Knee joint synovitis in Behçet's disease: a sonographic study

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ABSTRACT

Objective. *The aim of this study was to investigate, using ultrasound (US), knee involvement in patients with Behçet's disease (BD).*

Methods. *Knee US was performed in 30 unselected Italian BD patients. Signs of arthritis (joint effusion, synovial proliferation) and presence of bone erosions and Baker's cysts were recorded. Power Doppler evaluation was performed. A semi-quantitative score was used for each structure examined, whereby 0 was to indicate the absence of any change and score from 1 to 3 the presence of mild to severe changes. A sum of the single scores was obtained. Disease activity was evaluated to identify the correlation with the US modifications.*

Results. *Twenty (66.6%) patients had symptomatic articular involvement and US showed knee involvement in 18 of them (60%). Synovial proliferation was detected in 14 (46%, positive power Doppler in 4), joint effusion in 14 (46%), bone surface erosions in 3 (10%). Four patients, asymptomatic for joint involvement, showed US alterations. Eleven patients showed a total score between 1 and 3, while the other 7 had a score between 4 and 6. Subjects with a higher US score presented an increased prevalence of acneiform skin lesions with respect to the group with US score 1-3. Statistical analysis showed a positive correlation between disease activity and US score in group 2 (p=0.04).*

Conclusion. *This study confirms that peripheral joint involvement represents an important clinical aspect in italian BD patients and US evaluation is useful for the detection of this aspect.*

Introduction

Behçet's disease (BD) is a multi-systemic inflammatory disorder of uncertain aethiopathogenesis, now classified as a vasculitis. It is uncommon in western Europe and USA, being much more prevalent in eastern Mediterranean countries, South East Asia and Japan, following the so-called "old silk-route". Young onset (before the age of 25) and male sex represent risk factors for a more severe disease. The clinical spectrum of BD is wide and includes muco-cutaneous manifestations such as oral and genital aphthous ulcerations, skin follicolitis and erythema nodosum, eye disease with posterior uveitis and retinal vasculitis, articular, gastrointestinal, cardiovascular, renal, pulmonary, and central nervous system involvement (1, 2).

Traditionally, clinical manifestations of BD have been divided into major and minor, according to their prevalence (3). Even if vasculitic lesions, neurological involvement and arthritis are classified as 'minor', their relevance in terms of prognosis "*quod vitam et quod valitudinem*" should not be overlooked. In fact, vasculitis and brain complications may be clinically severe and even life-threatening and arthritis is one of the most frequent clinical features of the disease sometimes being destructive (4-7).

Within the past decade, musculoskeletal ultrasound (US) has become an established imaging technique for the diagnosis and follow-up of patients with rheumatic diseases and improved musculoskeletal imaging in rheumatology (8-12).

As far as we know, US has never been used to assess peripheral joint involvement in BD patients. The aim of this study has been to investigate, using US, knee involvement in patients with BD.

The knee has been selected because it is often involved in BD and it is a joint reliably studied by US (13-15).

Patients and methods

Thirty unselected Italian patients with BD have been studied, 9 women and 21 men with a mean age of 45 years (range 20-69 years) and an average dis-

ease duration of 8.5 years (range 2-21 years). The diagnosis was formulated according to International Study Group Criteria (16).

Glucocorticoids were used in 63.3% of patients with BD, immunosuppressive drugs (cyclosporine A, methotrexate, azathioprine) in 56.6%, infliximab in 13%. Four patients were in complete remission and did not receive therapy.

Disease activity in BD is difficult to define because of the wide spectrum of symptoms which can vary enormously among patients and fluctuate in the same patients over time. Moreover, there are no laboratory indices useful for reflecting clinical activity. Finally, important differences exist among ethnic groups regarding the prevalence and the severity of clinical manifestations. None of the previous disease activity scoring systems available for BD has been formally translated into Italian, nor has it had a cross-cultural validation in Italy. Therefore, we considered active those patients with worsening of clinical symptoms at the time of the present investigation who manifested two out of the following findings (oral and genital ulcerations, skin lesions, eye involvement, positive pathergy test, thrombophlebitis and arthritis), or multiple erythema nodosum with severe inflammation and with both elevated erythrocyte sedimentation rate and positive C-reactive protein (17). According to these criteria, 33.3% of patients had active disease.

US examination

All the patients were submitted to US of both knees. US examination was performed by a rheumatologist who was experienced in US scanning, using a Philips/HP Image Point HX machine with a 10MHz linear probe. Power Doppler (PD) was used with the following settings: PRF 1000Hz gain 18-30dB, low filter. The operator was blinded to the clinical and laboratory findings in all cases.

The knee was examined with the patient in supine position, performing both transverse and longitudinal scans of the supra patellar region and the lateral and medial recesses, according to EULAR guidelines for US (13). An arbitrary scoring system ranging from 0 to 14 for the assessment of knee involvement was applied. Sonographic signs of synovitis (joint effusion, synovial hypertrophy) were recorded assigning a partial score (0 for the absence, 1 to 3 according to severity); the presence of erosions of the bone surface was scored according to their number (1-2 erosions: score 1; 3-4 erosions: score 2; more than 4 erosions: score 3; absence of erosions: score 0); a score of 0 was assigned in the absence of Baker's cyst while the score was 1 in its presence. PD evaluation was performed for the analysis of vascularization of the synovial membrane with a scoring system ranging from 0 to 3.

Table I. Main clinical features of 30 Behçet patients.

Clinical features	*Patients (n/%)*
HLA-B51 allele	22 (73.3%)
Symptomatic articular involvement	20 (66.6%)
Aphtosis oral and/or genital	30 (100%)
Skin manifestations	20 (66.6%)
Ocular manifestations	25 (83.3%)
Nervous systems involvement	5 (16.6%)
Vascular manifestations	5 (16.6%)

Table II. US modifications in 30 Behçet patients.

US modifications	*Patients (n/%)*
Synovial proliferation	14 (46.6%)
Power Doppler positivity	4 (13.3%)
Joint effusion	13 (43.3%)
Erosions of bone surface	3 (10%)
Baker's cyst	1 (3.3%)

Statistical analysis

Fisher's exact test was used to evaluate the presence of correlations between clinical features, disease activity and US modifications in BD patients. *P* values less than 0.05 were considered statistically significant.

Results

Clinical features of BD patients are summarized in Table I. Twenty out of 30 patients (66.6%) had symptomatic articular involvement: 8/30 (26.6%) have arthralgias and 12/30 (40%) have arthritis, with involvement of different joints. Seven patients showed knee arthritis and the effusion was detectable during the physical examination. In 18/30 patients (60%) knee US assessment demonstrated significant abnormalities. The highest value of US score recorded in this cohort of patients

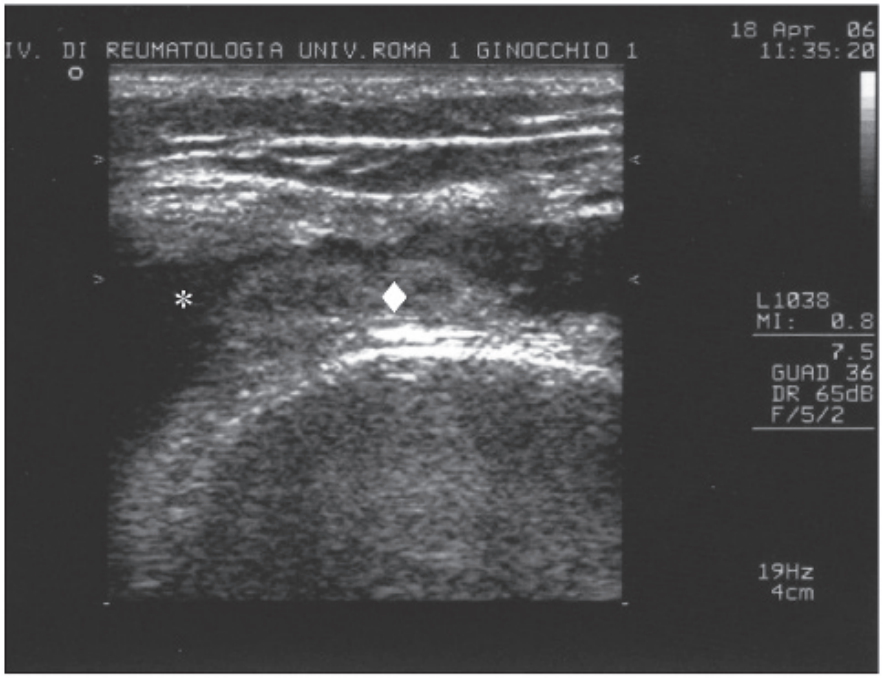

Fig. 1. Suprapatellar transverse scan knee joint: presence of joint effusion (*) and synovial proliferation (◆).

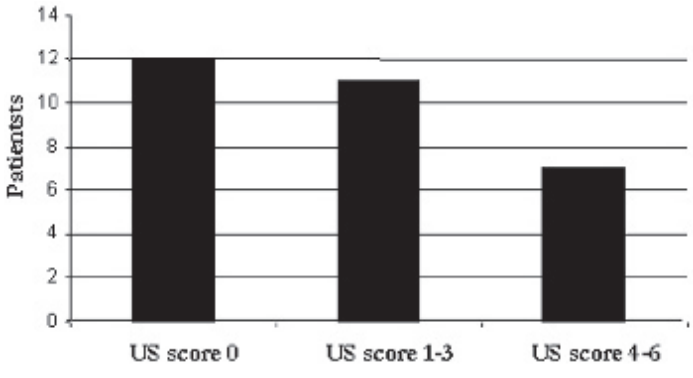

Fig. 2. US score distribution.

was 6. In particular, joint effusion was demonstrated in 14/30 (46%) as well as synovial proliferation (46%, with positivity of PD in 4/18, *i.e.*, 28%) Bone surface erosions were present in 3/30 (10%). Only one had a Baker's cyst. (Table II) (Fig. 1).

Interestingly, 4 patients asymptomatic for joint involvement showed US alterations (synovial proliferation in 4, joint effusion in 2).

Subgrouping these patients according to the score point (group 1 score 1-3, group 2 core 4-6), 11 patients were included in group 1, and 7 in group 2 (Fig. 2). Skin manifestations prevailed in the group with a higher score in comparison to group 1 (7/7 (100%) *vs.* 4/11 (36.3).

Twenty-two out of 30 patients had HLA-B51 allele; 13 out of 18 (72%) of patients with US modifications had HLA B51 *vs.* 9 out of 12 (75%) without sonographic knee involvement.

No correlation was found between the kind of therapeutic approach and joint involvement (clinical symptoms and/or the degree of changes recorded by US). Statystical analysis showed a positive correlation between disease activity and US score in the group 2 ($p = 0.04$).

Discussion

Joint involvement has not been included in any of the presently available classification criteria for BD. However, it occurs in 40-70% of patients, representing the first symptom in 18-34.5% of cases, while in 9% it is the only one (18, 19).

The arthritis of BD is usually intermittent, self-limited, not deforming (20) and an erosive arthropathy has been only rarely reported (6, 7).

In two large studies involving respectively 309 and 340 cases of BD patients with joint manifestations, monoarthritis, oligoarthritis and polyarthritis were seen in 12-17%, in 11.7-13.5%, and in 17%-19.8% of cases respectively (18). Children are more likely than adults to have joint manifestations and polyarthritis (21).

Monoarthritis and oligoarthritis affect essentially knees and ankles, with a marked male bias. They usually run an acute or recurrent course, with chronic forms being rare. Synovial fluid examination during acute attacks reveals inflammatory fluid, with increased viscosity and number of leukocytes (between 5000 and 50.000, with PMN predominancy) and normal protein and glucose levels (22).

Polyarthritis generally involves the large limb joints and the small joints of the hands and feet. Unusual forms include arthritis with deformities and/or destruction, pseudogout, rupture of popliteal cyst and myositis (18, 19). Acneiform skin lesions (papules and pustules) seem to be more frequent in patients with BD with joint involvement and some authors have suggested that the arthritis seen in BD may possibly be related to acne associated arthritis (23). BD is rarely associated with rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, relapsing polychondritis and amyloidosis, while the most frequently described association is with seronegative spondyloarthropathies. The inclusion of BD in the spondyloarthropathy (SpA) complex is still debatable. Several patients with coexisting AS and BD have been described in the literature (24-28) and some authors have found a high prevalence of AS or SI in patients with BD (29-31). Different ethnicity of BD patients, etherogeneity in the criteria selected for BD classification as well as observer variation in interpreting the radiographic result of anteroposterior view of the pelvis or the lack of appropriate control groups are all possible reasons for these discrepancies.

Several studies have dimostrated that high frequency US is accurate for detecting joint effusion and synovitis, even compared with magnetic resonance imaging (MRI) and direct arthroscopy visualisation (32-37) and over the last few years US has become an established imaging technique for the diagnosis and follow-up of patients with rheumatic diseases (9-12, 38). This conclusion has been based mainly on the visualisation of inflammatory and/or destructive joint changes that were not detected by clinical and radiographic examination (39).

US is most commonly used in the assesment of soft tissue diseases (particularly hypertrophy of the synovial membrane, tenosynovitis, bursitis) or detection of fluid collection and can also be used to visualise other structures, such as cartilage and bone surfaces (particularly presence of erosions).

PD US is a new technique of colour Doppler that improves the sensitivity to detect flow from small vessels and low velocitiy flow in microvascular level. PD US detects indirect signs of increased vascularisation associated with soft tissue inflammatory and infectious diseases and enthesitis in spondyloarthropathies. PD signal correlates highly with local clinical evaluation of joint inflammatory activity in the knee, metacarpophalangeal and interphalangeal joints in rheumatoid arthritis patients (40-43).

Effusion and synovial proliferation are considered the US characteristics of synovitis. In fact, synovial inflammation is characterized by hyperthrophic changes with angiogenesis, synovial cell hyperplasia and joint effusion (14).

As far as we know, this is the first study focused on the assessment of peripheral knee arthritis in BD with US, demonstrating a high prevalence of signs of synovitis. Most of our patients had a low US score confirming that in BD joint involvement is mild and parallels

general disease activity.

However, an erosive form was detected in 10% of the patients suggesting that also bone surface can be affected in BD. Interestingly, some patients asymptomatic for joint involvement showed US alterations. This finding confirms the high sensitivity of US in the detection of joint alterations in rheumatic diseases (8-11, 44). Acneiform skin lesions (papules and pustules) seem to be more frequent in patients with joint involvement as detected by US and this confirms some previous clinical observations about the increased prevalence of joint involvement in patients with follicolitis (22, 39, 40).

Even though this study was limited to the evaluation of a single joint, it confirms that articular involvement represents an important clinical feature in Italian patients with BD. US evaluation allows the study of this aspect, identifying the presence of synovitis signs also in patients with a negative clinical picture.

References

1. GÜL A: Behçet's disease: An update on the pathogenesis. *Clin Exp Rheumatology* 2001: 19 (Suppl. 24): S6-S12.
2. ESCUDIER M, BAGAN J, SCULLY C: Number VII Behçet's disease (Adamantiades syndrome) *Oral Diseases* 2006; 12: 78-84.
3. ZOUBOULIS CC, VAIOPOULOS G, MARCOMICHELAKIS N *et al*.: Onset signs, clinical course, prognosis, treatment and outcome of adult patients with Adamantiades- Behçet's disease in Greece. *Clin Exp Rheumatol* 2003; 21 (Suppl. 30): S19-S26.
4. YAZICI H, BASARAN G, HAMURYUDAN V *et al*.: The ten-year mortality in Behçet's syndrome. *Br J Rheumatol* 1996; 35: 139-41.
5. SERDAROGLU P: Behçet's disease and the nervous system. *J Neurol* 1998; 17: 145-47.
6. DUZGUN N, ATES A: Erosive arthritis in a patient with Behçet's disease. *Rheumatol Int* 2003; 23: 265-7.
7. AYDIN G, KELES I, ATALAR E, ORKUN S: Extensive erosive arthropathy in a patient with Behçet's disease: case report. *Clin Rheumatol* 2005; 24: 645-7.
8. GIBBON WW, WAKEFIELD RJ: Ultrasound in inflammatory disease. *Radiol Clin North Am* 1999; 37: 633-51.
9. GRASSI W, CERVINI C: Ultrasonography in rheumatology: an evolving technique. *Ann Rheum Dis* 1998; 57: 268-71.
10. WAKEFIELD RJ, GIBBON WW, EMERY P: The current status of ultrasonography in rheumatology. *Rheumatology (Oxford)* 1999; 57: 268-71.
11. MANGER B, KALDEN JR: Joint and connective tissue ultrasonography: a rheumatologic bedside procedure? A German experience. *Arthritis Rheum* 1995; 38: 736-42.
12. MANGER B, BACKHAUS M: Ultrasound diagnosis of rheumatic/inflammatory joint diseases. *Z Arztl Fortbild Qualitatssich* 1997; 91: 341-45.
13. BACKHAUS M, BURMESTER GR, GERBER T *et al*.: Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001; 60: 641-9.
14. WAKEFIELD R, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal Ultrasound Including Definitions for Ultrasonographic Pathology. *J Rheumatol* 2005; 32: 2485-7.
15. WALTHER M, HARMS H, KRENN V, RADKE S, FAEHNDRICH TP, GOHLKE F: Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 331-8.
16. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's Disease. *Lancet* 1999; 335: 1078-80.
17. DELUNARDO F, CONTI F, MARGUTTI P *et al*.: Identification and characterization of the carboxy-terminal region of Sip-1, a novel autoantigen in Behçet's disease. *Arthritis Research & Therapy* 2006; 8: 1-8.
18. BENAMOUR S, ZEROUAL B, ALAOUI FZ: Joint manifestations in Behçet's Disease. A review of 340 cases. *Rev Rhum* 1998. 65: 299-307.
19. BOUCHOU K, CATHEBRAS P, ROUSSET H: La maladie de Behçet. *JFORL* 1992; 41: 348-52.
20. BENAMOUR S: Manifestations rhumatismales de la Maladie de Behçet. *Ann Med Int* 1999; 562-70.
21. BENAMOUR S, TAK-TAK MT, RAFIK M, AMRAOUI A: *In* HAMZA M (Eds.): *Behçet's Disease*. *Proceeding of the Seventh International Conference on Behçet's Disease*. *Juvenile: Behçet's disease in Morocco in Tunis*. Pub Adhoua 1997: 134-8.
22. HAMZA M, AYED K, ZRIBI A: Maladie de Behçet. *In* Kahn MF, Peltier AP, Meyer O, Piette JC: *Maladies systémiques*. Paris Flammarion 1991: 917-47.
23. DIRI E, MAT C, HAMURYUDAN V, YURDAKUL S, HIZLI N, YAZICI H: Papulopustular skin lesions are seen more frequently in patients with Behçet's syndrome who have arthritis: a controlled and masked study. *Ann Rheum Dis* 2001; 60: 1074-6.
24. CHANG HK, CHO EH, KIM JU, HERR H: A case of coexisting Behçet's disease and ankylosing spondylitis. *Korean J Intern Med* 2000; 15: 93-5.
25. TOSUN M, USLU T, IBRAHIM IMAMOGLU H, BAHADIR S, ERDOLU S, GULER M: Coexisting ankylosing spondylitis and Behçet's disease. *Clin Rheumatol* 1996; 15: 619-20.
26. OLIVIERI I, GEMIGNANI G, BUSONI F *et al*.: Ankylosing spondylitis with predominant involvement of the cervical spine in a woman with Behçet's syndrome. *Ann Rheum Dis* 1988; 47: 780-3.
27. BEIRAN I, SCHARF J, DORI D, MILLER B: A change in ocular involvement in a patient suffering from ankylosing spondylitis and Behçet's disease. *Eur J Ophthalmol* 1995; 5: 192-4.
28. BORMAN P, BODUR H, AK G, BOSTAN EE, BAR N: The coexistence of Behçet's disease and ankylosing spondylitis. *Rheumatol Int* 2000; 19: 195-8.
29. DILSEN N, KONICE M, ARAL O: Why Behçet's disease should be accepted as a seronegative arthritis. *In* LEHNER T, BARNS CG (Eds.): *Recent Advances in Behçet's Disease*. *London:* Royal Society of Medicine Services, 1986: 281-4.
30. CAPORN N, HIGGS ER, DIEPPE PA, WATT I: Arthritis in Behçet's syndrome. *Br J Radiol* 1983; 56: 87-91.
31. OLIVIERI I, GEMIGNANI G, PECORI F, SEMERIA R, PASERO G: Coexisting ankylosing spondylitis and Behçet's syndrome: a report of six cases. *In* O'DUFFY JD, KOKMEN E (Eds.): *Behçet's Disease: Basic and Clinical Aspects*. New York: Marcel Dekker, 1991: 247-5.
32. OSTERGAARD M, COURT-PAYEN M, GIDEON P *et al*.: Ultrasonography in arthritis of the knee. A comparison with MR imaging. *Acta Radiol* 1995; 36: 19-26.
33. ALASAARELA E, TERVONEN O, TAKALO R, LAHDE S, SURAMO I: Ultrasound evaluation of the acromioclavicular joint. *J Rheumatol* 1997; 24: 1959-63.
34. JACOBSON JA, ANDERSEN R, JAOVISIDHA S *et al*.: Detection of ankle effusion: comparison study in cadavers using radiography, sonography and MR imaging. *AJR Am J Roentgenol* 1998; 170: 1231-8.
35. BACKHAUS M, KAMRADT T, SANDROCK D *et al*.: Arthritis of the finger joints. A comprehensive approach comparing conventional radiography, scintigraphy, ultrasound and contrast-enhanced magnetic resonance imaging. *Arthritis Rheum* 1999; 42: 1232-45.
36. RUBALTELLI L, FIOCCO U, COZZI L *et al*.: Prospective sonographic and arthroscopic evaluation of proliferative knee synovitis. *J Ultrasound Med* 1994; 13: 855-62.
37. KARIM Z, WAKEFIELD RJ, QUINN M *et al*.: Validation and reproducibility of ultrasonography in the detection of synovitis in the knee. *Arthritis Rheum* 2004; 50: 387-94.
38. GIBBON WW, WAKEFIELD RJ: Ultrasound in inflammatory disease. *Radiol Clin North Am* 1999; 37: 633-51.
39. OSTERGAARD M, SZKUDLAREK M: Ultrasonography: A Valid Method for Assessing Rheumatoid Arthritis? *Arthritis Rheum* 2005; 52: 681-686.
40. MARTINOLI C, PRETOLESI F, CRESPI G *et al*.: Power Doppler sonography: clinical applications. *Eur J Radiol* 1998; 28: 133-40.
41. NEWMAN JS, ADLER RS, BUDE RO, RUBIN JM: Detection of soft-tissue hyperemia: value of power Doppler sonography. *AJR Am J Roentgenol* 1994; 163: 385-9.
42. NEWMAN JS, LAING TJ, MCCARTHY CJ, ADLER RS: Power Doppler sonography of synovitis: assessment of therapeutic response. Preliminary observations. *Radiology* 1996; 198: 582-4.
43. HAU M, SCHULTZ H, TONY HP *et al*.: Evaluation of pannus and vascularization of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis by high-resolution ultrasound (multidimensional linear array). *Arthritis Rheum* 1999; 42: 2303-8.
44. WAKEFIELD RJ, GREEN MJ, MARZO-ORTEGA H *et al*.: Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann Rheum Dis* 2004; 63: 382-85.