DERMATOPATHOLOGY OF LYME BORRELIOSIS

S. Hödl, H. P. Soyer

SUMMARY

The dermatopathology of the entire spectrum of skin lesions in Lyme borreliosis is rendered in text and, in most cases, is illustrated. Special emphasis is placed on the histopathological findings in fresh tick bites as the site of entry for borrelia organisms, and their differentiation from other insect bites. The course of the lesions in the well-established *B. burgdorferi*-induced dermatoses is histologically described and illustrated. In addition, conditions in which considerable evidence points to a borrelial etiology are delineated. These include morphea-like plaques, lymphocytic infiltration of the skin, panniculitides, lichen sclerosus et atrophicus, and cutaneous B-cell lymphomas. Furthermore, the recent immunological findings in these diseases are elucidated.

KEY WORDS

Dermatopathology, Lyme borreliosis, recent tick bite, erythema chronicum migrans, lymphadenosis cutis benigna (Borrelial lymphocytoma), acrodermatitis chronica atrophicans, fibrous nodules, morphea-like plaques, lymphocytic infiltration of the skin, nodular panniculitis, lichen sclerosus et atrophicus, Borrelia burgdorferi-associated cutaneous B-cell lymphoma

Erythema chronicum migrans (Lipschütz 1913, Afzelius 1921), lymphadenosis cutis benigna (Bäfverstedt 1943), and acrodermatitis chronica atrophicans (Herxheimer and Hartmann 1902) have long been known as classic tick-borne dermatoses. However, these dermatoses were not united into one disease group with a common etiology until Borrelia organisms were discovered in ticks (4) and in the tissues of the aforementioned dermatoses (Lyme borreliosis, 10). In the past several years, strong evidence has surfaced that morphea (1), lichen sclerosus et atrophicus (1), Pfeifer-Weber-Christian-like panniculitis (15), eosinophilic fasciitis (14), and benign lymphocytic infiltration of the skin Jessner-Kanof (13) should be

included in the group of Borrelia-induced cutaneous diseases (2, 11). It should be stressed that the diagnosis of a cutaneous Lyme borreliosis should prompt a search for a multisystem disorder.

A number of modern laboratory methods have been developed for identification of Borrelia infections. These include cultivation of *B. burgdorferi* from lesional skin specimens, blood, and urine; indirect fluorescent antibody assay (12); ELISA for IgM and IgG antibodies to *B. burgdorferi* - currently still of limited value due to interlaboratory variabilities; and recently PCR assay of *B. burgdorferi* DNA sequences in blood and urine as well as PCR analysis of biopsy specimens. However, in spite of these powerful techniques, the correlation of clinical and pathological cutaneous findings remains the first step in the diagnosis of Lyme borreliosis of the skin.

In the following, the characteristic light microscopic histopathological features of the major cutaneous borrelioses are presented. Such findings should occasion further, i.e. confirmatory, diagnostic procedures. The histopathologist carries the responsibility for diagnosing Borrelia-induced skin diseases, thereby permitting the institution of timely therapeutic measures. Prompt treatment guards the patient from the possibility of serious damage to organs and organ systems (central and peripheral nervous systems; visceral organs - heart; joints), and ultimately from invalidity.

Histopathology of the Tick Bite

Dermatopathologists should be aware of the histopathological features of a recent tick bite, even if the specimen does not permit identification of the tick itself. The reaction pattern of a tick bite may be suggested by the type and distribution of inflammatory cells in the acute toxic phase a few hours after the bite. To some extent, differentiation from other insect sting and bite reactions, such as inflicted by mosquitoes, bedbugs, and *Sarcoptes scabiei*, is also possible in a biopsy of a fresh tick bite lesion.

An intra-epidermal blister containing erythrocytes and nuclear debris, and a superficial and deep infiltrate composed predominantly of mature neutrophils with admixed lymphocytes, histiocytes, and eosinophils is characteristic of a recent tick bite, as shown in Fig. 1. The neutrophilic infiltrate is found mainly between the collagen fibers, and is particularly dense surrounding the bite injury. The infiltrate decreases in density with increasing tissue depth, where accumulations in the area of the sweat glands and blood vessels may still be found. A neutrophilic

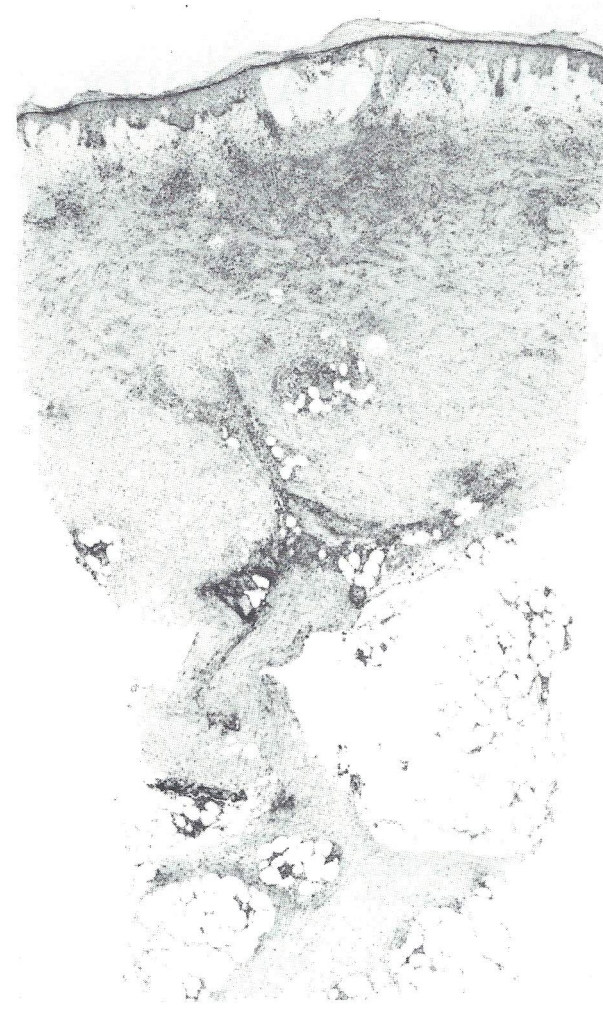

Fig. 1 Scanning power view of the tick bite lesion few hours after the bite (No. 7978/92, H&E): Intraepithelial blister, severe papillary dermal edema, and dense upper, mid, and deep dermal neutrophilic infiltrate.

panniculitis is seen in the fat tissue. A lympho-histiocytic infiltrate, intermingled with individual eosinophils surrounds the vessels of the upper and middle dermis. The dermo-epidermal junction appears sharply drawn owing to pronounced edema of the stratum papillare, in which dense focal aggregations of erythrocytes are seen (Fig. 1). In contrast to sting reactions from most other insects in which eosinophils predominate, tick and sand-flea bites are characterized by an essentially neutrophilic infiltrate (Fig. 2).

In a few days older tick bite lesions, the site is marked by a vertical zone of densely packed,

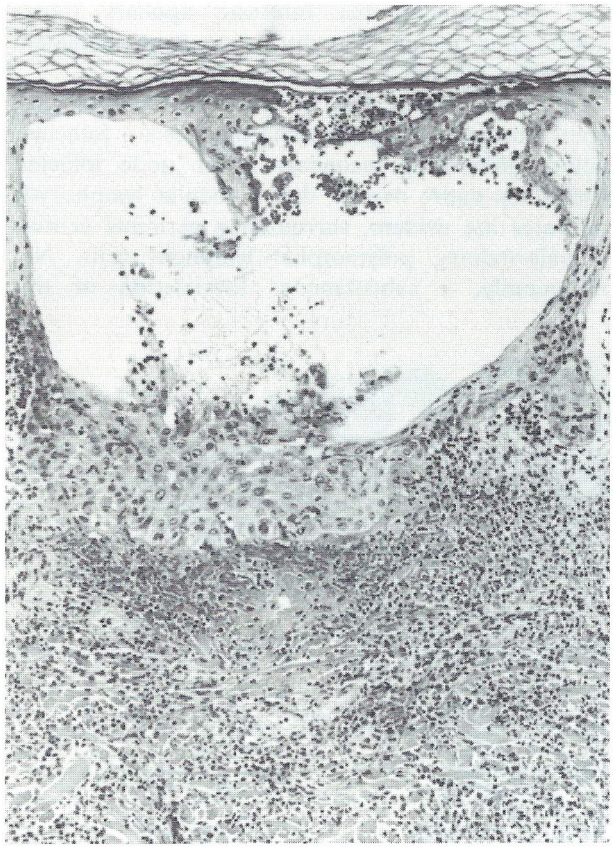

Fig. 2 Histological detail of Fig. 1: Dense infiltrate of mature neutrophils and nuclear debris between collagen bundles (x50).

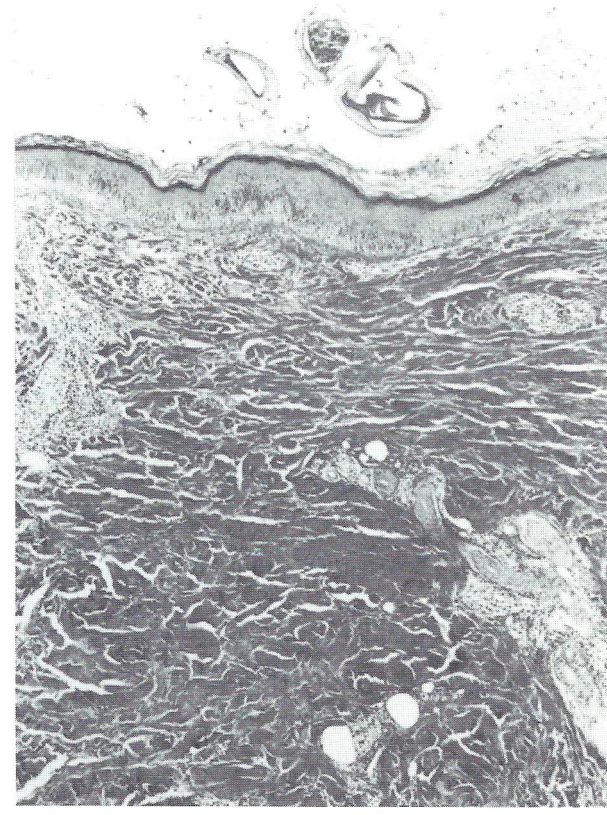

Fig. 3 Tick bite lesion, one day old (No. 10991/89, H&E): Vertical zone of densely packed sclerotic collagen bundles below the bite area, with tick fragments above the epidermis. Upper and middermal perivascular and deep dermal lymphocytic infiltrates around sudoriferous glands.

thickened, sclerotic collagen bundles in the upper and mid-dermis.

The lower portion of the thickened collagen bundles is rimmed by basophilic granular debris, and neutrophils or their nuclear debris is interspersed between the bundles. On both sides of the sclerosed collagen adjacent to the bite site, a superficial perivascular lymphocytic infiltrate prevails, whereas around sweat glands and within the fat lobuli lympho-histiocytic infiltrates predominate (Fig. 3).

Erythema chronicum migrans

In the clinically fully developed lesions of erythema chronicum migrans, observed in 38 patients at this clinic from 1991-1993, the salient histologic features are a thickened basket-weave horny layer, and atrophy of the epidermis with tiny spongiotic foci. A conspicuous finding (with rather rare exceptions) is the loss of pilosebaceous units and smooth muscle remnants. Interstitial edema and an increased number of fibroblasts or fibrocytes is present throughout the dermis. A moderate superficial and deep infiltrate composed mainly of lymphocytes, with admixed plasma cells and histiocytes, in perivascular coatsleeve arrangement is commonly seen around dilated vessels (Fig. 4). However, diagnosis of this particular disease is made chiefly by clinicopathological correlation. Erythema chronicum migrans signals the first stage of *Borrelia* infection, but may already be accompanied by symptoms of systemic disease.

Lymphadenosis cutis benigna (Borrelial lymphocytoma)

The earlobes and the areola mamillae are the sites of predilection for borrelial lymphocytomas,

but they may also occur in the face, on the trunk, or in the axillary or genital regions. They appear clinically either as solitary or aggregated multiple soft reddish nodules, accompanied by indolent regional lymphadenopathy. Because its etiology is known, borrelial lymphocytoma should be differentiated from other pseudolymphomas. Two main histopathological patterns of borrelial lymphocytoma can be differentiated, according to the pattern of infiltration and the type of cells involved.

cells predominate, the infiltrate appears rather polymorphic, making the distinction from malignant lymphoma difficult.

The other, albeit less common histopathological type of borrelial lymphocytoma manifests a follicular pattern, mimicking secondary lymph node follicles. Within the entire dermis, dense nodular lymphocytic infiltrates are evident, surrounding germinal centers of pale-staining polymorphic lymphoid cells. Not infrequently, a subcutaneous localization of this

Fig. 4 Erythema chronicum migrans (No. 17328/93, H&E, scanning power view): Mild superficial and deep perivascular infiltrate composed mainly of lymphocytes. Papillary and interstitial edema and increased number of fibroblasts throughout the dermis. Lack of pilosebaceous units.

The more common histopathological type displays a dense nodular or diffuse pattern of infiltration, and usually occupies the upper and middermis, but occasionally predominates in the deeper part of the dermis, and may then extend into the subcutaneous fat. Therefore, either top-heavy or bottom-heavy infiltrations occur. These are composed of small mature lymphocytes with an admixture of medium-sized lymphoid cells with pale-staining indented or cleaved nuclei. The proportion of these two cell types in the infiltrate varies considerably. Dense monomorphic infiltrates of small mature lymphocytes may be seen. Occasionally, this monomorphic pattern is disturbed by intermingled plasma cells, eosinophils, and multinucleate giant cells containing basophilic nuclear fragments. When the pale-staining lymphoid infiltration type leads to a bottom-heavy distribution.

It is noteworthy to mention that transitions occur between these two histopathological types, and that a mixed pattern exists.

Acrodermatitis chronica atrophicans (ACA)

Grossly, ACA exhibits markedly thinned, diaphanous, wrinkled, glossy skin with whitish and violaceous hues, located mainly on the extremities. Two stages in the course of this disorder must be considered: the early inflammatory edematous stage, and the atrophic stage of advanced disease (3,10). A concomitant manifestation of this disorder may be the development of fibrous nodules over the dorsal

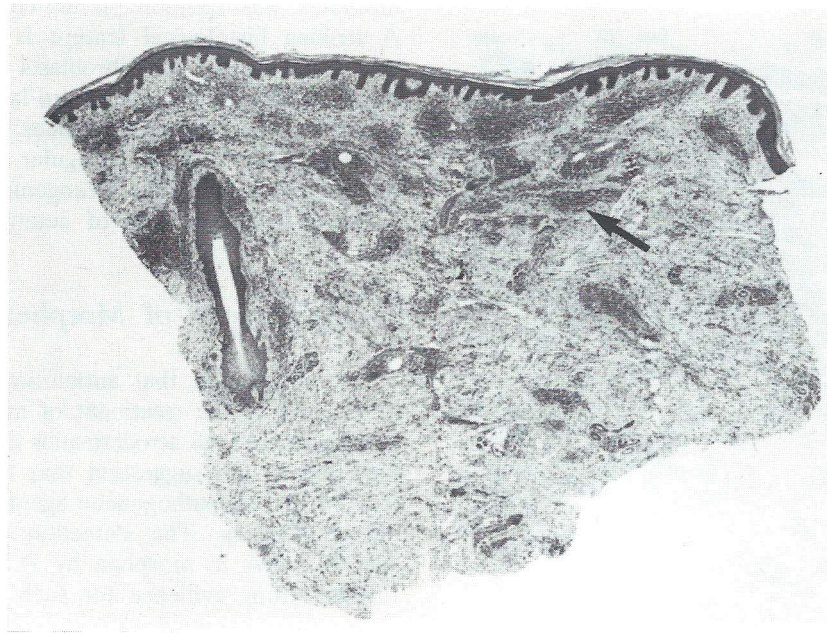

Fig. 5 Acrodermatitis chronica atrophicans, inflammatory edematous stage (No. 5173/87, H&E, scanning power view): Heavy, patchy, perivascular and periappendageal dermal infiltrate (arrow). The infiltrates within the papillary dermis tend to become confluent. Splitting of the collagen bundles by mucinous edema and pronouncedly increased number of fibroblasts throughout the entire dermis.

aspects of the elbows and knees.

In order to determine the salient histopathological features for the diagnosis of ACA, the slides from 78 patients in our files between 1978 and 1993 were examined.

Early inflammatory edematous stage of ACA

The overall architectural pattern reveals flattening of the epidermis, interstitial edema within the entire dermis, and patchy, tight perivascular and peri-appendageal infiltrates in the upper, middle, and deep dermis (Fig. 5). Around the upper vascular plexus, lymphohistiocytic and plasmacellular infiltrates are seen, which tend to coalesce in a lichenoid pattern. An admixture of plasma cells and histiocytes is also found within the infiltrate of the middle and deep dermis, and adipose tissue (Fig. 6).

The collagen bundles in the full breadth of the dermis are separated by interstitial edema. The colloidal iron stain (according to Mowry) reveals varying amounts of acid mucopolysaccharides deposited between the dermal collagen bundles and split fibers. Throughout the entire dermis, the number of fibroblasts is markedly increased.

Atrophic stage of ACA

As the lesion gradually becomes flaccidly atrophic, flattening of the epidermis develops, with loss of rete ridges and atrophy of the Malpighian layer. Adjacent to a subepidermal grenz zone, a lichenoid or sparse upper and middermal perivascular, variably dense, lympho-plasmacellular infiltrate with focal dominance of clustered plasma cells surrounding ectatic blood vessels are nearly pathognomonic features.

The blood vessels within the infiltrates are dilated and display conspicuous endothelial swelling. The breadth of the dermis is remarkably reduced, and edema splits up the collagen bundles (Fig. 7). The elastic fibers are either degenerated and greatly decreased, or entirely absent. An increased number of fibroblasts, some with bizarre configurations, can be seen interstitially, as well as giant cells with a floret-like arrangement of nuclei. The sweat glands are preserved, whereas there is complete loss of the pilosebaceous units. The subcutaneous fat may even be atrophic.

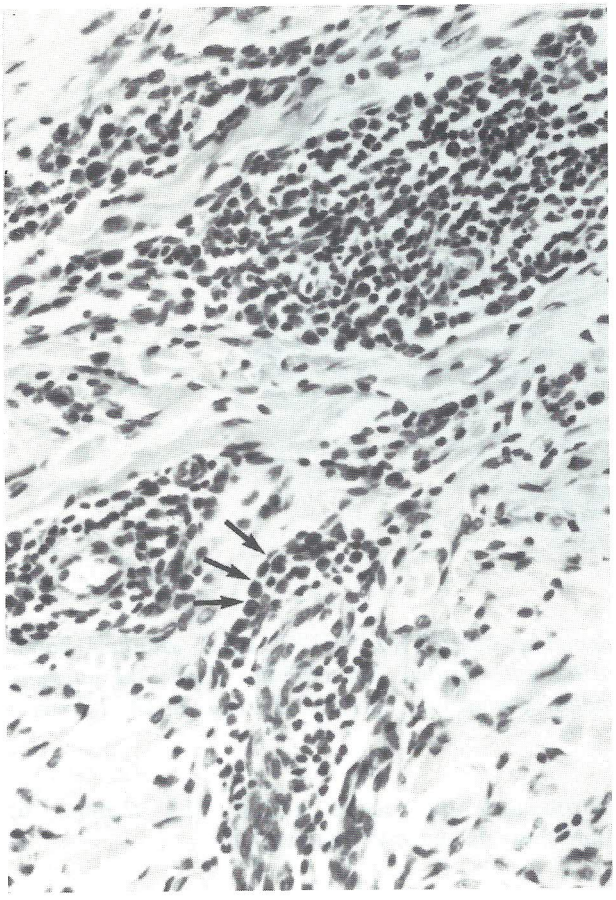

Fig. 6 Acrodermatitis chronica atrophicans, inflammatory edematous stage (arrowed detail of Fig. 5): Tight perivascular infiltrate composed of lymphocytes and varying numbers of plasma cells (arrows) (x250).

Histopathology of fibrous nodules

The fibrous nodules found on the dorsal aspects of the elbows or knees in ACA have a hard consistency, similar to that of cartilage. Their histopathological correlate is seen in coarse hyalinized collagen bundles within the middle and lower parts of the generally broadened dermis. They display either onionlike, intersecting, or cartwheel patterns, as may be seen in some fibrohistiocytic tumors. Areas of sclerosing collagen bundles arranged in a cartwheel pattern are reminiscent of a sclerosing fibroma. Apart from intersecting bundles, the collagen in the upper dermis is arranged parallel to the epidermis. This part of the dermis contains numerous small blood vessels surrounded by sparse lymphocytic infiltrates, with sporadic plasma cells and eosinophils. A striking histological feature is the pronouncedly increased number of fibroblasts within the entire dermis. Scattered throughout are large cells containing a single hyperchromatic nucleus, or bizarre multinucleate cells with an irregular or angulated cell outline and a floret-like arrangement of their nuclei. There is complete loss of cutaneous adnexa (Fig. 8).

Histopathology of Morphea-like plaques

The observation that antibiotics may be effective or curative in the treatment of morphea, as well as its coincidence with acrodermatitis chronica atrophicans, have led to the suggestion that borrelial organisms may be the etiopathogenetic agents in this sclerosing dermal process. The detection of *B. burgdorferi*-specific DNA in morphea by PCR amplification is further strong evidence for such an etiology (14).

Under scanning magnification, morphea-like plaques following tick bites display an atrophy of the epidermis and a thickened, sclerotic dermis with superficial and deep inflammatory infiltrates. These are characterized by a mainly dense, patchy, perivascular distribution, or by sheets of interstitial cell aggregations composed of lymphocytes and plasma cells, the latter often in clusters. The infiltrates are sporadically interspersed with eosinophils and large oligonucleate cells. Remnants of hair follicles may be surrounded by lymphocytic or plasmacellular infiltrates (Fig. 9).

The broadened dermis contains compact, hyalinized collagen bundles, and a pronouncedly increased number of fibroblasts which entrap collagen bundles to resemble the structure of a dermatofibroma (Fig. 10). Obviously, the general histopathological findings in Borrelia-induced morphea-like lesions may be interpreted as an exaggeration of the dermal changes seen in early ACA, apart from less inflammation, edema, and mucin quantity in the former.

Lymphocytic infiltration (LI) of the skin (Jessner-Kanof)

A close relationship between LI and lymphadenosis cutis benigna (borrelial lymphocytoma) has repeatedly been postulated. In 1992, Rabb et al. reported the case of a patient who presented with intermittent skin lesions most consistent with LI. The lesions failed to respond to topical treatment, but showed

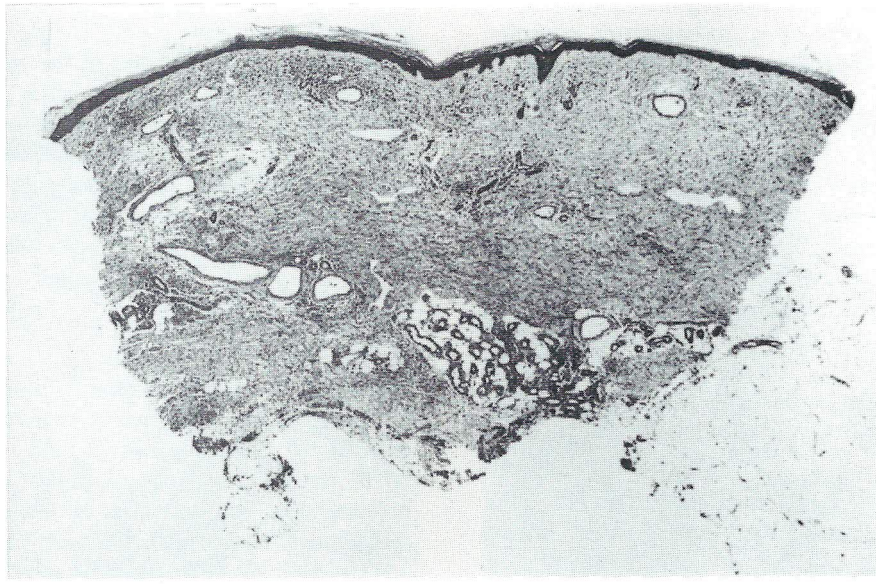

Fig. 7 Acrodermatitis chronica atrophicans, atrophic stage (No. 5673/83, H&E, scanning power view): Striking epidermal atrophy, dilated upper and middermal blood vessels, and a broad bandlike lympho- and plasmacellular infiltrate within the upper dermis are diagnostic hallmarks. Note the preserved eccrine sweat glands.

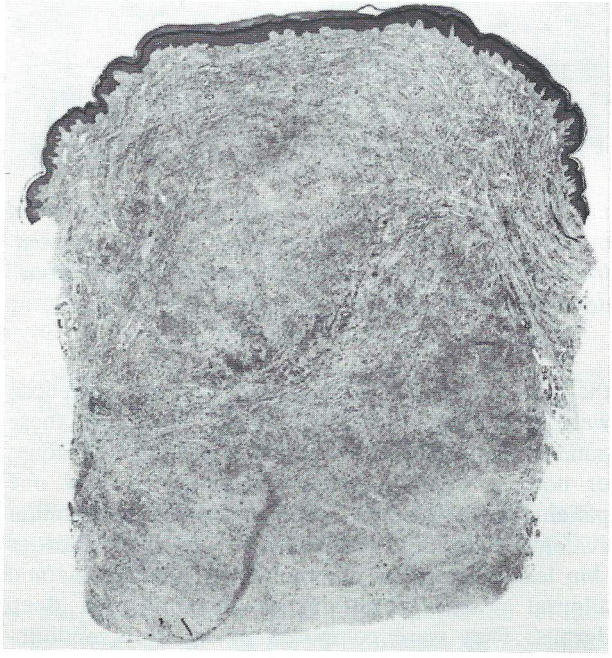

Fig. 8 Fibrous nodule (No. 7247/91, H&E, scanning power view): Coarse hyalinized collagen bundles with onionlike or intersecting or cartwheel patterns within the entire broadened dermis. The latter pattern is reminiscent of a sclerosing fibroma. The number of fibroblasts is increased. There is complete loss of cutaneous adnexa.

dramatic improvement following administration of doxycycline. PCR analysis was positive for *B. burgdorferi* DNA in the blood as well as in a biopsy specimen of the LI lesion (13).

Panniculitis in Lyme borreliosis

The observation of nodular panniculitides in patients positive for *B. burgdorferi* antibodies prompted the exploration of tissue for direct evidence of the etiologic agent. *B. burgdorferi* was cultured from blood as well as from subcutaneous adipose tissue obtained from a patient with the clinical picture of febrile nodular nonsuppurative panniculitis (15), and from patients with nodular panniculitis (7).

Lichen sclerosus et atrophicus

Extragenital LSA and ACA may occur simultaneously. Elevated titers of *B. burgdorferi* antibodies and evidence of treponemal structures within lesional skin strongly favor *B. burgdorferi* as the causative agent in this disease (1, 11). However, the results from other investigations are controversial.

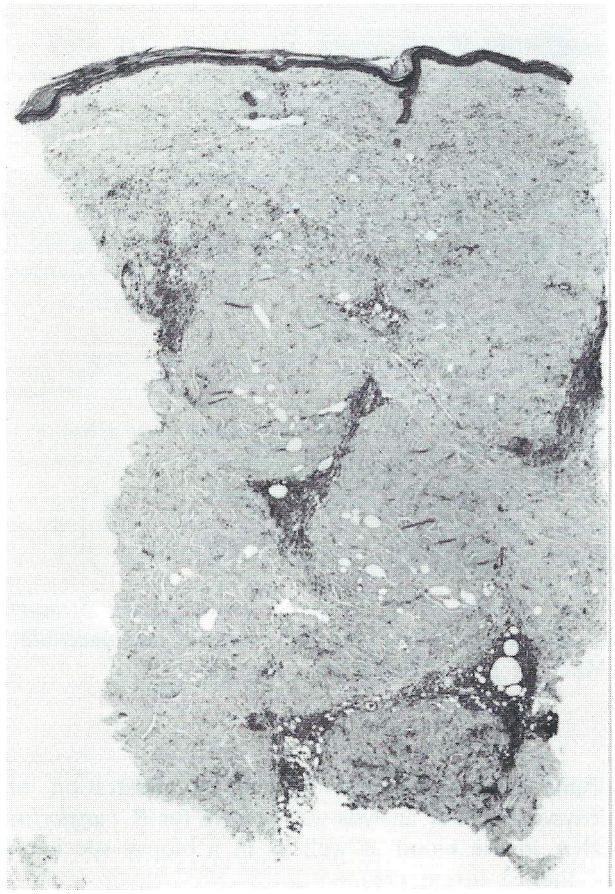

Fig. 9 Morphea-like plaque (No. 12250/91, H&E, scanning power view): Epidermal atrophy and pronounced thickening of the dermis with compact hyalinized collagen bundles. Mid and deep dermal, as well as subcutaneous inflammatory infiltrate composed of lymphocytes and plasma cells, often in clusters. Loss of pilosebaceous units, and atrophy of the subcutaneous adipose tissue.

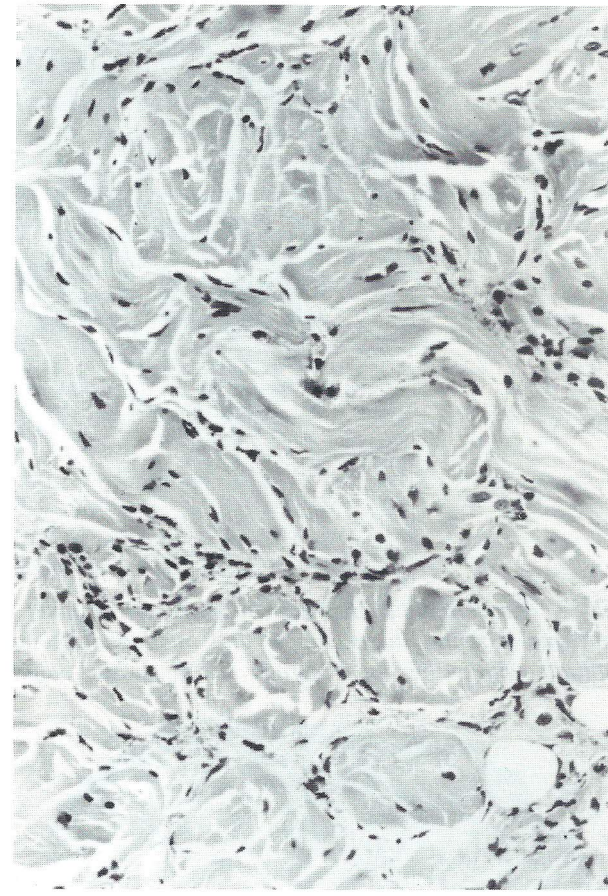

Fig. 10 Morphea-like plaque (detail of Fig. 9): Increased number of fibroblasts entrapping densely packed, hyalinized bundles of collagen, resembling a "fibrous" dermatofibroma (x250).

Borrelia burgdorferi-associated cutaneous B-cell lymphoma

Since the 1950s, there have been repeated reports of malignant lymphoreticular neoplasms in the area of lesional ACA (8). Malignant lymphomas also occur in clinically unchanged skin coincidentally with an extant ACA (6). Garbe et al. reported the occurrence of cutaneous low-grade malignant B-cell lymphomas in four patients, in whom simultaneous chronic *B. burgdorferi* infection could be proven. ACA was present in one of these patients, whereas the typical cutaneous manifestations of Lyme borreliosis were not evident in the others. However, these patients had exhibited ill-defined erythematous plaques or nodules existing for several years. In only one patient was systemic (bone marrow) involvement evident. Histologic examination of the tumorous skin lesions revealed predominantly perivascular and adnexal nodular infiltrates in the mid and deep dermis. They were composed of small to medium-sized cells with cleaved nuclei and intermingled with blastlike cells. In one case, a monomorphic infiltrate of small cells with cleaved nuclei was found, and in another, a centroblastic-centrocytic lymphoma with transformation into the centroblastic type was diagnosed. Their low-grade malignant nature was confirmed by their disease-free clinical course following

irradiation or excision of the nodules (5). In a patient whom we had observed, a nodular "reticulosis" in the region of an ACA regressed completely in response to radiation treatment (8), but following local recurrence she succumbed to generalized dissemination. In the event of a cutaneous B-cell lymphoma (or a pseudolymphoma), consideration should be given to borreliosis, especially when the patient comes from a geographic region where tick-borne diseases are common.

CONCLUSIONS

An overview of the histopathology of the cutaneous disorders associated with Lyme borreliosis is presented in this paper. It includes the spectrum of diseases in which the cutaneous affections are known to be caused by *B. burgdorferi* infection, as well as skin lesions in which infection by spirochetal agents has been recently proven or is strongly suspected. The changes in the histopathological features during the course of certain lesions are described and illustrated by photomicrographs.

Diagnostic hallmarks in the assessment of tick-borne spirochetal infections are superficial and deep, moderately dense, perivascular (and periappendageal) infiltrates composed of lymphocytes with an admixture of plasma cells in varying amount. The latter may come to predominate as the lesions continue. Interstitial mucinous edema and an increased number of fibroblasts, as well as pronounced fibrosis or sclerosis within the entire dermis are further conspicuous features which lend support to the diagnosis of a cutaneous borreliosis. Plasma cell-rich infiltrates within the sclerotic dermis may also lead to consideration of such an infection. Atrophy of the epidermis and dermis, bandlike upper dermal infiltrates composed of lymphocytes and plasma cells, and teleangiectatic blood vessels are nearly pathognomonic for the atrophic stage of acrodermatitis chronica atrophicans.

By taking this synoptic view of histopathological details into account, correct diagnosis of cutaneous disorders in Lyme borreliosis should be possible independently of clinical morphology. In certain cases, however, confirmation by immunoserological techniques is unavoidable.

REFERENCES

1. Aberer E, Stanek G: Histologic evidence for spirochetal origin of morphea and lichen sclerosis et atrophicus. Am.J.Dermatopathol.1987; 9: 374-379

2. Åsbrink E, Hovmark A: Lyme Borreliosis: Aspects of tick-borne Borrelia burgdorferi infection from a dermatologic viewpoint. Sem. Dermatol.1990; 9: 277-291

3. Burgdorf WHC, Worret WI, Schultka O: Acrodermatitis chronica atrophicans. Int. J. Dermatol. 1979; 18: 595-601

4. Burgdorfer W, Barbour AG, Hayes SF et al.: Lyme disease: a tick-borne spirochetosis? Science 1982; 216: 1317-1319

5. Garbe C. Stein H, Dienemann D, Orfanos CE: Borrelia burgdorferi-associated cutaneous B cell lymphoma: Clinical and immunohistologic characterization of four cases. J.Am.Acad.Dermatol.1991; 24: 584-590

6. Goos M: Acrodermatitis chronica atrophicans and malignant lymphoma. Acta derm.-vener.(Stockh.) 1971; 51: 457-459

7. Hassler D, Zorn J, Zöller L et al.: Noduläre Pannikulitis: eine Verlaufsform der Lyme-Borreliose? Hautarzt 1992; 43: 134-138

8. Hödl S: Knotige Retikulose auf Akrodermatitis chronica atrophicans. Hautarzt 1976; 27 (Suppl. I): 336-337

9. Kerl H, Kresbach H: Lymphoretikuläre Hyperplasien und Neoplasien der Haut. In: Spezielle pathologische Anatomie Bd.7 Histopathologie der Haut, 2.Aufl. W. Doerr, G. Seifert, E. Uehlinger (Hrsg.), redigiert von U.W. Schnyder, Springer Berlin Heidelberg 1979, pp.367-374

10. Lever WF, Schaumburg-Lever G (Eds.): Histopathology of the skin, 7th ed. Lippincott, Philadelphia 1990, pp. 359-361, 837-839

11. Neubert U: Klinische Aspekte der Borrelia-burgdorferi Infektionen. Z.Hautkr.1989; 64: 649-656

12. Park HK, Jones BE, Barbour AG: Erythema chronicum migrans of Lyme disease: Diagnosis by monoclonal antibodies. J.Am.Acad.Dermatol.1986; 15: 406-410

13. Rabb DC, Lesher JL, Chandler FW: Polymerase chain reaction confirmation of Borrelia burgdorferi in benign lymphocytic infiltrate of dermis. J.Am.Acad. Dermatol.1992; 26: 267-268

14. Rufli T, Gilli L: Hautborreliosen. In: Fortschritte der praktischen Dermatologie und Venerologie, Bd.13, O.Braun-Falco, G.Plewig, M.Meurer (Hrsg.), Springer Berlin Heidelberg 1993, pp.16-25

15. Viljanen MK, Oksi J, Salomaa P et al.: Cultivation of Borrelia burgdorferi from the blood and a subcutaneous lesion of a patient with relapsing febrile nodular nonsuppurative panniculitis. J. Infect. Dis. 1992; 165: 596-597

AUTHORS' ADDRESSES:

Dr. Stefan Hödl, MD, professor of dermatology, Department of Dermatology
University of Graz, School of Medicine, Auenbruggerplatz 8, A-8036 Graz, Austria
H. Peter Soyer, MD, assoc. professor of Dermatology, same address