Six months later a biopsy specimen showed a dense, diffuse lymphoplasmacytic infiltrate involving most of the dermis except for a thin Grenz zone. The appearance was consistent with lymphocytoma cutis. She had been bitten by a tick on the right ear in Switzerland 6 weeks before the onset of the lesion. Serologic tests by enzyme-linked immunosorbent assay for *Borrelia burgdorferi*, done 6 and 11 months after the bite, yielded optical density readings of 1.04 and 0.65, respectively; indirect immunofluorescence yielded titers of 1:256 and 1:128. A *Borrelia*-like organism was identified by a modified Steiner stain; immunohistochemistry was noncontributory. The spirochetal origin of lymphadenosis benigna cutis is briefly reviewed. (J AM ACAD DERMATOL 1991;24:621-5.)

Lyme disease is caused by the spirochete *Borrelia burgdorferi* and is usually transmitted through bites by ticks of the genus *Ixodes*. After inoculation erythema chronicum migrans (ECM) may develop. The organism may spread to other organs, notably the nervous system, the heart, and the synovium.

Skin manifestations of *B. burgdorferi* infection are not limited to ECM. Acrodermatitis chronica atrophicans (ACA) has been definitively linked to the organism and is considered to represent a late manifestation of infection. Virtually all patients with ACA have antibodies against *B. burgdorferi*, sometimes with very high titers. Furthermore, the organism has been cultured from affected skin. ACA may respond, especially in its early stage, to antibiotic therapy. ACA is seen only rarely in North America. Recently, *B. burgdorferi* has been implicated in morphea, although other investigators were unable to demonstrate a link. A role for the organism in lichen sclerosus et atrophicus has also been suggested.

Lymphocytoma cutis, or lymphadenosis benigna cutis (LABC), has also been considered a cutaneous manifestation of *B. burgdorferi* infection. We report such a case.

CASE REPORT

A 7-year-old, healthy white girl living in Basel, Switzerland, awakened in June 1988 with a part of a tick embedded in the upper anterior aspect of the right pinna. The tick was removed by her mother. No changes in the ear were noted until mid-July, when asymptomatic erythema and induration developed in the upper half of the pinna and gradually spread to involve most of the pinna and the earlobe.
earlobe (Fig. 1). During the first week of August, the patient received a 7-day course of oral erythromycin without improvement. After her arrival in Canada in October 1988, a 2-week course of oral cephalixin was given on the assumption that she had chronic cellulitis and subsequent topical therapy with 0.1% betamethasone-17-valerate followed by 0.05% betamethasone dipropionate ointment were equally ineffective.

A punch biopsy of the pinna was performed on December 12. Blood for serologic tests for *B. burgdorferi* was drawn 6 and 11 months after the bite. The inflammatory changes began subsiding after the biopsy. In mid-January 1989 the patient began a 2-month course of penicillin V, 300 mg orally three times daily. By May 1989 the lesion had regressed.

MATERIAL AND METHODS

Indirect immunofluorescence (IFA) and enzyme-linked immunosorbent assays (ELISA) were used to detect IgG antibodies to *B. burgdorferi* as described by Wilkinson. An optical density (OD) ratio of at least 0.38 (>2 SD above the mean OD ratio of 100 normal control sera) was considered positive. An IFA titer of 1:256 was considered positive and 1:128 as borderline. A 2 mm punch biopsy specimen was sectioned and stained with hematoxylin and eosin and Bosma's modification of Steiner's silver stain.

Immunohistochemistry was performed on deparaffinized and rehydrated sections with a murine monoclonal anti-*B. burgdorferi* antibody at dilutions of 1:20 and 1:200 (antibody H5332, gift of Dr. T. Schwann, Rocky Mountain Laboratory, Hamilton, Mont.). The two-step indirect peroxidase-antiperoxidase method was used with diaminobenzidine as chromogen. The sections were predigested with pepsin.

To obtain a positive control for the Bosma-Steiner stain and for the immunohistochemistry, *B. burgdorferi* organisms grown in liquid culture were spun down. The pellet was resuspended in human plasma to which thrombin was added. The fibrin clot with the entrapped spirochetes was then fixed and processed as described previously. A piece of normal skin was used as negative control.

RESULTS

Serologic findings. The ELISA yielded an OD of 1.04 on the first serum sample (6 months after tick bite) and 0.65 on the second serum sample (11 months after bite, after 2 months of penicillin V therapy). The IgG anti-*B. burgdorferi* titers were 1:256 and 1:128, respectively, by IFA.

Histologic findings. In the biopsy specimen the epidermis was normal. A thin Grenz zone was observed in the upper papillary dermis. The remainder of the papillary dermis and all the reticular dermis was occupied by a dense, diffuse infiltrate (Fig. 2) of small and large lymphocytes admixed with occasional histiocytes and plasma cells. A *Borrelia*-like organism was found with the Bosma-Steiner stain (Fig. 3).

Immunohistochemistry. At both dilutions a considerable amount of background staining with beaded granular deposits was seen. The edges of collagen fibers appeared to be accentuated, creating wavy, elongated structures. No convincing *Borrelia*-like structures were seen.

DISCUSSION

Spiegler in 1894 and Fendt in 1900 described cases of dense cutaneous lymphocytic infiltrates with features of "sarcoma" that had a benign clinical course. Kaufmann-Wolf in 1921 considered these lesions to represent benign "new growths" of lym-
phoid cells. Bäverstedt\textsuperscript{24} named the lesion \textit{lymphadenosis benigna cutis} in 1943 and considered it a reactive phenomenon. He distinguished two forms of the disease: LABC solitaria, consisting of a single dermal lesion, usually on the earlobe or the nipple, and LABC dispersa, consisting of multiple, often subcutaneous lesions without a site of predilection.\textsuperscript{3,24,25}

An infectious cause of at least some cases of LABC solitaria has been suspected for a number of decades. Bianchi\textsuperscript{26} noted the response of some cases to penicillin. Cases after tick bites were also described,\textsuperscript{27} some in association with ECM.\textsuperscript{28} Paschoud\textsuperscript{29} demonstrated the transmissibility of LABC through repeated passages between human beings by transplantation of lesional tissue; again, some cases were accompanied by ECM.\textsuperscript{30} This led him to postulate that both LABC and ECM represented different manifestations of the same chronic cutaneous infectious disease.\textsuperscript{31}

This theory of an infectious cause has recently been confirmed by demonstration of borreliae in lesions. \textit{Borrelia} organisms have been demonstrated with silver stains with varying success rates. De Koning et al.\textsuperscript{32,33} found organisms in five of five and seven of seven cases, whereas Neubert et al.\textsuperscript{34} saw them in only one of five and Weber et al.\textsuperscript{35} were unsuccessful in one case. These different findings may be related to variable densities of the organisms, duration of the disease, or antibiotic treatment before biopsy. Differences in technique and differences of opinion as to what constitutes a definite borrelial organism are additional problems. The offending organism has also been cultured in some lesions.\textsuperscript{36}

The relationship of LABC dispersa to \textit{B. burgdorferi} is still unclear.\textsuperscript{37}

LABC solitaria appears to be a rare manifestation of \textit{B. burgdorferi} infection; in large series of patients with a clinical and/or serologic diagnosis of Lyme disease the prevalence ranges from 0.6% to 1.3% of cases.\textsuperscript{4,38,39} The dense lymphocytic infiltrate presumably represents a reaction to the organisms. Although lymphoid follicles may be prominent,\textsuperscript{40} they are also lacking in a large proportion of the cases.\textsuperscript{25,36} In the serial biopsy specimens examined by Paschoud,\textsuperscript{29,41} large numbers of plasma cells and well-formed germinal centers were seen only in mature lesions of several months' duration. In the few cases in which the immunophenotype of the lymphoid cells was determined, a mixed infiltrate of polyclonal B cells as well as helper T and suppressor T cells was present.\textsuperscript{36,42}

\textit{B. burgdorferi} causes activation of both B and T cells and of macrophages.\textsuperscript{43} Antigenic differences between European and American strains of the organism\textsuperscript{44} may explain some of the minor differences in clinical presentation of the disease, such as the more prominent skin involvement in European cases.\textsuperscript{45} Of interest is the report of cutaneous lymphomas associated with high antibody titers to \textit{B. burgdorferi} and in association with ACA.\textsuperscript{46} Some of these lesions have the appearance of high-grade lymphomas, yet their behavior appears to be generally that of low-grade lymphomas, with very rare cases of systemic dissemination.\textsuperscript{46}

Although it is unlikely that all cases of LABC solitaria are \textit{Borrelia} lymphocytomas,\textsuperscript{1} we suggest that \textit{B. burgdorferi} infection should be looked for in
both benign- and malignant-appearing cutaneous lymphoid infiltrates.

REFERENCES

Diffuse melanosis in metastatic malignant melanoma

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The skin of a patient with diffuse melanosis as a result of malignant melanoma was examined by light microscopy, immunohistochemistry, and electron microscopy. Our findings indicate that the slate-blue discoloration in this patient was due to pigment deposition in dermal macrophages and endothelial cells. Multiple attempts to identify disseminated metastatic melanoma cells were unsuccessful. (J AM ACAD DERMATOL 1991;24:625-8.)

Melanosis resulting from metastatic malignant melanoma is characterized by a diffuse, slate-blue discoloration and was first described by Legg in 1884. Only a few patients have been described, and therefore the pathogenesis of the disease is still a matter of debate. Several hypotheses have been advanced, including unlimited spread of single disseminated melanoma cells that infiltrate the skin and internal organs, the dissemination of melanosomes produced by distant melanoma cells, and the oxidation of melanin precursors, which are then deposited in the tissues.

We report the clinical, immunohistochemical, histopathologic, and ultrastructural observations of a patient with diffuse melanosis resulting from metastatic malignant melanoma.

CASE REPORT

A 56-year-old white man had had a flat, pigmented skin lesion on the right shoulder for several years. During the last 10 months it increased in size and darkened. After extensive sun exposure in April 1984, the patient suddenly noticed multiple bluish black spots and nodules that spread over the entire body within 4 weeks. He also noticed a progressive slate-blue discoloration of the skin and mucous membranes and a pronounced darkening of the urine.

Physical examination revealed on the right shoulder a superficial spreading melanoma (Fig. 1), which was later verified by histopathologic examination. The entire skin (Fig. 2) and mucous membranes showed a diffuse blue-gray pigmentation. Multiple black, pigmented, firm nodules and papules were seen on the face (Fig. 2), the conjunctiva, the trunk, and the proximal aspect of the extremities. These nodules and papules were verified by histopathologic study to represent cutaneous metastases of melanoma. Lymphadenopathy, hepatomegaly, and splenomegaly were not observed. Routine laboratory investigations were within normal limits. The urine was dark brown, and the reaction for melanin precursors was positive (Thormehlen's test). Chest roentgenogram, bone scan, and abdominal and retroperitoneal ultrasound examinations revealed no evidence of metastases. Combined therapy of interferon alfa and cimetidine was given for 5 weeks without success. The clinical symptoms worsened, the cutaneous metastases increased in number and size, and the slate-blue discoloration of the skin turned to dark gray to black. The patient died 4 months after therapy had been instituted. Autopsy was refused.

Material and methods. The primary malignant melanoma was excised, and two cutaneous metastases were