

Synovitis in Spondyloarthritis

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Abstract: Recent studies using magnetic resonance imaging have suggested that the subchondral bone marrow and the entheses are the sites which are primarily involved in the peripheral and axial inflammation found in patients with spondyloarthritis. Histopathological analyses indicated that the typical morphological features at these sites reflect an inflammation (osteitis) at the bone cartilage interface and in the subchondral bone marrow. This finding implies that synovitis may be of minor importance, especially in comparison to other inflammatory joint diseases such as rheumatoid arthritis. Here, we summarize current available knowledge on synovial involvement in inflammatory processes related to SpA.

Keywords: Spondyloarthritis, synovitis, histopathology.

INTRODUCTION

The spondyloarthritis (SpA) comprise ankylosing spondylitis (AS), reactive arthritis, arthritis/spondylitis with inflammatory bowel disease and arthritis/spondylitis with psoriasis. The main link between these diseases is the similarity of clinical symptoms such as inflammatory back pain, the pattern of peripheral joint involvement with an asymmetrical arthritis predominantly of the lower limbs, the possible occurrence of sacroiliitis, spondylitis, enthesitis and uveitis, and the association with HLA-B27 [1]. The SpA can also be split into SpA with predominant axial or predominant peripheral involvement, but overlap occurs often, in > 30% of the cases. In axial SpA, the disease starts in > 90% with a sacroiliitis. Further in the course of AS the whole spine can be affected with spondylitis and arthritis of the intervertebral joints. The use of magnetic resonance imaging (MRI) techniques has been a major step forward in the management of patients with axial SpA regarding an earlier diagnosis, and for the detection and monitoring of inflammatory activity [2].

As a reaction to persistent inflammation with bone destruction new bone formation and ankylosis may occur as part of a repair mechanism if inflammation has resolved [3, 4]. Historical studies on the histopathology of inflammation in AS already revealed clear evidence that osteitis is the primary inflammatory event in AS [5-12]. Although published more than 50 years ago, these studies are still unique and give readable insights to possible disease mechanisms. Compared to all present studies of the nearer future entire dead bodies of AS patients with affected axial and peripheral joints were studied. In these reports osteitis was a predominant finding and synovitis seemed to be of less

importance. Additionally, to our knowledge immunohistochemical analysis of spinal synovitis except for sacroiliitis has not been undertaken so far. However, immunohistochemical analysis of synovitis in peripheral joint manifestations in different forms of SpA has extensively been studied by Baeten and colleagues [13-16].

SYNOVITIS IN ANKYLOSING SPONDYLITIS – VERTEBRAL COLUMN

Bony tissue samples from facet joints of the lumbar spine of AS patients who underwent a polysegmental correction of rigid hyperkyphosis were collected to further study inflammation in the axial skeleton by histopathological and immunohistochemical analyses [17]. This study showed that facet joints are directly involved in inflammatory processes in AS. Inflammation was located in the subchondral bone marrow and the enthesis at the articular processes from facet joints. Synovitis was not a predominant finding in this and other studies [7, 18]. It was striking that even after long standing disease duration, inflammatory activity was still present in the spine of AS patients with advanced ankylosis. The finding that T- and B cells next to high microvessel density in lesions with persistent inflammation suggested that several immunological mechanisms are involved in the pathogenesis of this disease [19]. Interestingly, a very recent study on the clinical response of AS patients to B cell depleting therapy with rituximab showed clinical improvement in TNF blocker naïve AS patients [20].

SYNOVITIS IN ANKYLOSING SPONDYLITIS – SACROILIAC JOINT

At the onset of AS sacroiliac joints of AS patients are primarily affected. Within the last decades numerous histomorphological descriptions of sacroiliac joints have been published while immunohistochemical analyses are rare. Inflammation in the subchondral and synovitis are the earliest histomorphological changes. In contrast to immunohistochemical observations in peripheral joints of

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rheumatoid arthritis patients the hypertrophic synovia displays only little synovial hyperplasia of the synovial layer cells and the subsynovial tissue consisted of macrophages and T lymphocytes [21-23]. Destruction of cartilage by synovitis has been reported as well as loss of synovium if the sacroiliac joint is completely ankylosed [8, 11, 22]. It is indeed suggestive that destruction of cartilage in sacroiliac joints of AS patients is not only caused by subchondral joint inflammation but also by synovitis. Immunohistochemical analysis and in situ hybridisation revealed that mononuclear cell infiltrates and TNF α might be important mediators during inflammatory processes in the subchondral bone of affected joints [21, 23].

SYNOVITIS IN DIFFERENT SPONDYLOARTHRITIDES – HIP ARTHRITIS

Historical studies on the histopathological findings in AS hip arthritis relied on case reports. However, some of them already gave interesting insights into the mechanisms involved during inflammatory processes. Bywaters studied the body of a 21 year old man who died due to fatal secondary amyloidosis [8]. This allowed the unique opportunity to study histopathological features in AS. The hip joint showed chronic inflammatory changes in the synovial membrane. However, these were mild and inactive with increased vessel density as reported by others in the synovial membrane of AS patients [24]. Only marginal cartilage erosion was observed at the surface. Interestingly, cellular infiltrates penetrating the bone end plate were mostly involved in cartilage destruction from below. More recent immunohistochemical analyses characterized the cellular components of acute inflammatory lesions in femoral heads of AS patients [19, 25]. Enthesial site of femoral heads and knees from AS patients undergoing endoprothetic surgery displayed inflammation driven by mononuclear cells consisting of CD4+ and CD8+ T cells [25]. In the subchondral bone marrow and at the bone cartilage interface of femoral heads of AS patients the number of subchondral T cells was significantly higher in areas with cartilage still on the surface compared to areas without cartilage while, in contrast, such a difference was not found in RA patients [19]. The importance of cellular changes in the bone marrow was highlighted by Francois and colleagues [22]. Angiogenesis as measured by microvessel density was significantly increased in AS patients compared to RA and OA. The number of osteoclastic foci in areas of bone resorption at the bone cartilage interface of femoral heads with cartilage on the surface was also significantly higher in AS compared to RA and OA [19]. In these samples some femoral heads had adjacent synovial membranes for further analysis which only revealed minor acute inflammatory lesions compared to the subchondral bone marrow (Appel, unpublished data). This was also a major difference in comparison to RA femoral heads. Thus, a very important conclusion from this study was that inflammation is primary located in the subchondral bone marrow and not in the synovial membrane. Furthermore, inflammation seems to be linked to the presence of cartilage and disappears once cartilage is destroyed. This concept is further supported by the use of MRI for the investigation of acute inflammation in AS. Several studies consistently reported subchondral bone

marrow oedema as the primary site of inflammation and as a consequence of inflammation at different sites such as sacroiliac joints [23], femoral head [26], manubriosternal joints [27].

SYNOVITIS IN DIFFERENT SPONDYLOARTHRITIDES – PERIPHERAL JOINTS AND JOINTS FROM THE ANTERIOR CHEST WALL

Most of the histomorphological descriptions discussing synovitis in AS are historical reports [5, 7, 18, 28]. Only few groups have undertaken systematic analysis of peripheral joints in SpA administering immunohistochemical analysis [13-15, 29-35]. Increased mononuclear cell infiltration and increased vascularity were frequently observed if patients with SpA and rheumatoid arthritis were compared. In SpA synovitis lymphocytic infiltrates consisting of CD3+, CD4+ and CD20+ cells [13] and plasma cells [29] were observed. Single cell analysis and the quantification of lymphocytic aggregates revealed lower frequencies of CD4+ and CD20+ lymphocytes than in RA synovium. Interestingly, this was not the case for CD8+ T cells. Studies before and during TNF blocker therapy revealed evidence that TNF α is an important pro-inflammatory cytokine also for peripheral joint inflammation in SpA. Mononuclear cell infiltrates decreased significantly during therapy [14]. Interestingly, T cell but not B cell infiltrates resolved during TNF α blocker treatment suggesting that T-cell types are important mediators of inflammation in SpA synovitis. Specific macrophage subsets like M2 macrophages and also polymorphonuclear cells are also seen in SpA synovitis [30]. These cellular components correlate well with global disease activity and decrease rapidly during successful treatment with TNF α blocking agents [14, 31]. Because Toll like receptors were also increased in active SpA synovitis it has been hypothesized that inflammation triggered by the innate immune system is also involved in the pathogenesis of SpA synovitis [16, 36]. Especially hypervascularity and the presence of tortuous vessels were identified as a typical feature in SpA which was also observed by others [24, 34] but not in RA. In summary, these studies revealed some evidence that neovascularization might be a more important mechanism in SpA compared to RA and therefore also a possible therapeutic target. We do not know of any immunohistochemical analysis of SpA patients comparing osteitis and synovitis in peripheral joints. However, peripheral arthritis in the knee seemed to be driven by inflammation in the synovial membrane which is also supported by MRI [37].

Engfeldt and colleagues had studied an acromioclavicular joint in an AS patient. Beside features of new bone formation they could also describe synovitis in the adjacent soft tissue with mononuclear cell aggregates and high vascularity [5]. This was accompanied by inflammation in the bone marrow, bone edema and bone destruction. Cruickshank studied additional samples from the anterior chest wall. The earliest changes in the manubriosternal joints were also a subacute osteitis in the subchondral bone marrow underneath the bone end plate. This consisted of inflammatory cell infiltrates and fibrous tissue with increased microvessel density.

SUMMARY

Histopathological analysis of joint inflammation in patients with AS or other SpA provide some evidence that joint inflammation within the axial skeleton and the chest wall as well as in the hip is mostly driven by inflammation in the bone marrow either at the enthesial site or in the subchondral bone marrow. Peripheral arthritis in the knee seemed be driven by inflammation in the synovial membrane, this is also supported by MRI.

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CONFLICT OF INTEREST

None declared.

ABBREVIATIONS

SpA = Spondyloarthritis
 AS = Ankylosing spondylitis
 MRI = Magnetic resonance imaging
 TNF = Tumor necrosis factor

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