Damage of Collagen and Elastic Fibres by Borrelia Burgdorferi – Known and New Clinical and Histopathological Aspects

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Abstract: Lyme Borreliosis, or Lyme’s disease, manifests itself in numerous skin conditions. Therapeutic intervention should be initiated as soon as a clinical diagnosis of erythema migrans is made. The histopathology of some of the skin conditions associated with Lyme Borreliosis is characterised by structural changes to collagen, and sometimes also elastic fibres. These conditions include morphea, lichen sclerosus et atrophicus and acrodermatitis chronica atrophicans. More recently, further skin conditions have been identified by the new microscopic investigation technique of focus floating microscopy: granuloma annulare, necrobiosis lipoidica, necrobiotic xanthogranuloma, erythema annulare centrifugum, interstitial granulomatous dermatitis, cutaneous sarcoidosis and lymphocytic infiltration; these conditions also sometimes cause changes in the connective tissue. In the case of ligaments and tendons, collagen and elastic fibres predominate structurally. They are also the structures that are targeted by Borrelia. The resultant functional disorders have previously only rarely been associated with Borreliosis in clinical practice. Ligamentopathies and tendinopathies, spontaneous ruptures of tendons after slight strain, dislocation of vertebrae and an accumulation of prolapsed intervertebral discs as well as ossification of tendon insertions can be viewed in this light.

Keywords: Lyme Borreliosis, collagen fibres, elastic fibres, skin, connective tissue, tendons, ligaments, diverticulum.

INTRODUCTION

Lyme Borreliosis causes skin symptoms at all stages of the disease [1-3]. The most common skin conditions associated with Lyme Borreliosis are morphea [1, 4-10], lichen sclerosus et atrophicus [LSA; 1, 4-6, 10-12], and acrodermatitis chronica atrophicans [ACA; 1, 6-8, 13], which possess an acute inflammatory stage followed by a chronic atrophic stage (Table 1-3). These skin conditions associated with Lyme Borreliosis are characterised by pronounced histopathological changes of the collagen fibres, but also occasionally the elastic fibres in their connective tissue structures [6,1,9,12,13]. The following also display similar disorders of their connective tissue: granuloma annulare, necrobiosis lipoidica and necrobiotic xanthogranuloma [1]. With the aid of a new histopathological technique, these skin conditions have also been found to contain Borrelia [13-17]. In some cases, LB was also detected in the connective tissue of patients suffering from pseudopelade of Brocq [18], Sudeck’s dystrophy [19], hemifacial atrophy [20] and sclerodema of Buschke [21].

There are also other skin conditions that do not display any particular connective tissue changes and optionally may occur as reactive skin conditions in Lyme Borreliosis. These include urticaria [22], erythema multiforme [23], erythema annulare centrifugum [13], microbial eczema [Müller: unpublished], erythema nodosum [3; Müller unpublished], pityriasis lichenoides chronica [24], acrodermatitis papulosa [Gianotti-Crosti syndrome], pityriasis rosea [21] perifolliculitis [24], panniculitis [25,26], lymphocytoma [synonym: lymphadenosis cutis benigna [Bäfverstedt’s syndrome; 27-29], benign lymphocytic infiltration [Jessner-Kanof syndrome; 30,31], sarcoidosis [32], B-cell lymphoma [33], pseudolymphoma [Müller: unpublished], Raynaud’s syndrome [34] and vasculitis racemosa [Müller; unpublished]. This paper will deal with skin conditions that cause histopathological changes to the collagen and elastic fibres.

Focus Floating Microscopy (FFM)

After the introduction of FFM, a number of dermatological conditions could be attributed to Lyme Borreliosis. FFM is a modified immunohistochemical investigation technique in which several strategies are combined in order to be able to identify microorganisms in tissue sections. In FFM, tissue sections are investigated in two planes: horizontally in a serpentine-like pattern, as is usual in cytology, and vertically, focussing through the entire thickness of the section (normally 3-4 µm). The tissue section is stained bright red with aminoethylcarbazol (AEC) and a light source is used that shines through the specimen approximately 10 times more strongly than usual. Thus a good contrast can be established between the microorganisms and the bright yellow collagen, optimising identification of the pathogen [14].
Table 1. Pathohistology of Morphea

| Early Phase                              | Sclerotic Stage                      |
|------------------------------------------|--------------------------------------|
| Oedematous swelling of collagen fibres   | Homogenised collagen fibre bundle    |
| Cell infiltration of lymphocytes, eosinophils and plasma cells | Decrease in strength of fibrils |
|                                          | Reduction in cell infiltrates         |
|                                          | Slit-like narrowing of vessels        |
|                                          | Loss of accessory structures of the skin |
|                                          | Hyaline sclerotic transformation of corium |

Table 2. Pathohistology of Acrodermatitis Chronica Atrophicans

| Inflammatory Stage                          | Atrophic Stage                                         |
|--------------------------------------------|--------------------------------------------------------|
| Oedematous swelling of hyalinised collagen fibres | Atrophy with disappearance of elastic fibres            |
| Undulating or ribbon-like perivascular lymphocytic infiltrates | Nests of Borrelia can be found in the collagen fibre bundles |
| Subepidermal haemorrhagic blisters due to infiltration of blood |                                          |
| Deposit of IgM, IgG, IgA, complement and fibrin |                                                        |

Table 3. Pathohistology of Lichen Sclerosus et Atrophicus

| Initial Phase                          | Late Phase                                      |
|----------------------------------------|-------------------------------------------------|
| Oedematous swelling of hyalinised collagen fibres | Atrophy with disappearance of elastic fibres |
| Undulating or ribbon-like perivascular lymphocytic infiltrates | Foci of Bb can be found in the collagen fibre bundles |
| Subepidermal haemorrhagic blisters due to infiltration of blood |                                          |
| Deposit of IgM, IgG, IgA, complement and fibrin |                                                      |

Cutaneous Manifestations of Lyme Borreliosis with Involvement of the Connective Tissue

Morphea

Clinical finding: At the beginning a spot-like focus can be seen with slight inflammatory erythema radiating outwards on all sides. It can occur in isolation or in groups. The erythema gradually completely disappears in the centre into a disc-like, ivory-coloured hardened area, that is surrounded by a bluish-violet, lilac-coloured ring [1,7]. Atrophy develops in the late phase, which is a hyper-pigmented dirty greyish-brown colour at the edges but usually without pigment in the centre. During this phase there may be a loss of hair and sebaceous glands. Morphea tends to occur on the trunk, less commonly on the extremities. The foci may develop individually and be disseminated but also merge into patches or become generalised and are then difficult to differentiate from scleroderma [1, 4-6, 10, 35, 36]. Atrophoderma of Pierini and Pasini [37, 38] is now considered to be an abortive form of morphea [39, 40].

Histopathology (Table 1): Two phases can be distinguished histologically. The early phase is associated with an oedematous swelling of the collagen fibres and cell infiltration of lymphocytes, eosinophilic granulocytes and plasma cells. This is followed by the second, sclerotic stage with homogenised collagen fibre bundles, a reduction in fibril strength, decrease in cell infiltration, slit-like vessels and loss of accessory structures of the skin in a hyaline sclerotic corium, in which only the arrector pili muscles are maintained [1, 6, 35]. Borrelia were detected in foci of morphea using FFM [9].

Acrodermatitis Chronica Atrophicans (ACA; Herxheimer’s Disease)

Clinical finding: ACA tends to occur over the large joints and distal parts of the extremities. It can also be seen on the face and trunk. It initially causes an oedematous skin swelling with slight erythema. Thread-like erythema may also develop on the extremities, characterised as ulnar striations on the forearms and tibial striations on the legs. As there are usually no subjective symptoms during this phase, early ACA of stage 1 Borreliosis usually goes unnoticed. In stage 2 there is pronounced atrophy of the skin, which becomes thin, flaccid and creases like cigarette paper. The following symptoms then develop: hair loss, telangiectasias, varicose veins and altered pigmentaton [1, 3, 8, 35].

Histopathology (Table 2): ACA starts with an inflammatory oedematous stage of the corium associated with perivascular lymphohistiocytic cell infiltration and plasma cells. This turns into an atrophic stage, where swelling and ho-
reaction, Borrelia were detected significantly more frequently - in 92.7% of cases (38/41) - than in the atrophic late stage where there was less inflammation – 26.7% of cases (4/15).

Granuloma Annulare (GA)

Clinical finding: One can see small, sharply-delineated, slightly reddened papules that are slightly shiny. As these grow they become bow or ring-shaped and the middle sinks slightly level with the skin. Secondary changes such as erosions and ulcers develop. Preferred sites are the backs of the hands and feet, but also joints of the hands, elbows, joints of the feet and buttocks. A distinction is made between the erythematous, subcutaneous, disseminated, perforating and plaque forms [1, 3, 35]. The presence of antibodies against Bb in cases of GA had been published in 1987 [41].

Histopathology: Histologically one can determine two distinct variants: foci of necrotic degenerated collagen, sometimes surrounded by histiocytes in palisade-like formation. In the more discrete (mild) course the histiocytes are embedded in the collagen. Histiocytic pseudorosettes were described in GA associated with a Borrelia infection [42, 43]. These are free-floating bundles of collagen that are surrounded by histiocytes. In 86.66% of cases that were investigated histologically (13/15), histiocytic pseudorosettes were detected with degeneration of the collagen. The fragmented collagen fibres are surrounded by CD68-expressing granulomatous cells [42]. Borrelia were detected in 80.9% of biopsies (127/157) of GA investigated [17]. In 85.2% of the cases investigated, the pathogen was detected in the localised form, i.e. much more commonly than in the diffuse form.

Necrobiotic Xanthogranuloma (NXG)

Clinical finding: One can find reddish-yellow to brown papules, annular plaques, scars and telangiectasias that tend to predominate in the periorbital region, but are also found on the trunk and proximal extremities [44, 45]. NXG is frequently associated with paraproteinemia, other neoplasms and lymphoproliferations [46, 47]. It has also been described in connection with sclerodermat [48].

Histopathology: The biopsies show granuloma without a palisade-like formation with numerous polynuclear giant cells and extensive necrobiotic areas over the entire dermis. In the central atrophic region of annular plaques there may be complete loss of elastic fibres [1]. In 6 out of 7 cases of NXG, Borrelia were found on their own, in pairs and in clusters. In 4 out of 6 positive cases, PCR was positive. In 2 cases it was normal [16].

Pseudopelade of Brocq

Clinical finding: Irregularly-configured, merging foci which remain sharply delineated compared with the unaffected skin. The affected skin usually glistens whitish-yellow and is atrophically thinned like cigarette paper and without follicular openings. Many hairs are lost, some tufts may remain [1]. A link with Borreliosis has been reported [18].

Histopathology: There is sclerosis with destruction of the elastic fibres and follicular openings. The former follicle areas are characterised by collagen fibres that run perpen-
dicular to the surface of the skin and arrector pili muscles that were maintained. The perifollicular and perivascular lymphocytic inflammations are only moderately pronounced [1, 35].

Structure and Function of Tendons and Ligaments

Tendons are support tissues which anchor the skeletal muscle in the periosteum. They are formed predominantly from collagen, to a lesser extent elastic fibres as well as intercellular substance. In short tendons the bundles of fibres run parallel with one another. In long tendons they wind around one another in steep spirals. Bundles of tendon fibres increase cross-cohesion and strength against shearing. The formation of fine waves enables the tendon to lengthen by approximately 4% under stress. This causes a certain loss of transferred force [49]. However, it enables a more gentle exertion of the muscles and reduces the risk of injury. The tendon develops gradually from the muscle and attaches with tendon fibres (Sharpey’s fibres) to the periosteum or perichondrium. In addition to collagen fibres, tendons that radiate into soft tissue like those of the mimetic muscles, the skin or the tongue muscles have numerous elastic fibres that extend like bristles into the soft tissue [49]; (Table 4).

Ligaments are high-tensile connective tissue ribbon-like structures that sensibly limit the range of movement. Their collagen fibres are not branched. They are not able to distend, they increase tensile strength and are flexible. A healthy ligament only tears at a load of between 6 and 10 kg/mm². The elastic fibres of ligaments have varying thicknesses, have sharp contours and branch unlike collagen fibres; they also form networks. They can resist acids and alkaline chemicals. They can only be made visible on fixed specimens by staining with orcein and resorcin-fuchsin. Elastic fibres have low resistance to distension. Once the extension force finishes they return to their original state. Distension of up to 2.5 times the original state is reversible [49,50].

The combination of elastic and collagen fibres has a functional significance. Collagen fibres, when arranged in parallel, become gathered. If the fibre bundle is stretched longitudinally the elastic fibres involved become taut. As soon as the stretching force diminishes, the taut elastic fibres pull the collagen fibres back to their original state. They are therefore critical to returning the ligament to the midpoint and prevent the collagen fibres from becoming entangled [49].

Reticular fibres are a third type of fibre that can be differentiated histologically from collagen fibres by their ability to become stained with silver. That is why they are also described as argyrophilic fibres. They are usually very delicate in structure, never occur in great quantities or thick bundles and are optically anisotropic. They have a thin skin and their task is to encase. They can be found at the edges bordering the connective tissue and adjacent non-connective tissue. The general consensus is that reticular cells produce collagen fibres [49].

Interaction of Borrelia Burgdorferi with Structures in Tendons and Ligaments

Borrelia are capable of breaking down soluble and insoluble ground substance within the extracellular matrix [51]. They activate metalloproteases, cause collagen to dissolve and can colonise as microcolonies in collagen fibres [52]. They inhibit the regeneration of collagen promoted by fibronectin, and hence delay the healing process or prevent it completely [53]. Binding to adhesins such as glucosamine glycan-binding protein [54], fibronectin-binding protein [55] and the proteoglycan decorin [11, 56, 57] are described. The last is probably responsible for the destruction of collagen, since direct binding to collagen I and II has not been detected. Mice with decorin deficiency were resistant to Borrelia [58]. Binding of the surface protein BmpA, BmpB, BmpC and BmpD to laminin inhibits cell-cell contact [59]. The same was established for the surface protein ErpX [60]. The involvement of gene conversion has also been established [61], as has the link to autoimmune disorders [62,63]. The persistence of Bb in human ligaments was described as early as 1993 [64]. In primates, Borrelia have been detected in the connective tissue of the aorta, the atria and the ventricles of the heart [65]. In endomysium biopsy Bb was detected in dilative cardiomyopathy in humans too [66]. Using FFM, Bb was also determined in the intestinal wall of an own patient who had to undergo surgery for acute diverticulitis. Serological tests revealed no antibodies [AB] in this case, even the immunoblot test was normal. This is not surprising since antibodies may not develop [11]. Activation of the conventional and alternative pathways of complement activation and the lysis of Bb triggered by this is absent in those cases [11]. The lymphocyte transformation test [LTT] was used

| Structure       | Tendon                      | Ligament                                      |
|-----------------|-----------------------------|-----------------------------------------------|
| Interstitial    | Tendon cells                | Unbranched collagen fibres which give tensile strength in the longitudinal direction |
| Interstitial    | Good flexibility            | Stable with acids and alkalies                 |
| Tendon fibres made from collagen | Slight distensibility       | In addition net-like structured branched elastic fibres with good distensibility|
| Task            | Support tissue to anchor the skeletal muscle with the periosteum | High-tensile connective tissue ribbon-like structure for sensible functional restriction of range of movement |
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diagnostically [2, 67, 68]. The lympho-proliferative immune response in EM, ACA, lymphocytoma and morphea was established as early as 1995 [9]. In agreement with the FFM result, LTT was positive to Borrelia antigens. There is a clinical link between Borreliosis and colon elongatum [Müller: unpublished cases].

Clinically, the interaction of Borrelia with the glucosamine glycan hyaluronic acid is very significant. This is an acid, high-viscous mucopolysaccharide that binds strongly to water and occurs in ground substance as the free form, the ester or bound to protein. It is used as a lubricant, to regulate water-binding and control permeability and diffusion. 1 g hyaluronic acid can bind with up to 6 l water. This glucosamine glycan is also able to prevent the penetration of infectious microorganisms. The reproduction of Borrelia might also be promoted by hyaluronidase. Binding of surface proteins to hyaluronic acid causes a reduction in pH, inactivation of proteoglycans, a decrease in cross-linking and a reduction in viscosity. Later on there may be displacement of gap junctions whose task is to regulate the transport of organic and inorganic ions in tissues that are poorly supplied with blood [69]. This relates to tendons and ligaments in particular. If this occurs, the initial oedematous swelling of the tendons will disappear, and finally the ligament fibres will dry out. The risk of tendon rupture increases in association with damage to the collagen fibres. The extent to which elastic fibres are also damaged was previously unknown. The function of porins is also altered by Bb [70].

Clinical Symptoms of Lyme Borreliosis in Tendons and Ligaments

While it is generally recognised that arthritis is a possible condition associated with Lyme Borreliosis and osteoarthritis is frequently the first sign in a joint, the involvement of tendons and ligaments was previously not given much consideration although the high affinity of Borrelia to collagen and elastic fibres was already recognised in the histopathological changes of skin conditions associated with Lyme Borreliosis. It is notable clinically that the symptoms in tendons and ligaments frequently develop independently of special strain or trauma to the affected tendons and/or ligaments and that there is an apparent contradiction between the symptoms experienced and that triggering event [71].

Insertional tendinopathies are often observed clinically. The most common locations are the epicondylitis humeri [tennis elbow], the meeting point of the tendons of the sartorius, gracilis and semitendinosus muscles in the medial region of the knee joint [pes anserinus superficialis]. The symptoms may radiate from there a hands-width cranially to the upper leg. The Achilles [or calcaneal] tendon or plantar fascia ligament may also be affected. Ruptures of the extensor tendons of the fingers, the quadriceps tendon, of cruciate ligaments and Achilles tendon and spontaneous vertebral dislocations have been seen clinically at low levels of strain in patients who were suffering from Lyme Borreliosis. In addition, carpal tunnel syndrome [CTS] and calcifications of the tendon insertions [periarthropathia homeroscapularis, calcifications of the patellar ligament, achillodynia and Haglund’s heel] have also been observed in this connection. Eosinophilic fasciitis [Shulman’s syndrome, Shulman’s fasciitis] is described in connection with LB [21].

Dysfunction of the Atlaido-occipital Joint

The atlaido-occipital joint has been reported to be another common and clinically significant site for symptoms [71]. The structural change of the ligaments which fix the atlas to the base of the skull [alar ligaments] or stabilise the dens axis [transverse atlantis ligaments], have special significance owing to their complex effects on cranio-mandibular function, vegetative control through sympathetic and parasympathetic nerves, the function of various centres of the brain stem, the induction of increased nitrogen oxide and peroxynitrite formation [72, 73], increased production of pro-inflammatory cytokines and cyclooxygenases [74], and finally also due to dislocation of vertebrae and intervertebral discs and accompanying myopathies [72].

Dysfunction of the atlaido-occipital joint without traumatic damage but correlated to chronic Lb has been described inducing a variety of symptoms [71]. 12 [18,8%] of the 64 patients reported had positive IgG antibodies in ELISA and 17 [26,6%] in immunoblot. IgM antibodies had not been found in any of the cases. In 57 (89,1%) patients the stimulation index (SI) in lymphocyte transformation test (LTT) was pathologically increased (SI > 3,0) in one of the four antigens investigated (B. burgdorferi, B. afzelii, B. garinii, Ospe). A functional magnetic resonance imagin (MRI) scan was carried out on 28 (49,1%) of the 57 patients with pathological SI in LTT. Structural damage has been described to the alar ligament, the transverse axis ligament included involvement of the spinal cord medulla with mechanically triggered myelopathy as it has been reported in cases following traumatic damage [75]. As published before [76], the number of CD57+ natural killer cells (NK-cells) was determined. 36 (78,3 %) of the examined 46 patients showed significant reduction of this cell type.

CONCLUSIONS

Morphological changes of the skin are histologically characterised by very similar pathological changes to the collagen and also elastic fibres in a whole range of skin conditions that occur with Lyme Borreliosis. Using FFM Bb was detected in the tissue within a clear time interval relative to disease transmission. Using this technique, it was possible to confirm skin conditions already known to be associated with Borreliosis and recognise new ones such as necrobiosis lipoidica or necrobiontic xanthogranuloma. The histologically-detected persistence of the pathogen does not correlate reliably with PCR or serological parameters.

Collagen and elastic fibres are essential structural elements of tendons and ligaments. Few publications to date have dealt with the possibility of their being affected in the context of Lyme Borreliosis, even though the first indications of this were published over almost two decades ago [64]. There is evidence that the presence of decorin in tendons and ligaments plays a critical role in infestation. Decorin-deficient mice were resistant to Bb. The extent to which the genetic expression of decorin plays a role has not been investigated to date. From own results on two brothers who contracted Lyme Borreliosis one after the other with pronounced symptoms in the tendons and ligaments, elements of individual susceptibility in addition to the special characteristics of the pathogen can be anticipated to play a
role in the symptoms in individual cases. Spontaneous ruptures of tendons and ligaments that are triggered by no or only slight trauma are clinically suspicious of Lyme Borreliosis. It would be good if, when treating tendons and ligament damage surgically, the possibility of Lyme Borreliosis would be considered more often and tissue obtained for histopathological examination using FFM.

Various factors are now known that imply that an isolated case of LB will not be overcome either by the individual power of the immune system or by the treatment implemented, but will take a chronic course. Animal studies have shown that even with adequate formation of antibodies only those cell populations that were carriers of surface markers were eliminated. Elimination of the entire population was not achieved [57]. Moreover, only a proportion of patients develop sufficient antibodies. In cases such as this the complement activation that leads to lysis of the pathogen does not occur [11]. In neuron and astrocyte cultures as well as in the brains of three patients, pleomorphic and cystic forms of Borrelia that indicate resistance to pathogens were detected extra and intracellularly using dark field microscopy, histochemistry and immunohistochemistry. The findings were similar to those obtained with Treponema pallidum [77].

Tendons and ligaments are a structurally and topographically ideal retreat for Borrelia. Their involvement is a further factor to indicate a chronic course of the disease. Serological antibody diagnostic techniques proved to be inadequate in cases such as this, possibly because the formation of antibodies is inhibited by the pathogen [11]. Immunological investigation on immune cells has widened the diagnostic spectrum. The sensitivity of LTT was superior to serological investigation of antibodies in the ELISA or immunoblot tests and correlated well with clinical symptoms. FFM was able to detect the pathogen directly in numerous skin conditions associated with LB, regardless of the results of serology or of PCR. LTT is a useful addition to the haematological diagnostic spectrum, especially for the diagnostic of LB of tendons and ligaments, as histopathology in those cases rarely can be done.

ABBREVIATIONS

| Abbreviation | Full Form |
|--------------|-----------|
| AB           | antibodies |
| ACA          | acrodermatitis chronic atrophicans |
| AEC          | aminoethylcarbazol |
| Bb           | borrelia burgdorferi |
| Bmp          | borrelia membrane protein |
| CD           | cluster of differentiation |
| CTS          | carpal tunnel syndrome |
| EM           | erythema migrans |
| Erp          | OspE/F related protein |
| FFM          | focus floating microscopy |
| GA           | granuloma annulare |
| IFN          | interferon |
| LSA          | lichen sclerosus et atrophicus |
| LB           | Lyme Borreliosis |
| LTT          | lymphocyte transformation test |
| NK           | natural killer cells |
| NL           | necrobiosis lipidica |
| NXG          | necrobiotic xanthogranuloma |
| Osp          | outer surface protein |
| PCR          | polymerase chain reaction |
| TNF          | tumor necrosis factor |

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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