

DERMATOPATHOLOGIC DIAGNOSIS OF LYME BORRELIOSIS

S. Hödl, H. P. Soyer and R. R. Müllegger

ABSTRACT

The goal of this study was to determine the general light microscopic findings which lend support to the histopathologic diagnosis of the main cutaneous manifestations of Lyme Borreliosis. Their diagnostic criteria are delineated and illustrated.

In culminating lesions of erythema migrans and acrodermatitis chronica atrophicans, a peculiar connective tissue reaction includes an increase in the number of fibroblasts, proliferation of collagen fibers, and interstitial mucinous edema. The cellular infiltrates are patchy perivascular in erythema migrans and either patchy and/or band-like in acrodermatitis chronica atrophicans. They consist of lymphohistiocytic cells with a variable admixture of plasma cells. The damage to elastic (and even collagen) fibers occurs in early acrodermatitis chronica atrophicans and is reflected by the phenomenon of elastophagocytosis. Reduction or lack of pilosebaceous units is a constant finding. In advanced lesions of acrodermatitis chronica atrophicans, a thinning of the dermal breadth is noticed, resulting from a decrease in collagen and elastic fibers.

Fibrous nodules and morphea-like conditions are characterized by excessive formation of collagen. Borrelial lymphocytoma exhibits two different patterns of infiltration, accompanied by dermal fibrosis and increased numbers of fibroblasts. Recent tick bites show a predominantly neutrophilic infiltrate.

By applying the results of this synoptic study, histopathologic diagnosis of dermatoborrelioses should be possible without the absolute necessity of clinical correlation.

KEY WORDS

Lyme borreliosis, synoptic dermatopathologic diagnosis, recent tick bite, erythema migrans, borrelial lymphocytoma, acrodermatitis chronica atrophicans, elastophagocytosis, fibrous nodules, morphea-like conditions

INTRODUCTION

Notwithstanding the various laboratory techniques (e.g. ELISA, immunofluorescence assay, immunoblot, PCR (1)) for diagnosing cutaneous borrelial disorders, the correlation of clinical and pathological findings

remains the first step towards the diagnosis of these endemic dermatoses. Apart from atypical forms, the gross appearance of the major dermatoborrelioses allows for a spot diagnosis in most instances. It has been stated that the histopathologic features are of little diagnostic value without the demonstration of

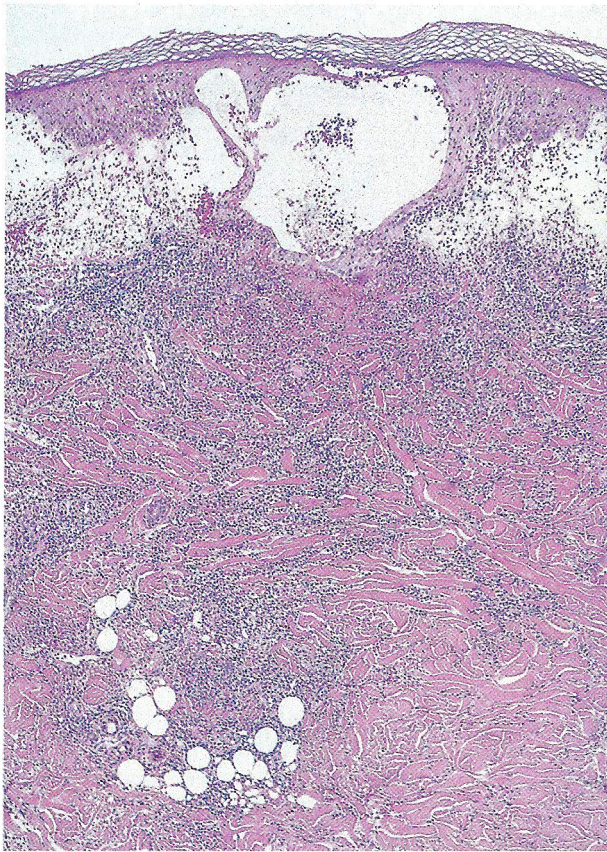


Fig. 1. Recent tick bite lesion (# 7978/92, H & E, scanning power view): Intraepithelial blister, diffuse upper and middermal and perivascular deep dermal neutrophilic infiltrate.

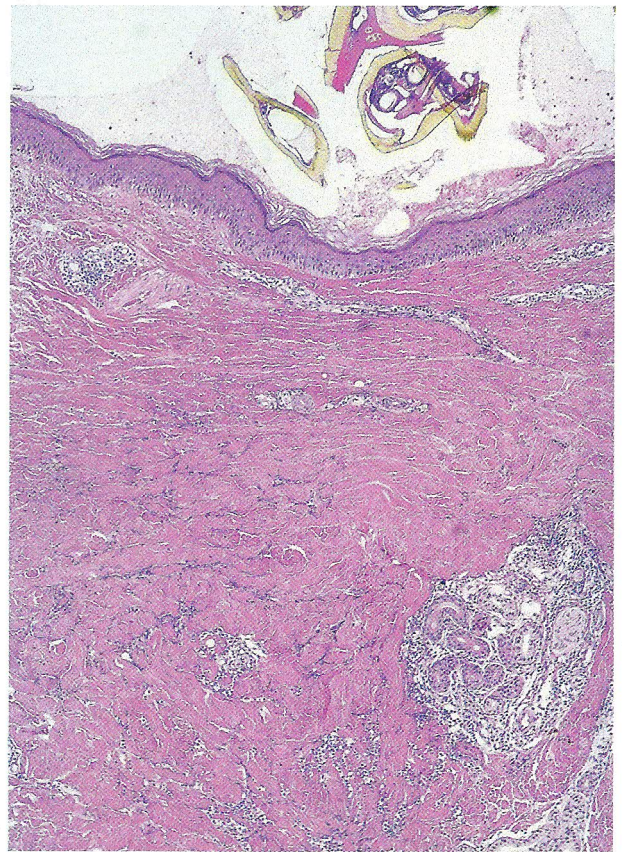


Fig. 2. Tick bite lesion, one day old (# 10991/89, H & E x 50): Vertical zone of densely packed sclerotic collagen bundles below tick fragments. Perivascular lymphocytic infiltrates with admixture of neutrophils.

spirochetes (2). However, these agents are difficult to detect in biopsy specimens, even when appropriate staining methods are used (2,3). Histopathologic changes taking place during the course of dermatoborreliosis are a further diagnostic challenge in the assessment of these disorders.

This group of diseases is caused by various strains of *borrelia*, however, these organisms may share pathologic sequelae in the infected skin. The goal of this study was to determine the general light microscopic findings which lend support to the histopathologic diagnosis of dermatoborreliosis.

MATERIAL AND METHODS

We analyzed histologic specimens of erythema (chronicum) migrans (EM) (41 cases), borreliolymphocytoma (BL) (5 cases), acrodermatitis chronica atrophicans (ACA) (82 cases), fibrous nodules (5

cases) and morphea-like changes (4 cases). Three cases of recent tick bites were also included. All histopathologic descriptions and illustrations are either of H & E or Orcein and Mowry-stained paraffin-embedded skin biopsy specimens.

RESULTS AND DISCUSSION

TICK BITE

The recent tick bite lesion exhibits an intraepidermal blister at the site of the bite injury, containing erythrocytes and nuclear debris and a superficial and deep dermal infiltrate mainly composed of mature neutrophils and admixed lymphocytes, histiocytes and a few eosinophils (Fig. 1). This predominantly neutrophilic infiltrate discriminates the tick bite from the sting reactions resulting from most other insects such as mosquitoes, bedbugs or *Sarcoptes scabiei*, in which eosinophils are preeminent.

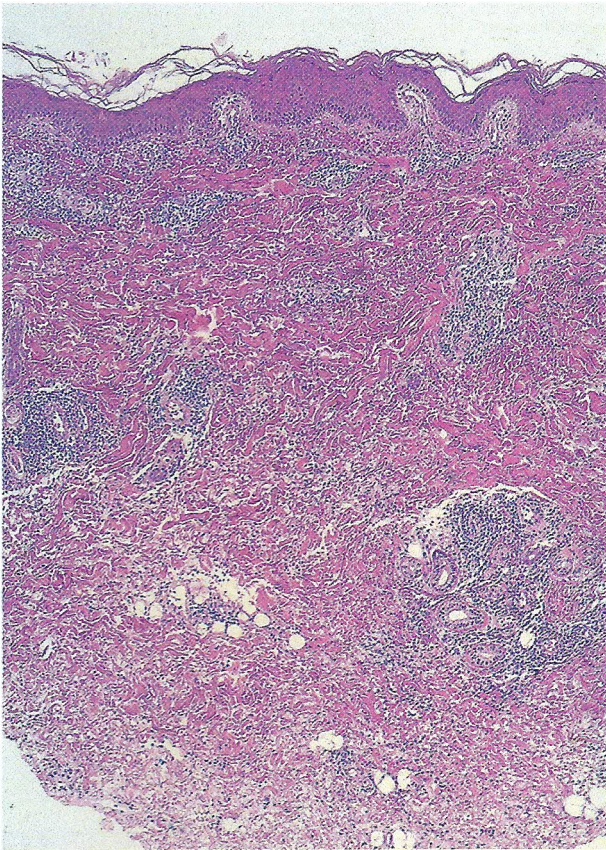


Fig. 3. *Erythema migrans* (# 17328/93, H & E, scanning power view): Moderate superficial and deep perivascular predominantly lymphocytic infiltrate. Interstitial edema, proliferation of fibroblasts and collagen throughout the dermis. Lack of pilosebaceous units.

In older tick bite lesions a few days old, the injury site is marked by a vertical zone of densely packed, thickened, sclerotic collagen bundles within the dermis. Neutrophils or their nuclear remnants are interspersed between the bundles (Fig. 2).

DERMATOPATHOLOGY OF LYME BORRELIOSIS

ERYTHEMA (CHRONICUM) MIGRANS

The clinically fully developed lesion consists histologically of a flattened, yet cytologically normal epidermis. The salient histological findings are fibrosis of the reticular dermis, interstitial edema in both the papillary and reticular dermis, increased numbers of fibroblasts and extensive loss of pilosebaceous units. Smooth muscle remnants of the arrector pili may be present, whereas the sudoriferous glands are

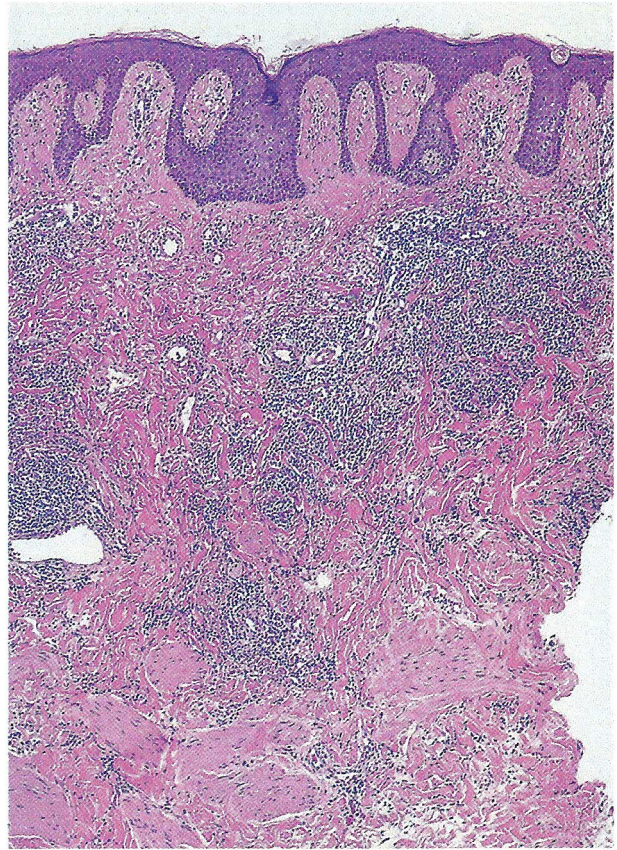


Fig. 4. *Borrelial lymphocytoma* (# 19744/95, H & E x 50): Diffuse infiltration of the upper and mid dermis with small lymphocytes and admixture of medium-sized lymphoid cells.

mostly preserved. A moderately dense, patchy, superficial and deep infiltrate, composed mainly of lymphocytes with admixed histiocytes, arranged around dilated vessels, nerves, and eccrine glands is commonly seen (Fig. 3). The histopathologic diagnosis of EM can be made on the basis of a picture encompassing all the above-mentioned morphologic components. However, a subtle clinico-pathologic correlation is often required.

BORRELIAL LYMPHOCYTOMA (LYMPHADENOSIS CUTIS BENIGNA)

The earlobes and the areolae of the mamillae are the sites of predilection for BL. However, it also occurs in the face or in the axillary and genital regions. The gross appearance is characterized by either a solitary or an aggregate of soft reddish or bluish-red nodules.

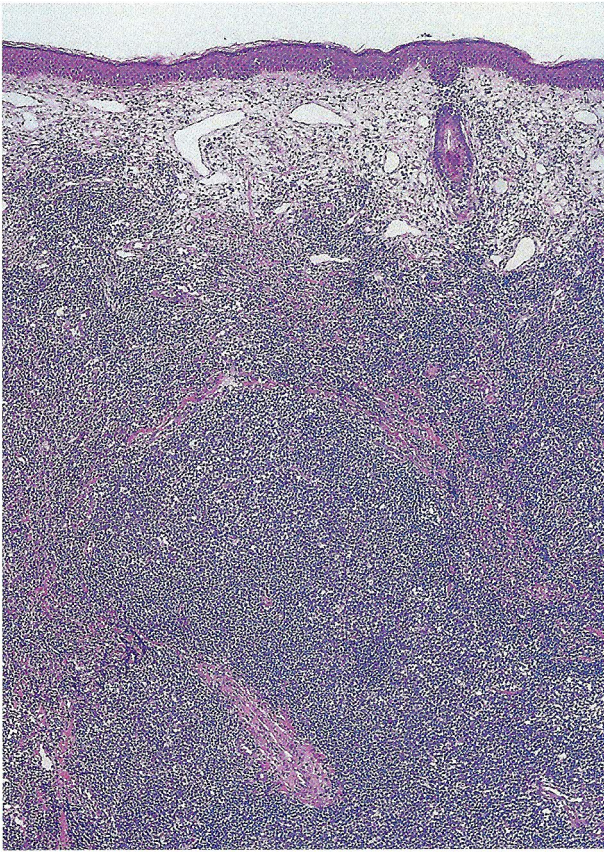


Fig. 5. *Borrelial lymphocytoma* (# 31658/93, H & E x 50): Dense nodular lymphocytic infiltrate surrounding germinal centers of medium-sized lymphoid cells (follicular type).

Two main histopathologic patterns can be differentiated according to the pattern of infiltration and the type of cells involved. The more common histopathologic type reveals a dense nodular or diffuse pattern of infiltration which usually occupies the upper and mid dermis. The infiltrate is composed of small, mature lymphocytes and a variable admixture of clustered, medium-sized lymphoid cells with pale-staining indented nuclei and plasma cells (Fig. 4). The component of pale-staining lymphoid cells may predominate, resulting in a polymorphic appearance of the infiltrate, thus making the distinction from malignant lymphoma difficult. The connective tissue background shows fibrosis, interstitial edema and increased numbers of fibroblasts. The latter features are obscured in the less common follicular type of BL, which is characterized by a dense, nodular lymphocytic infiltrate surrounding germinal centers of medium-sized, pale-staining polymorphic lymphoid cells. This pattern of infiltration mimics secondary



Fig. 6. *Acrodermatitis chronica atrophicans*, infiltrative edematous stage. Edema and bright red inflammation on the back of the hand (G.M., 58 year-old female). For corresponding histology see Fig. 7a and b.

lymph node follicles. The borders between the abutting units are effaced and the infiltrate occupies the entire reticular dermis, extending into the subcutaneous fat in places. The papillary dermis is spared from the infiltrate, but displays a conspicuous edema and dilated capillaries (Fig. 5). It should be mentioned that transitions between these two histopathologic patterns may occur.

ACRODERMATITIS CHRONICA ATROPHICANS

ACA arises as a primary well demarcated, bright red swelling, mainly located on the extremities. After months or years, the infiltrative edematous stage gradually progresses into the atrophic stage of advanced disease. At this point, ACA exhibits markedly thinned, diaphanous, wrinkled, glossy skin with whitish and reddish-violaceous hues. Therefore, two different pictures corresponding to the two stages in the

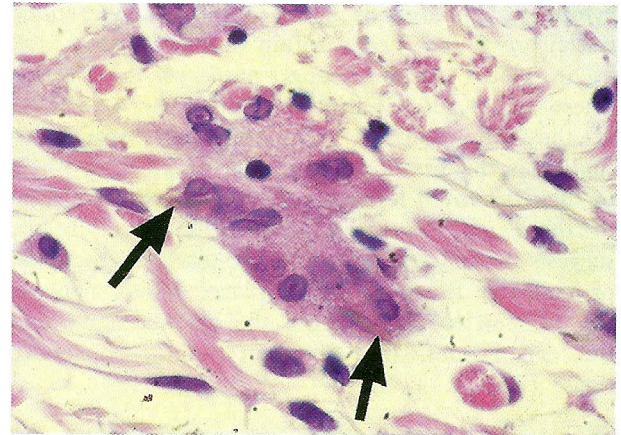
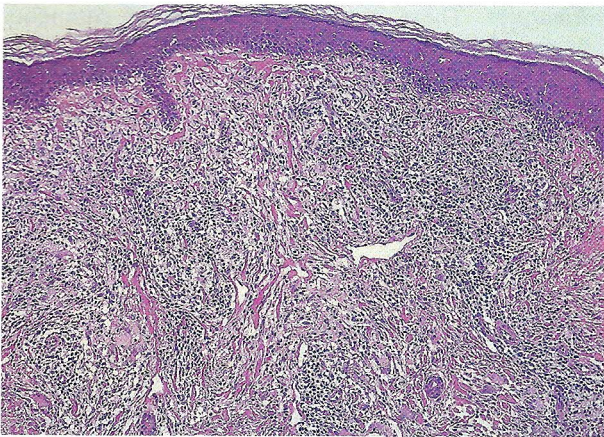


Fig. 7. *Acrodermatitis chronica atrophicans* (# 5651/95, H & E).

a) Subepidermal band-like lymphohistiocytic infiltrate (x100).

b) Elastophagocytosis: Elastic fibers (arrows) within the cytoplasm of a multinucleated giant cell (x 1000).

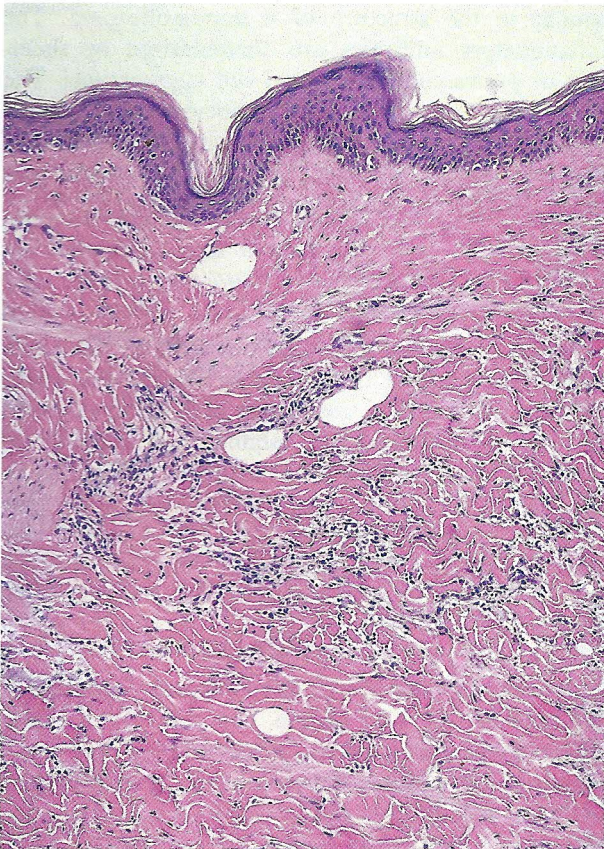


Fig. 8. *Sclerodermiforme condition in acrodermatitis chronica atrophicans* (# 12250/91, H & E x 100): Epidermal atrophy and markedly thickened dermis with densely packed hyalinized collagen, increased number of fibroblasts and focal lymphoplasmacellular infiltrates.

course of ACA must be considered. Occasionally, fibrous nodules and morphea-like conditions coincide within atrophic skin over the dorsal aspects of the elbows, metacarpus and knees.

INFILTRATIVE EDEMATOUS STAGE OF ACRODERMATITIS CHRONICA ATROPHICANS:

The architectural pattern is either composed of subepidermal, band-like and/or patchy perivascular infiltrates. The latter are present throughout the dermis in a chiefly top-heavy pattern. The band-like pattern may be accompanied by necrosis of basal keratinocytes and vacuolar alteration at the dermo-epidermal interface, as seen in lichen planus. The infiltrate is basically lymphohistiocytic, but plasma cells participate in variable numbers. The dermis itself shows fibrotic collagen, separated by interstitial mucinous edema and a markedly increased number of fibroblasts.

In rather rare cases of ACA (3 out of 58 patients in our histology files 1994 - 1995) the microscopic substrate discloses the mechanism of elastic fiber damage. From a clinical viewpoint, it is more often observed in the culminating inflammatory stage, as depicted in Fig. 6. However, it may also be encountered in the early, atrophic stage, when the lesions still contains a moderate perivascular, lymphoplasmacellular infiltrate, i.e. in a not fully „burned out“ lesion. The process of elastic fiber damage may be distinctly seen in lesions where the upper dermal band-like infiltration type of ACA is present. Large histiocytic cells with abundant eosinophilic

cytoplasm and one or more (multiple) palestaining nuclei are found focally within this infiltrate as well as in places within deeper parts of the dermis. These large cells occur either singly or in clusters in the formation of granulomas. A conspicuous finding is the presence of grayish or greenish fibers or their destroyed remnants lying within the cytoplasm of these multinucleated giant cells. This strongly suggests that phagocytosis of elastic (elastophagocytosis) or collagen fibers is taking place. Fibers may be clearly seen to extend from the cytoplasm, beyond the cell border, into the surrounding connective tissue (Fig. 7a + b).

ATROPHIC STAGE OF ACRODERMATITIS CHRONICA ATROPHICANS:

As the lesion gradually becomes flaccidly atrophic, the epidermis is reduced to a few layers and shows complete loss of rete ridges. Subepidermal lichenoid or sparse upper and middermal perivascular and perineural lymphoplasmacellular infiltrates surrounding dilated blood vessels are nearly pathognomonic features. The breadth of the dermis is remarkably decreased and edema separates the collagen bundles. When applying the orcein (elastica) stain, the elastic fibers are markedly decreased or entirely absent. An increased number of fibroblasts, some with bizarre configurations, can be seen interstitially. Single large mono- or binucleated cells with engulfed fragments of fibers are found here and there. The sweat glands are preserved, whereas pilosebaceous units are greatly reduced or completely absent.

FIBROUS NODULES

The fibrous nodules are commonly found on the dorsal aspects of the elbows, metacarpus, knees or on the ankles (juxtaarticular location) and consist of a dome-shaped, slightly red mass with a cartilaginous consistency. Their histopathologic correlate is the presence of coarse hyalinized collagen bundles within the middle and deep dermal parts of the broadened dermis. Occasionally the mass lies in the subcutis. Fibrous nodules display either onion-like, interlacing or cartwheel patterns, as may be observed in some fibrohistiocytic tumors or in sclerosing fibroma. A striking histopathologic finding is the markedly increased number of fibroblasts within the areas of proliferated collagen fibers. Sparse lymphocytic infiltrates with admixed plasma cells can be seen around small blood vessels in the subepidermal part and at the periphery of the peculiar collagen

formations. There is a complete lack of cutaneous adnexa when the lesion is confined to the dermis.

MORPHEA-LIKE AND SCLERODERMIFORME CONDITIONS

Grossly, these conditions appear as whitish or ivory-colored plaques or sheets of indurated, tightly fitting, scleroderma-like skin, located mainly on the lower leg and instep. Thus, the range of joint mobility may be limited. The disorder develops gradually within a period of several months.

Under scanning magnification, the plaques reveal a thinned out, flattened epidermis and a noticeably thickened, sclerotic dermis with superficial and deep, inflammatory infiltrates. The excessively broadened dermis contains compact homogeneous hyalinized collagen and a considerably increased number of fibroblasts which entrap collagen bundles in a pattern similar to the structure of a dermatofibroma. The inflammatory infiltrates are characterized by sheet-like or perivascular interstitial cell aggregations. The latter are composed of lymphocytes and plasma cells as well as sporadic eosinophils. Remnants of hair follicles may be present (Fig. 8). The subcutaneous fat is largely replaced by sclerotic collagen.

CONCLUSION

Although the major cutaneous entities of Lyme Borreliosis may be diagnosed by their gross appearance at first glance, correlation with histopathologic features is mandatory to establish an unequivocal diagnosis in these disorders. This procedure is especially important in atypical manifestations. Our study of a large series of skin biopsy specimens, taken from the main tickborne dermatoses, show that the representative histopathologic findings are as follows:

1. Recent tick bites show a predominantly neutrophilic infiltrate at the site of the bite injury and, thus, differ from reactions to other insect stings with largely eosinophilic infiltrates, such as mosquitoes, bedbugs, etc. (4,5).
2. A peculiar connective tissue reaction can be observed in culminating lesions of EM and ACA. This reaction includes a noticeable increase in the number of fibroblasts, proliferation of collagen fibers and an interstitial mucinous edema throughout the dermis. The edema consists of acid mucopolysaccharides (Mowry stain). The cellular infiltrates

exhibit a patchy, perivascular arrangement in EM and either patchy and/or band-like lichenoid patterns in ACA (6). The dominant inflammatory cells are lymphohistiocytic with a variable admixture of plasma cells. The damage to elastic (and even collagen) fibers is discernible in a few lesions of lichenoid ACA. Stretched fibers or their destroyed fragments are found within the cytoplasm of large epitheloid or multinucleated giant cells, representing elastophagocytosis. A reduction in or lack of pilosebaceous units is a constant finding. In advanced lesions of ACA a considerable thinning of the dermal breadth is noticed, resulting from a decrease in collagen and elastic fibers. In the end, the elastic fibers are completely absent as is the cellular infiltrate („burned out“ lesion). A lack of pilosebaceous units is a remarkable finding in both entities as well as in the following conditions.

3. Fibrous nodules (7,8) and morphea-like conditions in ACA (9,10) are characterized by excessive formation of collagen, either in an onion-like, matted fascicular or pronounced sclerosing manner. The perpetual presence of *borrelia* organisms may play a role in the peculiar reaction of the affected tissue (3).

4. BL shows two different patterns of infiltration: i) nodular or diffuse spread of small lymphocytes with admixed medium-sized lymphoid cells. ii) a follicular pattern mimicking secondary lymph node follicles (11).

By applying the results of this synoptic study, the histopathologic details of a suspicious lesion should supply ample information to diagnose the entire spectrum of dermatoborrelioses without the absolute necessity for clinical correlation.

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