The Utility of Tc-99m MDP Bone Scintigraphy for the Detection of Articular Involvement in Behçet's Disease

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Abstract: Introduction: Behçet’s disease (BD) is a chronic relapsing inflammatory disease. 40-70% of BD patients display rheumatic features with a 9% incidence as an initial presentation. However, there are no pathognomonic laboratory tests in BD and the diagnosis depends on the occurrence and grouping of sufficient clinical manifestations to allow the physician to either suspect, or definitely diagnose the condition. Our aim was to assess the utility of Tc-99m methylene diphosphonate (Tc-99m MDP) bone scintigraphy for the detection of articular involvement in BD patients and its impact on disease activity & severity scoring.

Methods: 25 BD patients diagnosed according to the international study group criteria for BD diagnosis (ISG) [18, 7, mean age 32.44±7.78, disease duration 6.98±4.61 year] were included and subjected to selected joint x-ray and bone scintigraphy.

Results: 25/25 was scintigraphically positive for arthritis [100%, 64%, 44%, 40%, 36% & 20% in wrist, Metacarpophalangeal, proximal interphalangeal (PIPs), distal interphalangeal (DIPs), Knees & ankles respectively]. 13/25 were clinically negative while scintigraphically positive for arthritis. 11/25 (44%) and 8/25 (32%) turned from inactive to active BD and from mild to moderate disease severity, based on their positive hand scintigraphy with treatment modification. 4/25 (16%) had recurrent oral ulcers with normal laboratory data and only positive hand scintigraphy; with follow-up they met ISG criteria.

Conclusion: skeletal scintigraphy is a simple diagnostic modality with a low radiation burden, when compared to conventional radiology. Hence, when used appropriately in the diagnostic algorithm of BD, bone scintigraphy can be used for detection of early joint involvement, assessment of the extent and activity status with guidance for the selected therapy.

Keywords: Behçet’s disease, bone scintigraphy, hand skeletal scintigraphy, vasculitis.

INTRODUCTION

Behçet’s disease (BD) is a relapsing systemic inflammatory condition of unknown etiology that is more prevalent in certain geographical areas and particular ethnic groups [1, 2]. It is now recognized as a multisystem disease with various organ involvement including skin, mucous membrane, eyes, joints, vessels, gastrointestinal tract and nervous system [3]. However, since vascular manifestations are common in this disease, it is regarded as vasculitis. The predominant histopathology in the inflamed tissues is infiltration of lymphocytes and monocytes through small veins walls without microscopic changes. Thrombophilia or thrombophlebitis involving small and large veins is also common whereas arteritis is rare. In this regard BD is unique when compared with other vasculitides [4].

There are no pathognomonic laboratory tests in BD and diagnosis depends on the occurrence and grouping of sufficient manifestations to either suspect, or definitely diagnoses, the condition [5]. Several clinical criteria have been developed to assist the diagnosis. The older O’Duffy criteria required oral aphthae, plus at least two of the followings: genital aphthae; synovitis; posterior uveitis; positive skin pathergy test (SPT); or meningoencephalitis, in the absence of inflammatory bowel disease or other collagen vascular disease [6]. New international study group criteria (ISG) for BD diagnosis was published [7], requiring the presence of recurrent oral aphthae (three times/year) plus 2/4 criteria with no other systemic diseases (Recurrent genital ulceration, Eye involvement, Skin lesions and Positive SPT).

Although, arthritis or arthralgias are not included in ISG [7], both are among the most frequent manifestations of BD [8]. Articular involvement was reported in 5-76% of BD patients [9] being intermittent, self-limiting, non-erosive, symmetric or asymmetric oligoarthritis, although polyarticular and monoarticular forms are also seen [10]. Arthritis or arthralgias are in the items of the BD activity and severity scores (Aydintug and Yosipovitch methods) [11, 12].

Although joint manifestations have become a well-known part of the spectrum of multisystemic involvement in BD, previous descriptions have been limited to conventional radiographic findings. These findings have been described as being normal or showing mild abnormalities consisting of nonspecific finding such as osteoporosis, and soft-tissue...
swelling with joint-space narrowing and marginal erosions only rarely [13].

The nuclear medicine role in rheumatology is evolving continuously since 50 years and currently, we have scintigraphic procedures and radiopharmaceuticals to image inflammation early with minimum radiation and cost burden [10, 14]. Tc-99m methylene diphosphonate (Tc-99m MDP) bone scintigraphy is a non-invasive method which can detect early sub-clinical arthritis in BD with no or mild symptoms and normal radiography [3, 15, 16].

In treatment guidelines of BD corticosteroids are included [17]; in the absence of disease activity steroids are injurious for the vascular endothelium while it is advantageous in active BD [18], thus the evaluation of disease activity is of great importance.

This study was conducted to evaluate the utility of Tc-99m-MDP bone scintigraphy in the detection of articular involvement in BD patients and to correlate it with clinical manifestations, disease activity and severity.

PATIENTS AND METHODS

25 BD patients diagnosed according to the ISG [7] were included in this study. Our data base included clinical data, SPT and laboratory results [Leukocytes count, hemoglobin (Hb), erythrocyte sedimentation rate (ESR) & C-reactive protein (CRP)] together with radiological and skeletal scintigraphic results. The patient was considered to have active disease state when at least two of the following manifestations were present; oral or genital ulcers, eye or skin or vascular lesions, arthritis, pulmonary and CNS involvement (Aydintug method) [11]. Severity score was calculated as the sum of “1, 2, 3 points” for each of the mild, moderate and severe disease manifestations respectively (Yosipovitch scoring model) [12].

Plain Radiography

Radiological joint survey was performed in the A-P and lateral views for all joints except for the hands where A-P and P-A views were done and specific views for sacroiliac joints. Joints were scored according to Larsen score: 0 = normal; 1 = soft tissue swelling and/or joint space narrowing; 2 = erosions with destruction of the joint surface (DJS) 25%; 3 = DJS 26-50%; 4 = DJS 51-75%; 5 = DJS >75% [19].

Bone Scintigraphy

Skeletal scintigraphy was performed only in the late post 2-3 hours phase following intravenous injection of 555-740 MBq of Tc-99m-MDP, using a dual headed rectangular, large field-of-view gamma camera (Phillips- vertex plus) mounted with a low-energy, high-resolution collimator with a 20% energy window setting centered at 140 keV. An experienced physician interpreted the scans. Hand scintigraphic interpretation was done using the four point Yurtkuran scale method: 0= none, 1= mild, 2= moderate, 3= severe [20].

Statistical Method

All data were analyzed and interpreted using a statistical package for social science (SPSS, version 11). Descriptive Statistics were represented as means and standard deviation, as well as frequencies and percentages. Contingency coefficient “r” was used as an index to describe the strength of the association between any two variables. The cross tabulation was used to detect the correlation between the variables. To test the significant difference between hand plain x-ray and hand bone scintigraphy, we use the non-parametric test (Wilcoxon Signed Ranks Test). P value of < 0.05 was judged to be statistically significant.

RESULTS

The study group included 18/25 (72%) and 7/25 (28%)♂ and ♀ respectively. Their mean age was 32.44±7.78 year with a mean disease duration 6.98±4.61 year. Their laboratory data are shown in Table 1, while the clinical manifestations in the last month prior to the study time were detailed in Table 2. The radiological survey showed Larsen’s score 0 (6/25) and 1 (19/25) BD patients (Table 3).

Table 1. Laboratory Data of the Study Population (n. 25)

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (x103)</td>
<td>9.27 ± 4.32</td>
</tr>
<tr>
<td>Hemoglobin (gm%)</td>
<td>11.84 ± 1.70</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>27.08 ± 15.32</td>
</tr>
</tbody>
</table>

*Per cubic millimeter of blood.

Table 2. Clinical Data of BD Patients and the Used Drugs (n. 25)

<table>
<thead>
<tr>
<th>Manifestations in the Last Month</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcers</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Eye manifestations</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Joint manifestations</td>
<td>12* (48)</td>
</tr>
<tr>
<td>Major vessels</td>
<td>8 (32)</td>
</tr>
<tr>
<td>CNS manifestations</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Recent deep venous thrombosis (DVT)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Positive Skin Pathergy Test (SPT)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Medical Treatment</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Steroids and other types of medications&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (56)</td>
</tr>
<tr>
<td>Other types of medications&lt;sup&gt;†&lt;/sup&gt; without steroids</td>
<td>8 (32)</td>
</tr>
</tbody>
</table>

<sup>†</sup>Immunosuppressive therapy, Colchicine.

Bone scintigraphy demonstrated articular involvement in the wrists of all BD patients. The frequency for other involved sites is detailed in Table 4. 4/25 (16%) had recurrent oral ulcers with normal laboratory data and only positive hand scintigraphy; with follow-up they met ISG criteria. The analysis of hand scintigraphy based on the 4 point scale method showed mainly the 2 point scale in the wrist and MCPs positive cases while 1 point scale in the PIPs and DIPs [20].

There was no significant correlation between the radiologically and scintigraphically based arthritis in BD patients with age, sex and disease duration. Regarding the
disease activity; 14/25 were in clinically active disease state and the remainders (11/25) were clinically inactive; however, bone scan was positive for hand arthritis in each of them thus turned them to the category of active disease state. As regards the clinical disease severity score; 10/25, 7/25 and 8/25 patients were classified into mild, moderate and severe scores respectively and based on the radiological and scintigraphic findings 5/10 (50%) and 8/10 (80%) were upgraded from mild to moderate categories respectively. Also, a statistically significant positive correlation was found between ESR and scintigraphically detected hand arthritis \((r=0.4, p<0.03)\). Using Wilcoxon Signed Ranks Test, there was a highly significant difference between hand x-ray and hand bone scan \((Z= 4.284, P<0.001)\) (Fig. 1).

Table 3. Radiological Findings of Abnormal X-Rays in BD Patients \((n=19)\)

<table>
<thead>
<tr>
<th>Plain X-Ray Findings</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juxta-articular osteopenia</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>Narrowing in PIPs†</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Reduced CMC‡</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Reduced IC† bone spaces</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Cyst in 3rd MCP§</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Narrowing in SIJ</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IPA Proximal interphalangeal, CMC Carpometacarpal joints, IC Intercarpal, MCP Metacarpophalangeal, SIJ Sacroiliac joint.

**DISCUSSION**

Multiple systemic associations of BD have been recognized including articular, vascular, gastrointestinal, cardiopulmonary and neurological involvement [3]. However the clinical characteristics of patients and the frequency of organ involvement is different from an area to another, as elicited from the different BD studies along the silk road lands as Turkey, North of Africa (Egypt, Tunisia, Morocco), and East of Asia as China, Japan and Korea, which suggest that geographic, environmental and genetic factors are of importance in the pathogenesis of the disease and its sequels [21]. Regarding sex ratio; our study population \((♂:♀ \text{ ratio } 2.1:1)\) was in concordance with the world wide reports. Reported examples are: \((188 \text{♂} \& 72 \text{♀})\) [22], and \((128/183 \text{♂} \& 54/183 \text{♀})\) [23].

### Table 4. Frequency of Scintigraphic Articular Involvement in BD Patients \((n=25)\)

<table>
<thead>
<tr>
<th>Region</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>MCPs†</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>PIPs†</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>DIPs‡</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Knee</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Ankle</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>SIJs§</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Shoulder</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Elbow</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>MTP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MCP Metacarpophalangeal, PIP Proximal interphalangeal, DIP Distal interphalangeal, SIJ Sacroiliac joint, MTP Metatarsophalangeal.

Up to 50% BD patients display rheumatic features including arthritis being intermittent, self-limiting, non-erosive and non-deforming usually monoarticular or symmetrical oligoarticular subacute arthritis [10]. Articular involvement in BD patients was aimed in this study using clinical, skeletal scintigraphy and radiological joint survey. 5-97% clinically based arthritis in BD was previously reported [3, 20, 24-26]. In our study 12/25 (48%) had clinically evident arthritis and this concurs with the incidence (about 50%) in the Mediterranean (Turkey, Egypt and Lebanon), and North Africans (Tunisia and Morocco) [23, 26-28], however in Asia (Oman) [29] or far Asians (Korea) [24, 26], this incidence shoots up to 75-97%. 2/25 (8%) of our cases had rheumatoid-like hand findings in the form of swelling of PIPs and MCPs. A Turkish study reported similar findings in 28.1% of their patients [20]. Although not uncommon to be found among BD, we must consider that BD is possible to present with severe arthritis though it is usually non-erosive.

Fig. (1). Radiographic and scintigraphic features of a BD patient. (A) Plain x-ray of hands showing juxta-articular osteopenia. (B) Bone scans of both hands showing increased uptake in bilateral wrists, Metacarpophalangeal & proximal interphalangeal joints. (C) Whole body scans with no other articular abnormalities.
Skin lesions and positive SPT were found in 24% & 16% respectively compared to 16% in a North African study [23], others reported higher positive SPT (51% & 61.4%) [20, 30]. These differences are attributable to geographic, environmental and genetic factors variability [21].

The involved joints in our study were detailed in Table 4 with the wrist and hand joints (100%), knee (36%), ankle (20%), and SIJ (16%) (Table 4), being 58.4% oligoarticular, 33.3% monoarticular and 8.3% polyarticular. In previous studies sacroilitis was found in less than 25% of BD patients [3, 24], so it should be considered in those patients with persistent low back pain. As mentioned earlier, clinically the knees (about 58%) and wrists (approximately 50%) were the most frequently affected sites, mostly oligoarticular [28, 31-33]. While the scintigraphically evidenced wrist arthritis reaches up to 75% [3, 20] deducing the higher sensitivity of scintigraphy.

12/25(48%) of BD patients had clinically based arthritis while the radiologically and scintigraphically detected arthritis were 19/25 (76%) & 25/25 (100%) respectively. This keeps with Sahin et al, who reported 25% & 84.4% clinically and scintigraphically based arthritis respectively [3]. These reports are in agreement with the elicited significant difference between the radiologically and scintigraphically based arthritis (Z-value=4.284, P-value=0.001) denoting that the hand bone scan was more comprehensive than hand x-ray. Also, radiological findings are non specific and we cannot rely on them for evaluating active joint arthritis [13]. The higher associated radiation dose compared to bone scintigraphy is another limiting factor. Using the 4 point scale for hand scintigraphy; 24% mild, 60% moderate and 16% high grade scores were detected in concordance with Yurtkuron et al. study, [20] where 29.2%, 62.5% and 8.3% had mild, moderate and high grade scores respectively.

The impact of the scintigraphically detected arthritis on the clinically estimated activity & severity scores was evaluated as a main goal in our study.11/25 BD were in the inactive clinical disease state with the Aydintug method. Based on scintigraphy all the 11 patients were found to have arthritis, mainly hands, suggesting the upgrading of their clinical disease state. Using the Yosipovitch method, 10/25, 7/25 & 8/25 BD patients had mild, moderate and severe clinical disease severity scores respectively. Also, bone scan was positive for arthritis in 8/10 (80%) of those of mild severity scores, thus they were promoted to the moderate severity score with the subsequent influence on their therapy selection. This is supported by the statistically significant positive correlation that was found between ESR and scintigraphically detected hand arthritis (r = 0.4, p 0.03). Elevated ESR was reported to associate exacerbations of arthritis in up to 80% of BD patients [17, 31]. We could consider ESR as a lab item in BD clinical portrayal regarding disease activity and follow-up. Our suggested impact of scintigraphy on estimating disease activity and severity is of high clinical relevance considering the influence on the therapy selection and corticosteroids usage, as the latter have a bipolar effect on vascular endothelium in BD depending on the inflammatory state, being determined by the activity and severity scores. In active exacerbations they are beneficial in reversing vascular endothelial dysfunction, but in remissions, they are deleterious for the vascular endothelium [34]. Moreover, there are some reports about monitoring treatment response in BD active arthritis by skeletal scintigraphy [35], this may reflect that scintigraphy could be an an objective parameter in assessing BD activity & severity. We noticed that 4/25 (16%) had recurrent oral ulcers with normal laboratory data and only positive hand scintigraphy; with follow-up they met ISG criteria. It was previously reported that the immunohistochemical analysis of the synovial tissue samples of newly diagnosed BD showed neutrophil infiltration essentially in the intimal lining layer with CD4 and CD8 T-lymphocytes subsets and documented presence of interferon gamma (INF-γ), Tumor necrosis factor alpha (TNF-α), interleukin (IL)-2, IL-4, IL-6 and IL-17 and other cytotoxic effectors (perforin) in the synovial fluid aspirates [36]. Our group noticed that the latter is similar to the currently proposed immunopathogenic model in BD [37]. Therefore, we suggest using bone scintigraphy as a reinforcing element in the early diagnosis of BD.

CONCLUSION
Skeletal scintigraphy is a simple diagnostic modality with a low radiation burden, when compared to conventional radiology. Hence when used appropriately in the diagnostic algorithm of BD, scintigraphy could be used for the detection of clinically quiescent arthritis and assessment of disease activity and severity states.

ABBREVIATIONS
BD = Behçet’s disease
Tc-99m MDP = Tc-99m methylene diphosphonate
ISG = International study group criteria for BD
SPT = Skin pathergy test
A-P = Antero-posterior
P-A = Postro-anterior

REFERENCES


