

Acrodermatitis Chronica Atrophicans: Histopathologic Findings and Clinical Correlations in 111 Cases

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We studied 111 consecutive, untreated and serologically confirmed patients with acrodermatitis chronica atrophicans. Emphasis was on the histopathologic patterns of erythematous and fibrous lesions, and on an assay used to correlate histopathologic findings with such clinical features as fibrous nodules, ulnar bands and the pain reaction allodynia. There was a significant correlation between allodynia and signs of marked inflammation, but not between allodynia and neural and perineural cell infiltrates or fibrosis. Moreover, there was no significant correlation between serum IgG titers to *Borrelia* and the density of inflammatory cell infiltrates or the proportion of plasma cells in tissue. Histopathologic examination did not reveal any important differences between fibrous nodules, ulnar bands and sclerodermatous lesions. The histopathologic pattern is not diagnostic *per se*, but characteristic enough to alert the experienced pathologist. Key words: Lyme borreliosis; pain reactions; allodynia; fibrous nodules; ulnar bands; sclerodermatous lesions.

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Acrodermatitis chronica atrophicans (ACA) is a late manifestation of Lyme borreliosis that is prevalent in Scandinavia and Central and Eastern Europe. It has recently been linked with one of the three genomic groups of *Borrelia burgdorferi*, i.e. *B. afzelii*, which is present in Europe and Asia but has hitherto not been found in North America (1, 2).

In 1986, we studied 32 patients with ACA with regard to the clinical and histopathologic picture, the course of the disease, and the relationship to erythema migrans (3). In the present investigation, we scrutinized another 111 consecutive and untreated ACA patients. Based on our latest results, we present a more extensive description of the histopathologic patterns seen in ACA, and assay to correlate such patterns with certain clinical features, e.g. fibrous nodules, ulnar bands, swelling of the feet, and the pain reaction allodynia.

MATERIAL AND METHODS

The studied patients comprised 74 women (67%) and 37 men (33%), varying in age from 25 to 90 (median 64) years. In all cases the medical histories and the clinical signs and symptoms were consistent with ACA (3), and the diagnoses had been verified by elevated serum IgG antibodies to *Borrelia*. ELISA with sonicated *B. afzelii* (strain ACA1) as antigen was used as previously described (4); values of 500–<2,000 were regarded as moderately elevated, and values $\geq 2,000$ as highly elevated.

At the time of examination, the patients were asked whether they had experienced the exaggerated pain reaction called allodynia, i.e. the kind of pain caused by a non-noxious rap to the skin (5).

In all cases, 4-mm punch biopsy specimens were taken from erythematous lesions, and in two cases also from sclerodermatous (scleroderma-like) lesions, before antibiotic therapy was initiated. In 45 cases, more than one biopsy was performed. Altogether, 157 biopsy specimens were secured: 41 were from feet, 40 from hands, 26 from elbows, 16 from thighs, and the remaining 34 from other sites. The material was fixed in 10% formalin and then embedded in paraffin. Sections were routinely stained with haematoxylin (htx)-eosin, and with periodic acid-Schiff (PAS) and Weigert van Gieson stains. In selected cases, sections were also stained for elastin and mast cells. In seven cases with dense inflammatory cell infiltrates the PAP immunoperoxidase staining technique with DACO antibodies against T-cells (UHCL1, CD43), B-cells (L26, 4KB5), and macrophages (Mac 387, CD68) was used on paraffin-embedded material.

The χ^2 -test was used in the statistical calculations.

RESULTS

Clinical data

The median duration of the ACA lesions was 2–3 years. Thirty-eight patients had noticed their skin lesions for 1 year or less and 19 for more than 10 years. The lesions had started on a lower limb in 65 of the patients, on an upper extremity in 45, and on the face in one. At the time of diagnosis, 49 patients had involvement of two or more extremities.

All patients displayed typical ACA lesions, i.e. more or less erythematous, often bluish-red, non-scaling lesions with indistinct borders. Sometimes there was also oedematous non-pitting swelling, which, according to the patient histories, could vary in intensity from one occasion to the next. In many cases, marked swelling affected a foot, making it necessary for some of the patients to wear larger shoes or rubber boots. Twenty patients (18%) had fibrous nodules, of which 16 were situated near or on the elbow, 3 in the knee region, and 1 close to a big toe. Eight patients displayed ulnar bands, and one patient had a similar band in the pretibial region. Two patients had concomitant indurated, sclerodermatous plaque lesions that were ivory in colour. Ten patients had subluxations of small joints of the hands or feet underlying erythematous lesions; there was no evidence of arthritis. Six patients had areas of advanced skin atrophy.

Forty-three patients had moderately and 68 highly elevated serum IgG titres to *Borrelia*.

One-hundred patients answered the question about whether or not they had experienced allodynia. This kind of pain occurred when a bony prominence underlying ACA lesions was lightly bumped against a hard object, for example the edge of a table. It was distinctly described as a sudden, sharp, intensive pain lasting from only a few to 30 s. Fifty-four patients said that they had experienced allodynia. In addition, many patients complained of intermittent but more persistent pain in the extremities.

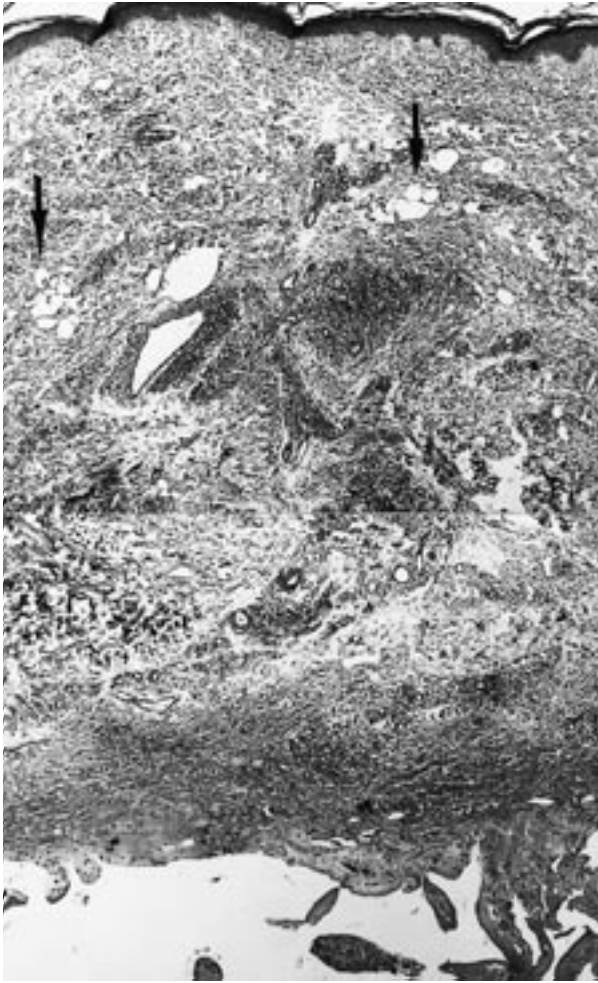


Fig. 1. Ulnar band. Elbow, 76-year-old male. There is marked inflammation in the dermis and subcutis with dense patchy inflammatory cell infiltrates and areas of oedema. In the upper half of the dermis dilated lymphatics and small groups of what we refer to as vacuoles (arrows) can be seen. In subcutis, below an area of oedema, fibrosis is blending into sclerosis.

Histopathologic findings

With few exceptions, the 157 biopsy samples comprised the whole dermis and thus encompassed the dermal-subcutaneous interface as well. Ninety of the samples (57%) included a substantial part of the subcutaneous fat tissue. In 67 of these (74%), the subcutis showed inflammatory changes (Figs. 1 and 2). These changes were equivalent to, or milder than, those seen in the dermis, although in a few cases they were more prominent.

Epidermis

In 80 patients (72%) the epidermis did not show any significant changes, though slight acanthosis with hyperkeratosis and exocytosis of a small number of lymphocytes could be seen. In 21 cases the epidermis was markedly thin, but otherwise normal. In a further 10 cases, the epidermis was thin and displayed, in small areas, one or several changes considered typical for lichen planus. However, unlike lichen planus, the inflammatory cell infiltrate



Fig. 2. Fibrous nodule. Elbow, 81-year-old female. The epidermis is slightly acanthotic and hyperkeratotic. There is slight papillary oedema, and in the upper dermis telangiectases and dense patchy cell infiltrates are discernible. In the deep dermis and subcutis there is marked fibrosis. The dermal-subcutaneous interface is obscured. A large, dense cell infiltrate containing a small nerve (upper arrow) and a small vessel (lower arrow) can be seen in subcutis. Htx-eosin.

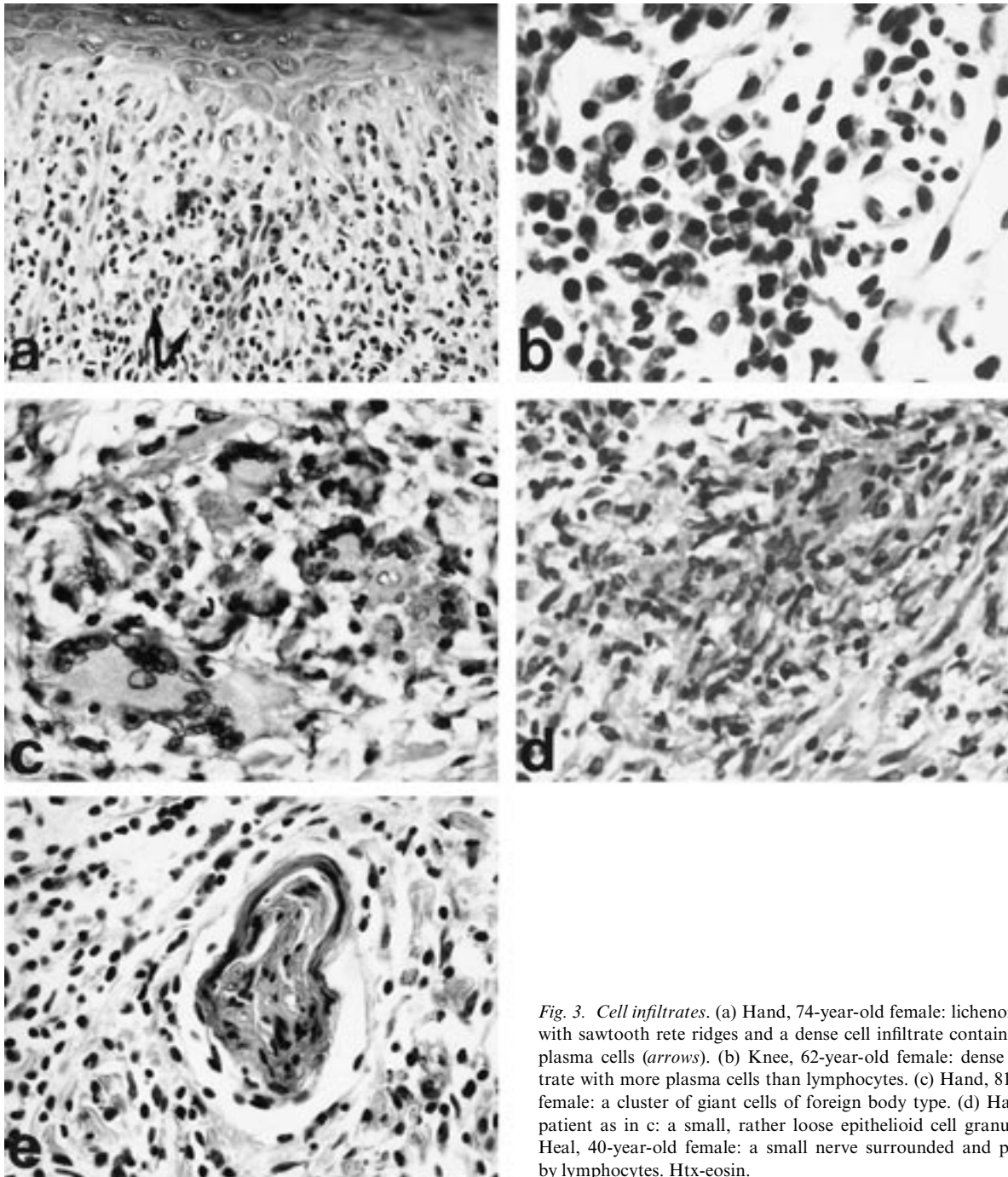


Fig. 3. Cell infiltrates. (a) Hand, 74-year-old female: lichenoid picture with sawtooth rete ridges and a dense cell infiltrate containing many plasma cells (arrows). (b) Knee, 62-year-old female: dense cell infiltrate with more plasma cells than lymphocytes. (c) Hand, 81-year-old female: a cluster of giant cells of foreign body type. (d) Hand, same patient as in c: a small, rather loose epithelioid cell granuloma. (e) Heal, 40-year-old female: a small nerve surrounded and penetrated by lymphocytes. Htx-eosin.

was not confined to the subepidermal compartment, and there was a rich or moderate admixture of plasma cells (Fig. 3a).

Cell infiltrates

The density and extent of the inflammatory cell infiltrates were roughly graded as sparse, moderate, or large, and were considered moderate or large in at least one biopsy specimen from 61% of the patients. The infiltrates were patchy and/or diffuse (Figs. 1 and 2), and in the upper dermis they were sometimes band-like. Patchy infiltrates were seen around vessels, hair follicles and sweat glands. The follicles and glands were not involved, although in a

few biopsy specimens small infiltrates of lymphocytes were seen in hair muscles.

Whether dense or sparse, the cell infiltrates consisted mainly of lymphocytes with a variable admixture of plasma cells. In 75 cases (68%) the proportion of plasma cells was high in at least one specimen, and in about 15% of the biopsy specimens plasma cells seemed to outnumber lymphocytes (Fig. 3b). In 36 cases (32%) only scattered plasma cells were noted. The admixture of plasma cells could vary considerably between two specimens taken from different lesions. Plasma cells were very often arranged in clusters and differed in number from one compartment to the next. Frequently, more plasma cells were seen in the deep dermis and subcutis than in the superficial dermis. Immu-

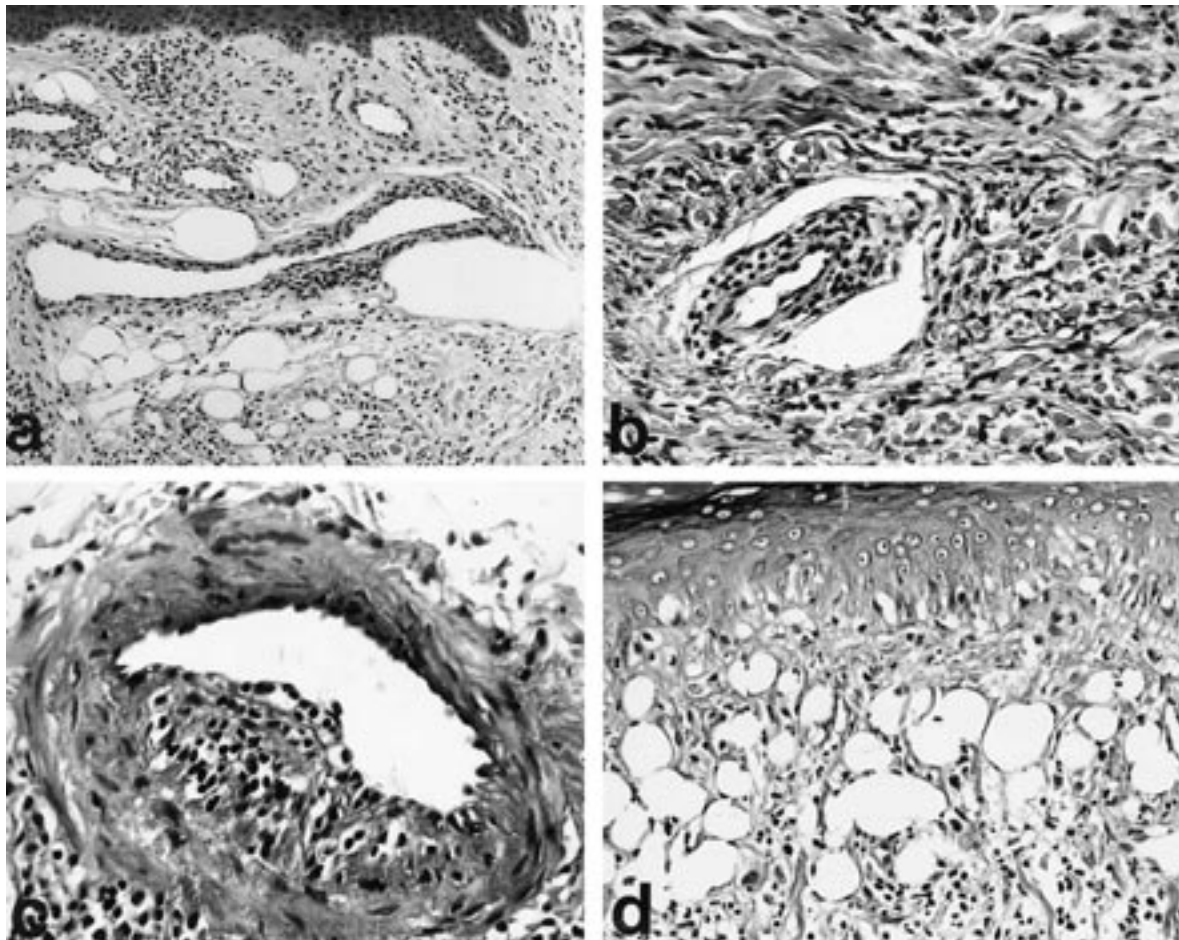


Fig. 4. Vascular patterns. (a) Elbow, 54-year-old male: in the upper dermis are one large and a few small dilated blood vessels, and several dilated lymphatics; below the large blood vessel is a group of vacuoles. (b) Nodule on the elbow, 45-year-old female: a vascular structure like those seen in Kaposi's sarcoma: dilated lymphatic containing a connective tissue bud with a central vessel. (c) Hand, 53-year-old female: a rather obtrusive subendothelial lymphocytic infiltrate is present in the wall of a larger vessel in the upper subcutis. (d) Wrist, 79-year-old female: a dense band of vacuoles is seen close to the epidermis. Htx-eosin.

noperoxidase PAP staining, performed in seven cases, revealed that the lymphocytes were T-cells mainly expressing UHCL1 antigen. None or only very few lymphocytes expressed B-cell antigen, in spite of the presence of numerous plasma cells.

In addition to lymphocytes and plasma cells, we observed fibroblasts and histiocytes, and in many specimens also multinucleated giant cells (Fig. 3c), epithelioid cells and mast cells. In dense cell infiltrates, the admixture of these cells was often conspicuous. As a rule, epithelioid cells were diffusely scattered, although small epithelioid cell granulomas were found in five cases, and in two of those the granulomas were present throughout the dermis (Fig. 3d). Neutrophils, eosinophils, extravasated red blood cells, and iron pigment were observed in a few cases. In the seven cases investigated with immunoperoxidase staining, the main part of the macrophages was positive for CD68 antigen.

Nerves

Parts of small nerves, large enough to be examined, were identified in 110 of the 157 biopsy specimens. In eight cases single nerves were tightly surrounded by inflammatory cells, mainly lymphocytes (Fig. 2). In only two of these were lymphocytes seen penetrating the nerve (Fig. 3e).

Blood vessels, lymphatics, and oedema

Dilated blood vessels and/or lymphatics were noted in practically all of the biopsy specimens and were striking in 19 cases. Also, there could be proliferation of small vessels, and in two cases vascular structures similar to those described in early Kaposi's sarcoma were observed. Leucocytoclastic vasculitis was not seen. However, in three cases there were distinct infiltrates of lymphocytes in the walls of a few middle-sized and larger vessels located in the dermis and at the dermal-subcutaneous border (Figs. 1 and 4a–c).

Marked diffuse oedema was noted in 20 cases. The oedema split up the collagen bundles, reducing them to thin threads. In 11 cases, "vacuoles" resembling fat cells were found in the upper half of the dermis, singly, in small groups, or as a massive band close to the epidermis (Figs. 4a and d).

Fibrosis-sclerosis

In addition to the changes described above, considerable fibrosis-sclerosis was noted in 32 biopsy specimens from 28 patients, and included 10 fibrous nodules, 6 ulnar bands, and 2 sclerodermatous lesions; the remaining 14 specimens were

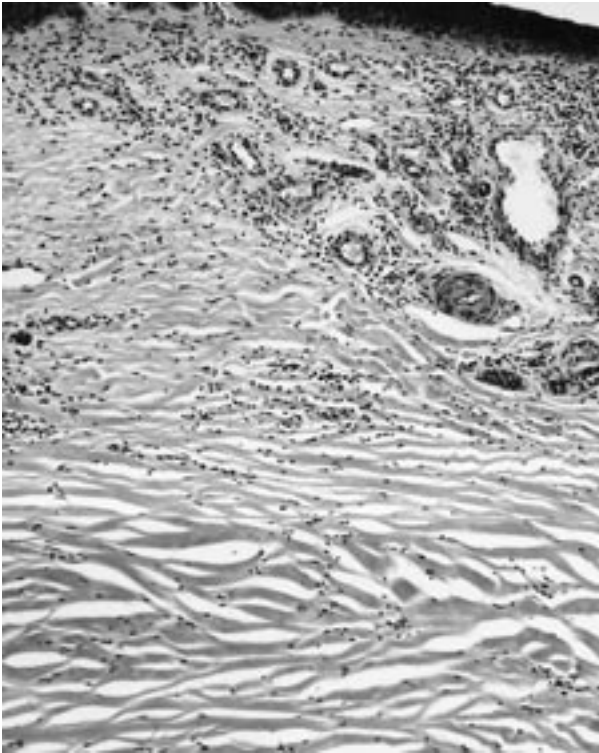


Fig. 5. Sclerosis. Hand, 54-year-old male (same patient as in 4a). Conspicuous sclerosis in the dermis and subcutis is seen as thin interlacing bundles of collagen oriented parallel to the epidermis. In the right upper corner there is an area of active inflammation with many small blood vessels and sparse infiltration of inflammatory cells. Htx-eosin.

taken from erythematous lesions where fibrosis-sclerosis had not been observed clinically. Subcutis was involved in 29 of 32 biopsy specimens, and in 15 of these the dermis was involved as well.

Fibrosis, i.e. a markedly increased number of fibroblasts and collagen bundles, is illustrated in Figs. 1 and 2. Sclerosis, supposedly the result of fibrosis, appeared as thickened and closely packed, eosinophilic collagen bundles, as large sheets of collagen, or as thick layers of rather thin, interlacing collagen bundles oriented parallel to the epidermis with only a sparse number of fibroblasts (Fig. 5). Fibrosis, slight or absent in the upper dermis, increased towards the subcutis and there sometimes merged into different-sized areas of sclerotic collagen (Fig. 1). Fibrotic lesions could contain small areas of fibrinoid necrosis, and in one specimen (a fibrous nodule) there was a pattern similar to that seen in *necrobiosis lipoidica*. In a few cases the sclerosis was obtrusive and involved subcutis and the major part of the dermis (Fig. 5). Also, groups of atrophic sweat glands tightly surrounded by connective tissue were seen.

Clinical-histopathologic correlations

Fibrosis-sclerosis was found in all 10 biopsy specimens from fibrous nodules that contained subcutaneous tissue, in all 6 specimens from ulnar bands and in both of the samples from sclerodermatous lesions.

Examination of biopsy specimens from the feet of 15 patients with shoe problems revealed markedly dense cell infiltrates in 9 of the cases, fibrosis in 4, telangiectases in 2, and diffuse

oedema in 1. Although the material is small, the findings suggest that the inflammatory cell infiltrates are an important causal factor.

Biopsy specimens were taken from 49 areas in which allodynia was experienced. Conspicuous inflammation, reflected as markedly dense cell infiltrates, was noted in 41% (20/49) of the specimens as compared to only 25% (20/81) of specimens taken from areas without allodynia ($p < 0.025$). No correlation was found between allodynia and neural and/or perineural cell infiltrates, or between allodynia and marked fibrosis. Furthermore, no statistically significant correlations were found between the density of inflammatory cell infiltrates, or the proportion of plasma cells in tissue and serum IgG titres to *Borrelia*.

DISCUSSION

The most important histopathologic findings were, as noted earlier (3), the presence of telangiectases and the fact that cell infiltrates consisted mainly of lymphocytes with a fair admixture of plasma cells, even though there were no indications of eczema (dermatitis) or other epidermal damage that could have explained the occurrence of plasma cells. The present study has increased our knowledge, especially in regard to the composition of the inflammatory cell infiltrates and the pattern of fibrous lesions, and, in a few cases, has revealed the involvement of middle-sized and larger vessels and small nerves. In addition, our findings show that the subcutaneous tissue was affected in a large percentage of cases.

We found a lichenoid pattern in 9% of cases. This is in harmony with the findings of Montgomery, but contradictory to those of Aberer et al. (6, 7).

In about a third of our cases only scattered plasma cells were observed, which means that the presence of only a few such cells does not exclude the diagnosis. The immunohistochemical investigation performed on tissue samples from seven patients revealed no B-cells, or only very few, in spite of a substantial occurrence of plasma cells. This indicates that the plasma cells did not develop at the site. The presence of numerous mast cells and dispersed epithelioid cells has been noted in the early German literature (8, 9), but, to our knowledge, epithelioid cell granulomas have thus far not been described in connection with ACA.

Peripheral neuropathy and symptoms of spontaneous pain and paraesthesia frequently occur in patients with ACA (5). Spontaneous pain was common in our patients, but could not be correlated to any histopathologic pattern. However, it was noted that the two patients with neural lymphocyte infiltration complained of unusually severe pain in the area concerned. The exaggerated pain reaction, allodynia, is a characteristic symptom and may therefore be helpful in diagnosing ACA. Nevertheless, this reaction is not well known, hence it is often overlooked. Allodynia is believed to be nociceptive rather than neurogenic, i.e. it is probably caused by the release of cytokines (5). This theory is in harmony with our finding that a conspicuous inflammation, seen as markedly dense cell infiltrates, was found more often in biopsy specimens from areas with allodynia than in those from allodynia-free areas. Also, at the first post-treatment examination 1 month after the initiation of therapy, allodynia had disappeared in almost all patients concerned.

Leucocytoclastic vasculitis or occluded vessels have been noted by others (7, 10), but were not observed in the present

study. However, in a few cases, distinct lymphocytic infiltrates were noted in the walls of middle-sized and larger vessels. In two cases we observed a vascular pattern similar to that described in early Kaposi's sarcoma (11), which is further confirmation that this phenomenon is not unique to Kaposi's sarcoma (12).

We observed a moderate to considerable number of so-called vacuoles in biopsy specimens from 11 patients. These structures have also been noticed in earlier studies of ACA patients: Benjamowitsch & Maschkilleisson (8) interpreted them as single fat cells or shreds of fat cells in the subpapillary area, and Montgomery (6, 13) described them as islands of fat cells and fat droplets that signified fatty degeneration. We have previously suggested that the vacuole-like structures arise as a result of some kind of lymphoedema (3). It has been shown (14) that lymphatic capillary plexus start as blind tubes in the dermal papillae, and that prelymphatics (i.e. paths of the least resistance leading through connective tissue towards the lymphatics) do exist, and those two findings suggest that what we call vacuoles represent either lymphoedema or lymphostasis. According to modern pathologists, the old term fatty degeneration wrongly implied that fat could appear as a result of some obscure degenerative process (15).

Clinically, oedema-like swelling was a common sign in our patients. In contrast, histopathologic examination revealed marked diffuse oedema in only 18% of cases. It is likely that the presence of a large number of telangiectases, vacuoles, or markedly dense cell infiltrates, or combinations of these phenomena, may give the same clinical impression as diffuse non-pitting oedema.

Histopathologically marked fibrosis-sclerosis was noted in 25% of patients. Our findings indicate that the process starts in the subcutis and deep dermis. It was not possible to differentiate between fibrous nodules, ulnar bands and sclerodermatous lesions. It could be that fibrosis-sclerosis is significant for the development of the non-arthritis and non-traumatic subluxation of small joints observed in ACA (3). In three patients who had that kind of lesion, and where biopsy specimens were taken, marked fibrosis-sclerosis was found in the overlying tissue. One of these patients is demonstrated in Fig. 5. This patient also had an ulnar band on the same side. It has been stressed that elastic fibres are absent in scleroderma-like lesions and are present in idiopathic localized scleroderma (16). In our two cases with scleroderma-like lesions the staining results were contradictory: in one case elastic fibres were absent and in the other they were well preserved. Presumably, the presence or absence of elastic fibres is not crucial for the differential diagnosis.

Without any further specification, the term atrophy is sometimes used in both clinical and histopathologic descriptions to denote some characteristic feature in erythematous lesions of ACA. However, atrophy of the skin can affect the whole skin, or only a part of it. In lesions with clinically advanced atrophy, both the epidermis and the dermis show a markedly reduced thickness, and the dermis consists of thin, closely packed collagen bundles. In our study, erythematous lesions had a conspicuously thin epidermis in only 28% of cases. However, Aberer et al. (7) noted epidermal atrophy in 70% of their cases. We have not regarded an epidermis that is thin, but otherwise normal, as significant, because most of the biopsy specimens were taken from elderly people and often from the dorsal aspects of hands and arms. Atrophy was expressed in different ways in the dermis and was usually seen

together with conspicuous oedema where the collagen bundles were split up and reduced to thin threads. Thus, at the time the biopsy specimens were taken, there was atrophy of the collagen bundles. Presumably there was also a diminution of the substantial thickness of the dermis, difficult to evaluate due to the oedema. In addition, dense inflammatory cell infiltrates occasionally obscured the architecture of the dermis and made estimation of the thickness uncertain. In some cases, thickening of the dermis and subcutaneous tissue was due to sclerotic connective tissue composed of thin (atrophic) interlacing collagen bundles. Also, groups of atrophic sweat glands were observed in thickened fibrotic tissue.

The diagnosis of ACA based on clinical data, serology, and microscopic examination can be further confirmed by successful treatment. In our study, most of the patients were free from signs and symptoms of active disease 1 year after treatment. Ulnar bands and fibrous nodules were considerably reduced or had often vanished already after 3 to 4 months. In patients with more advanced and protracted disease, signs such as slight erythema and swelling could persist. New biopsy specimens taken from such areas showed (compared to specimens taken before treatment) a marked reduction in the number of inflammatory cells, whereas vessels were still dilated, which explains the residual signs. Although the histopathologic pattern in ACA is not diagnostic *per se*, it is characteristic enough to alert the experienced pathologist to consider a possible diagnosis of ACA, even without knowledge of the clinical picture and serology.

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