Lyme Borreliosis in the Severe Combined Immunodeficiency (scid) Mouse Manifests Predominantly in the Joints, Heart, and Liver

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The authors describe the histopathologic evolution of Lyme disease in severe combined immunodeficiency (scid) and normal C.B-17 and C57BL/6 mice inoculated with Borrelia burgdorferi. Starting on day 7 after inoculation, all scid mice infected subcutaneously in the tail with a low-passage European tick isolate of B. burgdorferi had clinical evidence of arthritis characterized by redness and swelling of tibiotarsal joints. Later on, other joints, ie, metatarsal and ulceraral joints were also affected. The infection of scid mice resulted in a persistent spirochetemia and the development of a multisystem disease with chronic progressive inflammation of joints, heart, and liver. Major histopathologic alterations included 1) severe joint lesions, characterized by the presence of hyperplastic inflamed synovial lining cells associated with the erosion and destruction of cartilage and/or bone; 2) pancarditis with infiltrations of mononuclear cells in the endocardium, myocardium, and pericardium; and 3) hepatitis with mononuclear cell infiltrations confined to the portal field and central vein, granulomatous reactions, and eventually the development of liver fibrosis. In addition, smaller more confined lesions were found in kidneys, lung, brain, and striated muscle. The inflammatory infiltrates in the various organs were associated mostly with Mac-1+ cells, largely monocytes and macrophages, as well as some polymorphonuclear leukocytes, but not B and T lymphocytes. Infective spirochetes could be readily isolated from blood and joints and were found at the site of inoculum and the myocardium. In contrast, subcutaneous inoculation of normal C.B-17 or C57BL/6 mice with spirochetes in general did not result in clinical signs of arthritis. Only 10% to 20% of the C57BL/6 mice, but none of the C.B-17 mice, showed clinical evidence of oligoarthritis, which appeared not before day 36 after inoculation. In general, the infection of normal mice resulted in minimal lesions in various organs, and no spirochetes could be visualized or reisolated from their tissues. The data demonstrate that Lyme borreliosis may develop in mice in the absence of detectable specific B and T cells and thus suggest an immunologic control of the disease in this species. The scid mouse model therefore can be used to define the components of the immune system responsible for the suppression and/or the progression of the disease. (Am J Pathol 1990, 137:811–820)

Lyme disease has become a serious health threat for humans in many areas of the world. The illness is caused by the spirochete Borrelia burgdorferi and transmitted to the human host primarily by ixodic ticks.1 The major clinical features of this spirochetosis include manifestations in the skin, joints, central nervous system, and the heart.2 Histopathologic studies have shown that Lyme arthritis may become chronic, resulting in erosion of cartilage and bone.3 The synovial lesions of Lyme disease patients revealed certain histopathologic features similar to those found in patients with rheumatoid arthritis, such as the presence of T cells, plasma cells, and macrophages.4 Heart biopsies from patients with Lyme disease presented transmural myocarditis with lymphocytic and plas-
ma-cellular infiltrations. According to several case reports, patients with B. burgdorferi infection were shown to have also myositis, which was characterized by perimysial and intramuscular infiltrates of macrophages, B and T cells. In addition, hepatitis of a granulomatous or recurrent form was observed. Although the pathogenesis of Lyme borreliosis is far from being understood, the observed histopathologic features have been suggested to be immunologically induced in response to persisting spirochetes. Laboratory models for Lyme arthritis have recently been described; neonatal and weanling rats as well as nonirradiated and irradiated hamsters, after their previous inoculation with B. burgdorferi, develop arthritic lesions resembling those in human Lyme arthritis. The fact that the pathologic response was much less pronounced in adult than in neonatal rats and in nonirradiated than in irradiated hamsters suggested an immunologic control of the disease in these species. This assumption was supported also by our preliminary findings that only immunodeficient but not normal mice develop a chronic disease in response to B. burgdorferi. Here we give a more detailed report of the histopathologic development of Lyme borreliosis in severe combined immunodeficiency (scid) and in normal mice.

Materials and Methods

Animals

Adult mice of the strains C.B-1 scid (homozygous for the scid mutation) C.B-17, and C57BL/6 (B6) were bred at the Max-Planck-Institut für Immunbiologie, Federal Republic of Germany, under specific pathogen-free conditions. Female and male animals between 6 and 10 weeks of age were used. Numbers of animals used to perform the histopathologic studies are listed in Table 1.

Bacteria and Inoculation Protocol

The low passage B. burgdorferi (two in vitro passages) strain ZS7 was originally isolated from a female Ixodes ricinus tick collected by flagging in the Freiburg area as described previously. To avoid loss of virulence of spirochetes, aliquots of the first passage were frozen at −70°C. For further expansion, spirochetes were thawed and propagated once in vitro for another 10 days in Barbour-Stoenner modified Kelly’s medium (BSK) in a humidified atmosphere of 5% CO2 at 33°C as described.

After 10 days the cultures were centrifuged at 10,000g (Sorvall, Bad Nauheim, Federal Republic of Germany) for 15 minutes, the sedimanted bacteria were washed once in phosphate-buffered saline (PBS) and counted under a dark field microscope. Mice were inoculated with 1 × 108 viable B. burgdorferi organisms subcutaneously in the tail. B. burgdorferi organisms were reisolated from infected mice by inoculation of blood or joint fluid into BSK supplemented with 8 µg/ml kanamycin and 230 µg/ml fluorouracil. Cultures were examined daily with a dark field microscope for spirochetes.

Preparation of Tissue

Various times after inoculation with B. burgdorferi (Table 1) the mice were killed and different organs (heart, liver, kidneys, lungs, spleen, brain, eyes, legs, and tail) were removed and fixed in 5% formaldehyde in PBS for embedding in paraffin or in methacrylate (Kulzer, Friedrichsdorf, Federal Republic of Germany) or in liquid nitrogen for preparation of cryostat sections.

Formaldehyde-fixed extremities were decalcified in 5% trichloracetic acid in PBS for 1 hour.

Sections (2 to 4 μ thick) were stained with hematoxylin and eosin (H&E) and embedded in Entellan (E. Merck, AG, Darmstadt, Federal Republic of Germany).

Immunohistology

Immunohistology was performed using the streptavidin-biotin-peroxidase system as described in detail. The following monoclonal antibodies (MAb) were used: rat anti-mouse L3T4 MAb (H-129-19.6, provided by Dr. M. Pierres, Centre d’Immunologie, Luminy, France) for CD4+ T cells, rat anti-mouse Ly2 MAb (53-6.7, provided by Dr. J. Ledbetter, Genetic Biosystems Inc., Seattle, WA) for CD8+ T cells, rat anti-mouse Mac 1 (Boehringer Mannheim, Mannheim, Federal Republic of Germany) for macrophages/monocytes, rat anti-mouse IgG, and rat anti-mouse IgM (Boehringer Mannheim, Mannheim, Federal Republic of Germany).

For detection of B. burgdorferi organisms in the affected tissues, a peroxidase-labeled anti-B. burgdorferi flagellin (41 kd antigen) MAb prepared by Prof. Vermes (api Bio Merieux, Lyon, France) was used.

Scoring of Histopathologic Alterations

The tissue sections from individual organs of scid and normal mice were studied prospectively and assigned a score of “+” to indicate normal histology (d0; Table 1). For comparison of the various histopathologic alterations, the following scores were used:

I. Evaluation: +, severe; ±, moderate; −, no lesion
**Table 1. Evaluation of Histopathologic Findings in B. burgdorferi-Infected Mice** of Strains scid, C.B-17, and B6

<table>
<thead>
<tr>
<th>Days after infection</th>
<th>Heart</th>
<th>Joint</th>
<th>Liver</th>
<th>Kidney</th>
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<tr>
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Normal C.B-17 (n = 8), B6 (n = 25), and scid mice (n = 28) were killed at various times after inoculation and histologically investigated. Tissue sections from uninfected mice were studied prospectively and assigned a score of "--" to indicate normal histology (d0). To characterize the severity of the various lesions the following scores were used: I. Evaluation: + severe, ± moderate, - no lesion. II. Lesions: Joint: intra-articular (+--), periarticular (;++++) infiltration with mononuclear cells, erosion (---+). Heart: infiltration with mononuclear cells in myocardium (+++-), pericardium (++--), endocardium (++--). Liver: perivascular infiltration with mononuclear cells (++--), necrosis (---), granulomatous reactions, non-vascular mononuclear cell accumulation (+--). Kidney: infiltration with mononuclear cells (+). Samples were properly coded and examined under double-blind conditions.

Note the significant lesions in the heart and joint of inoculated scid mice, which is in a sharp contrast to the findings in normal C.B-17 and B6 mice. Nevertheless, the histopathologic alterations in B6 mice tested at days 56/59 differed markedly between individual animals.

* Not determined.

**Results**

**Clinical Features of Lyme Borreliosis in scid and Normal Mice**

In a previous study, we showed that scid but not normal C.B-17 mice develop arthritis early after inoculation with a low passage European isolate (ZS7) of *B. burgdorferi*. We now have extended this study by monitoring both clinical features and histopathologic alterations in infected scid mice and in normal C.B-17 or B6 mice for a period of 28 weeks. All scid mice studied were tested for specific immune responses. As shown previously, they expressed only low amounts of total Ig (less than 7.5 μg/ml IgM, less than 400 μg/ml IgG) and no detectable *B. burgdorferi*-specific Ig or T cells were observed during the entire observation period. This is in sharp contrast to normal C.B-17 and B6 mice, which expressed on the average 0.3 to 2.5 mg/ml total IgM and 2 to 6 mg/ml total IgG and developed high titers of *B. burgdorferi*-specific antibodies (10 to 94 μg/ml IgM, 30 to 700 μg/ml IgG), as well as specific T cells (data not shown; see also Schaible et al14 and Schaible et al16) during infection. Early arthritic changes characterized by reddening of the tibiotarsal joints were visible in infected scid mice at 7 days after inoculation. From this time on, there was a swelling of the hind paws, which increased with time after inoculation and did not resolve during the entire observation period (195 days). Beginning day 30 after infection, similar signs of arthritis also were observed in other joints, ie, metatarsal and ulnarcapal joints.

In contrast, no reddening or swelling of any joint was observed in normal C.B-17 or B6 mice during the first 3 weeks after inoculation with *B. burgdorferi*. Later on (more than 36 days), there was evidence of oligoarthritis in 10% to 20% of B6 mice. The latter clinical symptoms usually abated after 10 to 15 days but did not resolve entirely and reappeared at later stages of infection. None of the scid or normal mice died during the entire observation period.

**Histopathology of scid and Normal Mice Inoculated with *B. burgdorferi***

Significant histopathologic changes were detected in various organs of scid mice inoculated subcutaneously in the tail with *B. burgdorferi*, as early as 1 week after inoculation. In the further course of the disease, chronic progressive inflammatory reactions developed in various organs and persisted throughout the entire period of study (195 days; Table 1). Histopathologic alterations were most pro-
nounced in synovial joints, tendons, heart, and liver but not, or only minimally, in kidney, lung, or striated muscle. In contrast, C.B-17 or B6 mice inoculated with *B. burgdorferi* developed no, or if at all, scant sites of inflammatory reactions. In the latter situation, inflammatory reactions appeared delayed and mostly only in organs such as the heart and joints. However, the lesions were much less pronounced than in scid mice detected at the same time of observation.

The most prominent inflammatory and destructive lesions in scid mice infected with *B. burgdorferi* were noticed first in the tibiotarsal joints and the periarticular connective tissues. As shown previously, examination of the tibiotarsal joints of these mice 7 days after inoculation showed foci of synovial hyperplasia, which were characterized by a pronounced accumulation of mononuclear cells. In this and all the other inflammatory lesions found in other organs such as the heart, many cells in the mononuclear infiltrates were Mac-1⁺, indicating an origin of the macrophage–mononuclear cell lineage. No B or T cells were present in inflammatory lesions. Later, as the disease progresses, additional joints, i.e., the ulna-carpal and metatarsal joints, developed similar histopathologic changes. By day 36, the most prominent tissue alterations included severe joint lesions characterized by the presence of hyperplastic inflamed synovial lining cells attached to sites of cartilage and/or bone destruction (Figure 1a, b). Concomitantly, inflammatory pathologic changes were noted in periarticular tissues, such as ligaments, tendons, fascia, and skeletal muscle (Figure 2a to c). Severe tendosynovitis was most common and varied from hyperplasia of the synovial sheaths, through a florid synovitis with dense polymorphic infiltrates, to foci of inflammatory lesions within the tendon. The lesions observed in the periarticular leg tendons resembled closely the pathology observed around the injection site in the tail (data not shown). The acutely inflamed tail showed lesions ranging from inflammatory changes, principally localized to the connective tissue septa, to diffuse interstitial inflammation characterized by interfiber polymorphic and mononuclear cell infiltrations. Moreover, inflammatory tissue infiltrations were observed distantly in skeletal muscle. There, the focal, rather random sites of inflammatory reaction were occasionally accompanied by tissue necrosis (data not shown).

Examination of the heart of scid mice inoculated with *B. burgdorferi* developed a pronounced and severe cardiomyopathy. As early as on day 7 after infection, mononuclear cell infiltrates appear in the endocardium (Figure 3) and/or pericardium (data not shown). Subsequently, a more diffuse accumulation of monocytes was associated with prominent neutrophilic infiltrations. Furthermore, with progression of the disease, myocardial involvement became evident (Figures 4, 5). The eventually occurring progressive mycarditis was characterized by massive mononuclear cell infiltration, many of which expressed Mac-1 (Figure 6), interstitial edema, and isolated muscle fiber necrosis (Figures 4, 5). In addition, spirochetes were present in the interstitial space of the inflamed myocardium (Figure 4, inset). The observed myocyte was closely associated with the presence of macrophages and monocytes. In addition to the widely present infiltrations largely distributed in the perivascular, subendocardial, and subepicardial connective tissue, more localized foci containing necrotic amorphous material surrounded by a rim of mononuclear cells and fibroblasts resembled Aschoff bodies. Often, large modified mesenchymal cells known as Anitschkow myocytes (‘caterpillar cells’), and sometimes multinucleated Aschoff giant cells, were noticed (data not shown).

The pathologic changes in the liver of *B. burgdorferi*-inoculated scid mice were characterized initially at day 7 after injection by rather small mononuclear infiltrations confined to the portal field. Subsequently, perivascular infiltration of central veins with mononuclear cells (data not shown) and more severe changes eventually resulting in liver fibrosis were observed. The scattered developed from delicate irregular strands of newly deposited fibrillar connective tissue to the formation of rather broad, varying-sized bands of fibrotic tissue and interconnecting bridges (Figure 7). Sites of granulomatous reactions developed and were occasionally associated with the areas of fibrosis (Figure 7). The occurrence of these granulomatous lesions was clearly distinct from the foci of extramedullary hematopoiesis frequently observed in various strains of mice. Despite the presence of fine granular material suggesting the presence of *B. burgdorferi*, the significance of these lesions is not well understood. It is of interest that mice developing the most severe cardiomyopathy presented, in addition to the inflammatory and granulomatous changes in the liver, signs of central hemorrhagic necrosis, most likely caused by severe chronic passive congestion.

From the other organs studied, kidneys and lungs contained only rather small perivasculary mononuclear cell infiltrates. In the brain of two infected scid mice at 21 days after inoculation, sites of mononuclear cell infiltration were observed (data not shown). In contrast to most of the other organs, no significant histopathologic findings distinct from those in uninfected control scid mice were found in the spleen of scid mice inoculated with *B. burgdorferi* during the entire observation period; however the widening of internodular and nodular areas typical for this organ in the immunodeficient mouse was observed.21 From all the tissue samples examined, spirochetes resembling *B. burgdorferi* were only detected at interstitial sites of the myocardium (Figure 4, inset) and at the site of inoculation. However, the infectious agent could be
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Discussion

This study shows that immunodeficient (scid) mice but not normal mice inoculated with *B. burgdorferi* develop a persistent spirochemia and a multisystemic progressive infection that involves mainly the joints, heart, and liver. The spirochete-induced arthritis in scid mice is characterized by synovial proliferation, infiltration of inflammatory cells, and erosion of cartilage and bone. However, inflammatory lesions in periarticular tissues, i.e., tendonsynovitis, represent key manifestations of the disease. Histopathologic changes of the joints have also been described in other animal models for Lyme borreliosis, such as rat\(^1\) and hamster,\(^{12,13}\) as well as in humans infected with *B. burgdorferi;\(^2\) emphasizing a major role of this agent in the development of a destructive arthritis. In addition, we show that scid mice inoculated with *B. burgdorferi* develop rather consistently pancarditis, and hepatitis as well as moderate lesions of lungs, kidneys, and skeletal muscles. The inflammatory infiltrates observed in the various organs of scid mice studied were largely associated with Mac-1\(^+\) cells of the macrophage/monocyte cell lineage.\(^{19}\) Neither B nor T lymphocytes were detected, which was not surprising because of the fact that the majority of scid mice lack functional lymphocytes and that only some (2% to 23%) were shown to contain very few clones of Ig-producing plasma cells and T cells.\(^{22}\)

Because we did not find detectable amounts of *B. burgdorferi*-specific antibodies and only observed marginal levels of total Ig in any of the inoculated scid mice...
Figure 2. a,b: Tibiotarsal joint of a scid mouse 36 days after inoculation of $1 \times 10^8$ B. burgdorferi ZS7; inflammatory cell infiltrates are found throughout the tibiotalar joint and periarticular tissue including ligaments, tendons, fasciae and muscle (275X, H&E stain). c: Higher magnification of a subdermal periarticular infiltration with mononuclear cells and polymorphonuclear leukocytes around the joint (875X, H&E).
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Figure 3. Heart of scid mouse 195 days after inoculation of $1 \times 10^8$ B. burgdorferi ZS7: inflammatory infiltrate of mononuclear cells and polymorphonuclear leukocytes in the endocardium and myocardium (380X, H&E).

used during this and earlier studies, these findings strongly indicate that the pathogenesis described in this mouse strain develops in the absence of a specific immune response. At first glance this is surprising in view of the histopathologic features reported in patients infected with B. burgdorferi, showing that in all cases studied histologic alterations were associated with inflammatory infiltrates, consisting mostly of T cells, plasma cells, and macrophages. This was taken to suggest that immune-mediated pathways are mainly responsible for the histopathologic features observed. However a recent study on the development of spontaneous arthropathy in the autoimmune MRL-lpr/lpr mouse strain indicated that the initial pathologic changes that occurred in the joints of these mice, including cartilage and bone destruction, evolved in the absence of any inflammatory cells, such as neutrophils and lymphocytes. The latter observations and our data on the development of Lyme arthritis in scid mice suggest that nonimmunologic pathways initiate tissue destruction in joints and other organs and that antigen-triggered lymphocytes may only participate in later stages of inflammation.

Several possibilities could be envisaged to explain the induction of severe chronic disease by B. burgdorferi in mice devoid of lymphocytic function. The fact that only viable, low-passage organisms are able to induce the disease in scid mice is in agreement with other recent reports in hamsters and rats and indicates an active role of pathogenic spirochetal components in the infection. In fact, B. burgdorferi has been shown to attack and to penetrate through vascular endothelial cells in vitro. Most probably it is this invasive capacity of the organism that is responsible for their tissue colonization in vivo. The spirochete itself and/or the resulting degradation products...
then may initiate the various inflammatory reactions. After dissemination into various organ sites, *B. burgdorferi* may bind directly to and stimulate macrophages or natural killer cells that are contained within the inflammatory foci in the infected tissues of scid mice. This activation may lead to the production and release of inflammatory mediators, such as interleukin-1 (IL-1), gamma interferon and tumor necrosis factor (TNF), as recently described for *Listeria monocytogenes* infection in scid mice.

It is not clear why humans may become ill when infected with *B. burgdorferi*, while the natural host, the immunocompetent mouse, remains relatively unaffected. This is surprising, as both species are able to generate humoral and cellular immune responses to *B. burgdorferi*. It is possible that the differences in the development of *B. burgdorferi* infection in humans and mice are due to qualitative differences of B- and/or T-cell responses or to different kinetics of the protective immune responses. In fact, we and others have found that during experimental infection of mice, the first *B. burgdorferi*-specific antibodies to be detected in the serum are those directed to the main spirochetal surface components, termed OspA and OspB (and Schaible et al, unpublished data), and that these antibodies, but not those to flagellin, on passive transfer are able to protect scid mice against infection. In contrast, in patients with Lyme disease the first antibodies to be detected are those specific for the 41-kd flagella-associated antigen, whereas antibodies to OspA and/or OspB are rarely seen (and Schaible et al, unpublished data). Because the 41-kd flagellin is not a component of the outer cell surface of *B. burgdorferi*, but rather confined to the periplasmic space, antibodies raised against this structure early in Lyme disease are likely to be insufficient to bind to and

**Figure 5.** Heart of scid mouse 195 days after inoculation of $1 \times 10^8$ *B. burgdorferi* ZS7; note the necrosis of the myofibrils associated with the presence of mononuclear and polymorphonuclear leukocytes in the myocardium (1000X, H&E).

**Figure 6.** Unfixed cryostat-section of the heart of a scid mouse 21 days after inoculation of $1 \times 10^8$ *B. burgdorferi* ZS7; perivascular infiltrating cells staining (peroxidase) with anti-Mac-1 MAb in the myocardium (1000X).
eventually neutralize the intact spirochete. The later appearance or lack of the presumably protective antibodies to surface structures OspA and/or OspB in humans may allow time for the spirochetes to disseminate into immunoprivileged sites.

The fact that only few normal mice developed inflammatory reactions in response to B. burgdorferi suggests that spirochetes may survive, probably in immuno-privileged sites, and cause the disease despite high titers of circulating B. burgdorferi-specific antibodies and/or T cells. Alternatively, specific antibodies and/or T cells generated in the course of the disease may be involved in the alteration, nature, and extent of organ manifestations. In fact, the presence of plasma cells and T cells as major responder cells in most, if not all, visceral and organ sites in patients with Lyme disease has suggested that the histologic alterations may be caused by an interplay of humoral and cellular immune elements. Moreover, the detection of circulating immune complexes associated with active Lyme borreliosis has led to the proposition that they are responsible for the inflammatory arthritis in this disease.34,35 The finding, however, of persistent symptoms including arthritis, panniculitis, or neurologic derangements in patients treated with antibiotics has been attributed to autoreactive T cells generated in the course of anti-infectious therapy.36 However, as the conditions for an adequate antibiotic therapy are not known at present, it is possible that persisting symptoms are due to residual spirochetes.

In conclusion, our histologic studies in scid mice demonstrate that B. burgdorferi is able to induce in the absence of any detectable specific immune response a wide variety of histopathologic alterations in various organs that resemble the pathogenetic features of human Lyme disease. Furthermore this animal model allows us to study the humoral and cellular components of the immune system responsible for the protection against the spirochetes.

References


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