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Joint Involvement and Synovial Histopathology in BD

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Abstract

Behcet's disease (BD) is a polysymptomatic and recurrent systemic vasculitis with a chronic course and unknown cause. Joint involvement in BD is common. Arthritis and arthralgia in BD are known to be the most common rheumatologic findings. Arthropathy in BD is monoarthritis or asymmetrical oligoarthritis affecting larger joints, and it is usually acute or recurrent with a self-limiting course. Bone deformity and destruction are rare. Autoantibodies are typically negative, and the presence of anti-CCP antibodies at high titers favors a diagnosis of rheumatoid arthritis (RA). Although joint involvement is clinically well recognized, few histologic studies have been reported. In this chapter, we focused on the synovitis and synovial histopathology in BD.

Keywords: Behcet's disease, arthritis, joint, synovia, synovitis

1. Introduction

Behcet's disease (BD) is a polysymptomatic and recurrent systemic vasculitis with a chronic course and unknown cause [1]. Joint involvement in BD is very common. Arthropathy in BD is monoarthritis or asymmetrical oligoarthritis, and it is usually acute or recurrent [2, 3]. In addition, arthritis associated with BD is usually self-limiting and non-deforming; bone erosive change of joints is extremely rare [4]. It typically affects larger joints (knees, ankles, wrists, and elbows). Unusual findings include arthritis with deformities and/or destruction. The synovial histopathology shows a wide range of features, including lining cell hyperplasia, angiogenesis, granulation tissue, and lymphoid follicle formation. Usually, autoantibodies are typically negative, and the presence of anti-CCP antibodies at high titers favors a diagnosis of RA. First-line treatment includes non-steroidal anti-inflammatory drugs, or corticosteroids for severe cases, whereas colchicine has shown some efficacy for the treatment of recurrent and refractory arthritis. Although joint involvement is clinically well recognized, few histologic

studies have been reported. We review joint involvement in BD patients with both typical and atypical findings. In this chapter, we focused on the synovitis and synovial histopathology in BD. In addition, we introduce rare cases, and we have encountered with synovial findings.

1.1. Typical joint involvement

Joint manifestations are very common, being present in 40–75% of BD patients. According to a retrospective review of 340 cases, joint involvement is the initial manifestation of BD in 18.2% [5]. The knees, ankles, wrists, and elbows are frequently affected, while the involvement of small joints in the hands and feet is less common. Most cases demonstrate monoarthritis or oligoarthritis and usually run an acute or recurrent course [2]. Polyarthritis and the chronic form are rare. In addition, arthritis associated with BD is usually benign, self-limiting, and non-deforming. Bone erosive change of the joints is extremely rare [4]. Joint deformities and destruction have been reported in only a few cases [6].

According to another retrospective review of 176 cases [7], rheumatic manifestations were noted in 45%. Articular manifestations were the initial disease manifestation in 16.5%. Inflammatory arthralgia was observed in 81% mainly in the large lower limb joints. Arthritis was less common: oligoarthritis, 7.5%; monoarthritis, 6.5%; and polyarthritis, 5%. The disease course was acute in most patients. Axial involvement was noted: spinal pain in 2.9%, isolated sacroiliitis in 7.5%, and definite ankylosing spondylitis in 5%.

Frikha et al. [8] reviewed the medical records of 553 BD patients. Rheumatologic manifestations were observed in 71.1%, being second after cutaneo-mucosal involvement. Rheumatologic manifestations in BD are defined as inflammatory arthralgia, peripheral arthritis, intermittent hydrarthrosis, popliteal cysts, and spondylarthropathy (low back pain with sacroiliitis). Definite arthritis was noted in 50%. The most frequent manifestation is a non-erosive and non-deforming monoarthritis or asymmetrical oligoarthritis, commonly subacute and self-limiting, typically affecting the larger joints.

1.2. Hand involvement

In a recent randomized study in Turkey, clinical hand involvement was investigated in 57 BD patients [9], and the prevalence of hand involvement in BD was found to be relatively high. Thus, terminal phalangeal pulp resorption was observed in 29.8%, which might be induced by the vasculitic process due to repeated digital infarcts. Rheumatoid-like hand findings were noted in 28.1%, dorsal interosseous atrophy was observed in 20.1%, and erythema of the digitis was identified in 20%. Twenty-four patients (42.1%) showed scintigraphic abnormalities.

1.3. Atypical joint involvement: erosive changes

Erosive changes due to joint involvement by BD are also infrequent. Thus, Vernon-Roberts et al. [6] reported that two of six patients with BD showed radiologically erosive changes in the hip and manubriosternal joints. Armas et al. [10] reported radiologically well-defined

“punched-out” erosive arthropathy in the head of the first metacarpophalangeal (MCP) joints. Düzgün and Ateş [11] reviewed erosive arthropathy in BD patients with references to 11 papers. Erosive changes were reported in axial joints (sacroiliac) and peripheral joints such as intertarsal and MTP (metatarsophalangeal) joints of the foot, intercarpal and MCP joints of the hand, knee, wrist, and hip joints [2, 4–6, 10–13]. Enthesis was also noted in calcaneal joints. More recently, Aydın et al. [14] reported an unusual case of BD with extensive erosive arthropathy radiologically mimicking psoriatic arthritis. In their case, erosive changes at the styloid process of the left ulnar bone were notable. Yurdaku et al. reported five out of 47 BD patients who had radiologically erosive lesions in a prospective study [2]. We also reported [15] a female patient with BD who demonstrated arthritis in the sternocostal joint showing erosive changes, which rarely occur in BD [16]. Taken together, erosive change can be found in various joints, although it is an atypical change in BD.

1.4. Atypical joint involvement: destructive arthritis

In the review of 553 BD patients by Frikha et al., as mentioned above, only eight patients (1.4% overall, 2% of patients with rheumatic involvement) had destructive arthritis (defined by radiological changes: erosions and/or geodes and/or global narrowing of the joint space and/or ankylosis) [8]. The involved joints included knee joints, sternoclavicular joints, the wrist, foot, and tarsal scaphoid, whereas the spine or sacroiliac joint was not affected. On the other hand, sacroiliitis and enthesitis have been reported in BD, although their prevalence is low [17, 18].

1.5. Synovial histology

It has been reported that approximately 40–50% of patients with BD have synovitis [2, 19], although there have been a limited number of reports on the synovial histology in BD [2, 6, 20]. Yuradaku et al. reported the findings of synovial biopsy in 12 patients, revealing superficial ulceration, paucity of plasma cells, and, in five instances, lymphoid follicle formation [2]. Vernon-Roberts et al. indicated that only superficial zones of the synovial tissue were affected. In seven of eight specimens, the superficial zones were replaced by densely inflamed granulation tissue composed of lymphocytes mixed with macrophages, vascular elements, fibroblasts, and neutrophils [6]. Gibson et al. [20] noted that synovial changes in BD are similar to those observed in early RA, and demonstrated hypertrophy and hyperplasia of synovial lining cells, hypervascularity, subsynovial accumulation of inflammatory cells, and replacement of superficial zones of the synovial membrane by densely inflamed granulation tissue. However, immunofluorescent studies indicated that the consistent deposition of IgG might be characteristic of BD [20]. Moll et al. [21] described the macroscopic features of early untreated knee synovitis in BD and psoriatic arthritis (PsA). They reported the presence of extensive fibrinoid membranes and large areas of erythematous synovitis without villi or a distinctive vascular pattern in early and untreated BD. Cañete et al. [22] noted that polymorph nuclear neutrophils and lymphocytes were indicators of cytotoxic molecules in early untreated synovitis in BD. Thus, the histopathological characteristics of synovial tissue in BD may be diverse.

1.6. Presentation of synovial histology in our cases

We previously reported the synovial histology and destructive joint manifestations in three BD patients who underwent orthopedic surgery [23]. *They all had morning stiffness.* The joints affected in these cases were the ankle, wrist, elbow, and knee. Case 1 *presented bleeding from ulcers of the small intestine* and complained of polyarthrititis (both ankles, wrists, and PIP joints) and severe recurrent pain in the left ankle and intermittent claudication. *The patient was diagnosed as having BD (incomplete type) was with oral prednisolone (15 mg/day).* Radiographs of the left ankle revealed a sclerotic joint space and osteoporotic change, for which arthrodesis was performed. Histological studies of synovial tissues revealed non-specific chronic synovitis and the infiltration of lymphoid cells around the vascular cells with fibrinoid changes. There was no sign of vasculitis.

Case 2 underwent Darrach's procedure for the right wrist joint. Histological findings showed neither the formation of lymphoid follicle formation nor infiltration of plasma cells, although some neutrophils and lymphocytes were detected. She had the chronic form of polyarthrititis of the right wrist and elbow, left knee, both ankles, and PIP joints and received synovectomy. *She had been treated with NSAIDs for arthritis.* Radiographs revealed joint space narrowing in the right elbow and left knee. Synovial tissue from the elbow showed hyperplasia of the synovial lining cells and the infiltration of plasma cells, with the formation of numerous lymphoid follicles. Synovial tissue from the knee showed hyperplasia of the synovial lining cells, and the perivascular infiltration of lymphoid cells.

Case 3 had chronic arthritis *on left knee, both wrists and PIP joints*, and radiography revealed bone atrophy and ankylosis of the left knee, erosive changes of the PIP joints, and destructive changes of the wrists, mimicking rheumatoid arthritis. Synovectomy was then performed, and histopathological findings showed hyperplasia of the lining cells, the deposition of fibrin, infiltration of inflammatory cells, and marked vascularity. These features cannot be differentiated from those of rheumatoid arthritis.

1.7. Synovial immunopathology in BD

Cañete et al. [22] investigated the differences in synovial immunopathology between early active and untreated BD and PsA. There was marked CD15⁺neutrophilic inflammation in the intimal lining layer in BD synovitis. This increased number of polymorphonuclear neutrophils (PMNs) has been reported not only in the synovium but also in the skin and central nervous system. As for lymphocytes, CD3⁺T cells, but neither CD20⁺ B cells nor CD138⁺ plasma cells, were increased in BD [22]. Specific T-cell subsets are associated with sterile neutrophil-rich inflammation as observed in BD synovitis, and this may explain the simultaneous increase of both T cells and PMN [24]. The analysis of the T-cell population in SF showed that there was no clear shift in the CD4/CD8 ratio or Th1/Th2/Th17 profile. The synovial fluid levels of perforin, an effector molecule of cytotoxic cells, showed a significant increase in BD [22]. This suggests the relevance of cytotoxicity in BD synovitis [25, 26]. Suh et al. [27] reported that antigen-driven clonal B-cell proliferation occurs in the synovium in BD. They identified immunoglobulin transcripts clonally expanded in the synovium in BD.

1.8. Humoral protective factors in synovial fluid or blood

As with BD, the pathogenesis of arthritis and protective mechanisms against erosive changes needs to be elucidated. The plasminogen activation system can contribute to the pathogenesis of destructive joint disease. Ertenli et al. [28] demonstrated that *synovial fluid* (SF) in BD is inflammatory in nature. They reported increased SF IL-1 β levels in BD patients. In SF, levels of IL-1 β , IL-1ra, and TGF- β were higher in BD than *osteoarthritis* (OA) [28]. Thus, they speculated that IL1ra and TGF- β might serve as protective factors against cartilage destruction. Pay et al. [29] also reported that BD and RA patients had higher synovial IL-1 β than OA patients. MMP-3 and proinflammatory cytokines except IL-1 β were expressed in small quantities in BD synovitis; this may explain the non-erosive character of BD arthritis. Thus, IL- β may be involved in the pathogenesis of BD synovitis. In addition, relatively lower levels of IL-18 in the SF of BD patients might be the cause of less marked inflammation in BD arthritis. Recently, Karasneh et al. [30] reported that IL-1 gene cluster polymorphisms, including the *IL-1B* gene, are associated with an increased risk of BD. Therefore, the detection of increased synovial IL-1 β levels in BD patients could be determined genetically by functional polymorphism, leading to differential gene regulation and expression.

Ozturk et al. [31] reported that systemic bloodstream and local SF plasminogen activator inhibitor-1 (PAI-1) antigen levels and PAI-1 activities were higher in BD patients than RA patients and healthy controls. PAI-1 may promote hypofibrinolysis of BD vasculopathy and also plays a protective role against arthritis in BD patients. They speculated that elevated PAI-1 antigen and activities in the synovial fluid of BD patients contribute to the unique nonerosive character of BD.

1.9. Proinflammatory factors in synovial fluid or blood

Aktas Cetin et al. [32] reported that in peripheral blood mononuclear cells (PBMCs), CD4, CD25, HLA-DR expression and intracellular IL-12, and TNF- α levels of CD3 $^{+}$ T cells were increased in BD compared with HC. Compared with AS patients, CD25, HLA-DR surface expression, and intracellular IFN- γ and TNF- α levels in T cells were elevated in BD. Th1 polarization occurred in both the peripheral blood and SF of BD patients with arthritis. Duygulu et al. [33] demonstrated that the levels of both serum and erythrocyte nitric oxide (NO), the most abundant free radical in the body, were elevated in BD patients and associated with disease activity. In addition, synovial NO levels were positively correlated with serum levels. Turan et al. [34] analyzed the production of soluble TNF receptors, sTNFR1 and sTNFR2, in BD patients. sTNFR2 plasma concentrations are closely linked with active BD and especially with arthritis. The expression of TNFR molecules in mast cells of mucocutaneous lesions indicates the fundamental role of the TNF/TNFR pathway in BD.

Erdem et al. [35] demonstrated that the expression of CXC chemokines, including IL-8, GRO- α , and ENA-78, was lower in the SF of patients with BD than in those with RA. All CXC chemokines and VEGF were induced by IL-18, which are involved in angiogenesis and the development of pannus. Thus, the lower levels of these chemokines in the SF of BD patients may explain the lack of pannus formation or erosion in BD arthritis.

Ertenli et al. [28] reported higher levels of synovial IL-8 in BD than OA patients. They suggested that elevated synovial IL-8 might play a pivotal role in the process of neutrophil migration in BD synovitis and reflect a nonspecific inflammatory process. Erdem et al. [35] speculated that synovial IL-8 levels increased via the attraction of more neutrophils to SF, and this, in addition to its angiogenic properties, might be responsible for the development of acute synovitis.

1.10. Metabolomic evaluation of BD in synovial fluid: potential biomarkers

Ahn et al. [36] investigated possible metabolic patterns and potential biomarkers of BD with arthritis on metabolic profiling of SF from BD patients with arthritis and seronegative arthritis (SNA). They identified 123 metabolites. Compared with SNA, BD patients with arthritis exhibited relatively high levels of glutamate, valine, citramalate, leucine, methionine sulfoxide, glycerate, phosphate, lysine, isoleucine, urea, and citrulline. Finally, they identified two markers, elevated methionine sulfoxide and citrulline, associated with increased oxidative stress, providing a potential link to BD-associated neutrophil hyperactivity. Gultamate, citramalate, and valine were selected as putative biomarkers for BD with arthritis.

1.11. Anti-cyclic citrullinated peptide (Anti-CCP) antibodies and BD

Anti-CCP antibodies are a more reliable diagnostic marker for RA and closely associated with the prognosis in RA patients [37]. Recently, a significant correlation was reported between anti-CCP antibodies and joint symptoms in patients with familial Mediterranean fever [38]. In a study of 189 Korean BD patients, only seven patients (3.7%) were positive for anti-CCP antibodies, five of which (71.4%) had polyarticular joint involvement, and the other two (28.6%) had oligoarticular involvement. Among the seven patients, one patient with an anti-CCP antibody titer of over 100 U/mL fulfilled the diagnostic criteria for both BD and RA. Of course, all BD patients without articular involvement were negative on an anti-CCP antibody test [39]. Since it has been demonstrated that anti-CCP antibodies are elevated prior to the development of RA, we need to be careful when diagnosing BD patients who show arthritis in the presence of positive anti-CCP antibodies.

1.12. Sonographic study

Ultrasound (US) evaluation is useful for the detection of joint involvement. Synovial proliferation, joint effusion, and bone surface erosions are detectable, and even asymptomatic joint involvement showed US alterations [40]. Ceccarelli et al. performed knee United States in 30 BD patients and found that 60% of patients showed knee involvement based on United States. They detected synovial proliferation in 14%, joint effusion in 46%, and bone surface erosions in 10% of patients. They also pointed out that subjects with a higher US score showed a positive correlation with disease activities such as acneiform skin lesions. Gok et al. performed high-frequency United States and power Doppler ultrasonography (PDUS) examination of knee joints [41]. By ultrasonography, synovial hypertrophy scores were lower in patients with BD than in those with RA and spondyloarthropathy. However, no difference was found between BD, RA, and spondyloarthropathy patients based on PD signal scores using PDUS. Gok et al. also investigated ultrasonographic findings and synovial angiogenesis modulators.

Cumulative effusion scores were positively correlated with angiopoietin-1, angiostatin, and basic fibroblast growth factor (bFGF), while they were negatively correlated with thrombospondin-1 levels. Synovial hypertrophy scores were positively correlated with angiostatin and bFGF levels and negatively correlated with thrombospondin-1. No correlation was found between PD scores and modulators of angiogenesis.

1.13. Magnetic resonance imaging study and Tc-99m-MDP bone scintigraphy

Magnetic resonance imaging has been reported to be sensitive for detecting early arthritis of BD. Choi et al. showed synovial thickening and effusion based on a high signal intensity on T2-weighted images of two BD patients with arthropathy [42].

Sugawara et al. reported radiography and magnetic resonance imaging of hand and wrist arthritis in four BD patients [43]. They concluded that characteristics on imaging of arthritis in BD patients vary and may be similar to those of psoriatic arthritis patients. Erosion in the distal interphalangeal joint was seen, but the type of erosion was of the gull-wing type, being different from RA variants.

Joint scanning with 99m Tc is a more valuable tool for the prediction of hand joint inflammation than radiography [44]. Bone scintigraphy is also more sensitive for the earlier diagnosis of joint involvement, especially in sacroileal joints [45].

2. Conclusion

In summary, arthritis and arthralgia are common in BD patients, and joint manifestations of BD patients are diverse: sometimes mimicking rheumatoid arthritis, PsA, and spondyloarthritis radiologically. In addition, the histopathological characteristics of synovial tissue in BD may be various.

Thus, despite the rarity of destructive arthropathies, this unusual form should be known and considered in the differential diagnosis of other rheumatic diseases.

Abbreviation

BD

Behcet's disease

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