Polyarthritis in MRL 1pr/1pr mice

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Summary. Mice of the inbred strain MRL/MpJ-1pr/1pr are affected by a systemic autoimmune disease and a spontaneously occurring polyarthritis. To characterize the arthritis a histopathological study was performed on the joints of the four limbs and of the spinal column of 7, 16, 22 and 28-week-old animals of both sexes. Polyarthritis, the severity of which increased with age was detected in all mice. Proliferation of the synovial lining cells, already evident in 7-week-old animals, was the initial lesion. In the majority of cases infiltrates containing lymphocytes with a few plasmocytes, histiocytes, polymorphonuclear neutrophils and eosinophils were detected later on. The most pronounced changes were observed in the hind-paws, the fore-paws, the knee and hip joints, paired articulations being symmetrically involved. A pannus was seen at the most in 10% of the joints leading to limited and superficial destruction of the cartilage. Rheumatoid nodules were not seen. From 16 weeks of age deposits of unknown nature, often surrounded by phagocytosing macrophages and/or neutrophils, were observed in the articular and/or extra-articular connective tissue and in the vessels. There was a positive correlation between their presence and the intensity of the arthritis. The articular lesions in our study differ from those in rheumatoid arthritis because they lacked the specific and characteristic histological features of the human disease.

Key words: Polyarthritis - MRL/1pr/1pr Mice - Pannus - Tissue deposits

Introduction

MRL/MpJ-1pr/1pr (MRL/1) mice spontaneously develop an autoimmune disease characterized by the presence of antibodies to nucleic acid and viral glycoprotein, IgM and IgG rheumatoid factors, hyperglobulinaemia, immune complexes and hypocomplementaemia [1, 2]. They also mount an acute-phase response as the disease progresses [3]. Pathological changes include T-cell lymphoma, glomerulonephritis, vasculitis and polyarthritis. The association of spontaneous polyarthritis with the occurrence of rheumatoid factor in the serum suggested that MRL/1 mice might be an interesting model for the study of human rheumatoid arthritis (RA) [2, 4]. The purpose of our study was to characterize the inflammatory articular lesions occurring in these mice. Small and large joints and the spinal column from male and female mice were investigated.

Materials and methods

Mice. MRL/1 mice were originally developed at the Jackson Laboratories (Bar Harbor, Maine) and subsequently bred at the animal facilities of CIBA-GEIGY (Tierfarm Sisseln, Switzerland). The investigations were performed on female mice aged 7, 16, 22 weeks and on males aged 7, 16, 22 and 28 weeks. Each group consisted of 10 mice, except the group of 7-week-old male and female mice which comprised 5 mice of each sex and the 22-week-old male group in which only 8 mice were available. Mice were killed with ether inhalation. Fore-paws, hind-paws, knee joints, hip joints, elbow and shoulder joints at both sides, as well as the spinal column were excised and processed for histological examination.

Histology. Joints were fixed for a minimum of 2 weeks in 10% buffered formalin, then decalcified for 4–6 weeks in phosphate buffer (0.06 M, pH 7.4) containing 0.23 M EDTA. After embedding in paraffin, the joints were cut into 10 μm thick serial sections which were stained with hematoxylin and eosin (HE). Some slides were stained with Congo Red for amyloid deposits, or with a CI Basic Blue-41-like dye (CIBA-GEIGY) for metachromasia or with Turnbull blue for iron, or with period-acid-Schiff (PAS) method. In addition, various reactions were performed on cryostat sections of non-decalcified and non-fixed joints obtained from an additional group of 22 to 24-week-old mice. The joints were snap-frozen in liquid nitrogen and stored at -70°C. Cryostat sections of 5 μm thickness were treated either by the Von Kossa method, or with the De Galantha's reagents, Sudan Red, or with ethidium bromide (0.5 mg/ml in 0.15 M NaCl) to reveal the presence of calcium, urate, lipid and deoxyribonucleic acid, respectively. Reaction for acid phosphatase was also performed.

For the histopathological evaluation a checklist was used to record and classify various pathological findings according to their presence or intensity on a 0 to + + + scale.

Statistical evaluations. Two non-parametric statistical tests, the Kolmogorov-Smirnov test and the Fisher exact probability test, were used to look for association between the degree of arthritis, and the presence of deposits, vasculitis and bone resorption.
Results

At the autopsy, none of the mice showed any gross abnormalities in their joints. Therefore, only histopathological changes will be described.

7-week-old mice

All mice showed slight modifications in most of the joints examined (Fig. 1). Inflammatory changes were more prominent in the female mice, the interphalangeal joints of the fore-paws being the most frequently and most severely affected. Initial changes consisted of mild to severe proliferation of the synovial lining cells (Fig. 2), occasionally with slight proliferation of the synovial stroma cells. In only a few instances did the proliferating cells lead to minimal destruction of the cartilage periphery and of the neighbouring bone (Fig. 3). Villous projections of the synovial membrane were rarely seen. Infiltrates of lymphocytes, histiocytes and a few eosinophils were found occasionally spreading beneath the synovial lining cells or throughout the synovial membrane (Fig. 4).

Resorption of cortical bone was detected in all animals and occurred independently of the presence of inflammatory articular lesions (Fig. 5). The bone defects contained connective tissue and/or lymphocytes and histiocytes.

Intra- or extra-articular vasculitis along with peri-vasculitis was found in 40% of the male mice. Lymphocytes and histiocytes infiltrated the vessel wall either focally or diffusely and spread around the vessels. In some cases the inflammatory changes of the vessels were associated with necrosis.

16-week-old mice

All animals showed a polyarthritis (Fig. 1, Table 1). The lesions were more severe than in the 7-week-old mice and were more pronounced in the females. The polyarthritis was distributed symmetrically, affecting paired joints to a similar degree. The proliferation of the synovial lining cells was prominent, especially in the fore- and hind-paws. The proliferating synovial cells formed a pannus in half the mice, affecting only 6% of the joints. The pannus was most frequently observed in the costovertebral and intervertebral joints and the hind-paws, growing over and into the peripheral areas of the cartilage and leading to superficial destruction (Fig. 6). Inflammatory infiltrates consisted either of lymphocytes or of lymphocytes with histiocytes, polymorphonuclear neutrophils and eosinophils. Plasmocytes were rare. The inflammatory infiltrates were also seen in the extra-articular space around tendon sheaths and nerves, occasionally extending into tendons and nerves themselves. Proliferation of the synovial connective tissue was often detected, and fibrosis of the capsule was occasionally seen, especially in the fore- and hind-paws.

In 60% of the mice and in one third of the joints, deposits were seen localised in the joint capsule, the synovial membrane (Fig. 7) and/or in the extraarticular tissue (Fig. 8). They were granular, globular or spindle-shaped and were found either extracellularly and/or in macrophages and synovial lining cells. Occasionally the material was found within vessels (Fig. 9), in the vessel wall or perivascularly (Fig. 10). The deposits were found