Vascular Changes in Psoriatic Knee Joint Synovitis

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ABSTRACT. ***Objective.*** To evaluate the diagnostic utility of standard arthroscopy supported by a computerized image analysis system; and to examine and quantify the macroscopic appearance of blood vessels in selected anatomical areas, comparing 2 groups of patients with PsA and RA with refractory knee joint synovitis (KJS) for vascular marking (VM) features and VM scores, as well as for the relationship between respective VM scores and local and systemic KJS disease activity indices.

Methods. Standard arthroscopy was carried out on 39 knees (20 PsA, 19 RA). Videorecordings of the examination were reanalyzed using a computer image analysis system and software. The appearance of vascular markings was assessed and separately scored for the areas of surface synovium (capsular, CVM), villous proliferation (villous, VVM), and synovium adherent to cartilage (pannus, PVM). Indices of systemic (erythrocyte sedimentation rate, ESR) and local KJS disease activity (clinical index) were obtained before arthroscopy. The morphology and scores of the distinct VM were compared between PsA and RA groups, as was the relationship between respective VM scores and ESR and KJS clinical indices.

Results. Distinctive VM features were observed for PsA and RA KJS in each separate synovial architecture examined. VVM and CVM scores were significantly correlated with each other in PsA knees, and were significantly higher in PsA compared with RA. In both diseases, VVM and CVM scores were not related to KJS duration or activity or to ESR values, but in RA they were directly correlated with KJS activity. Moreover, the VVM capillary feature "meandering with tight convolutions," considered unique to psoriatic skin, was observed in the synovium of 13 PsA (65%) and one RA KJS (5.5%). The mean KJS duration of the PsA group with typical VVM was significantly lower than the group without VVM (2.6 ± 1.77 vs 9.4 ± 8.28 yrs).

Conclusion. Our macroscopic observations of distinct changes in VM expression in selected anatomical areas of PsA and RA KJS suggest possible pathogenetic differences between the 2 diseases. The typical morphology and higher intensity of villous vascularization, in both early and chronic disease, and the different clinical relevance of VVM scores in PsA compared with RA KJS support the potential use of vascular markings as reliable outcome measures of the PsA process in KJS. (J Rheumatol 2001;28:2480–6)

Key Indexing Terms:
KNEE ARTHROSCOPY
PSORIATIC ARTHRITIS
VASCULARITY
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Synovial inflammation in large joints such as the knee is very common in both psoriatic (PsA) and rheumatoid arthritis (RA), but it is difficult to distinguish clinically[1,2]. The heterogeneity of PsA, with at least 5 clinical subsets, may complicate diagnosis[3-5]. The spectrum of knee joint synovitis (KJS) varies from mono/oligoarticular rheumatoid factor (RF) negative type without psoriasis to RF positive type with both psoriasis and polyarticular involvement[6,7].

Vascular abnormalities, first noted by Lawrence[8] and Espinoza, *et al*[9], have been described as the most significant histopathological changes in the synovial membrane of patients with PsA, involving large joints in particular[9]. Various types of changes in synovial microvascular architecture in PsA and RA KJS have been confirmed[10-12].

Characterization of the local macroscopic picture of synovial inflammatory changes *in vivo* seems to be a prerequisite for accurate interpretation of its microscopic counterpart[13]. Arthroscopy, allowing direct visualization of the synovium, is now an important diagnostic tool in rheumatology; it is also useful as an outcome measure for disorders characterized by chronic synovitis[13-15].

Increased vascularity, seen as an apparent increase in the number of discrete vessels, is one of the basic macroscopic variables used to define the intensity of synovitis[13,14]. The prevailing morphologic patterns of synovial vascularity —

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vascular markings (VM) such as "straight vessels" or "bushy capillaries" — were recognized from the beginning[16], along with capsular and synovial vascular network changes, with increasing "capillary widening" scored in meniscal lesions, osteoarthritis, and RA[17].

The introduction of diagnostic arthroscopy in the study of early inflammatory arthritis[18] provided important new insights for the macroscopic scoring of synovitis[19]. Indeed, in comparisons of knee joint synovitis in early onset spondyloarthropathy and RA for grading macroscopic features[19], increased vascularity was observed in 100% of cases of both PsA/reactive arthritis (ReA) and RA knee synovitis — almost 2 to 3 times the frequency of "villous hypertrophy" and "granularity," respectively. Moreover, a distinct vascular pattern (tortuous or straight branching vessels) was found to distinguish PsA/ReA and RA, respectively, in the majority of patients[19]. These findings in a very early stage of the disease point to possible pathogenetic differences between spondyloarthropathy and RA KJS. Nevertheless, no study has addressed the issue of the persistence of early hypervascularity changes and, in particular, of vascular marking patterns in chronic disease.

We evaluated the diagnostic utility of standard arthroscopy equipped with an image analysis system to examine the macroscopic appearance of blood vessels in selected anatomical areas. We compared 2 groups of patients with refractory KJS of PsA and RA for vascular marking features and distinct VM scores, as well as for the relationship between respective VM scores and local and systemic KJS disease activity indices.

MATERIALS AND METHODS

Patients. We enrolled 20 patients with PsA (by Wright and Moll criteria[3]) — total 20 knees, 18 poly, 2 oligoarticular; and 18 patients with RA (by 1987 American College of Rheumatology criteria[20]) — 19 knees, 18 poly, one oligoarticular. Patients attended the rheumatology clinic at Padova General Hospital, with persistent active synovitis of the knee (characterized by pain, tenderness, and effusion) that was resistant to intraarticular corticosteroid injections (at least 6 weeks before entry into the study) and at least 6 months' second-line drug treatment (methotrexate, sulfasalazine, cyclosporine A) and < 10 mg prednisolone daily. All patients gave written informed consent to participate.

Mean disease duration was 6.5 years and mean knee synovitis duration 5 years in PsA, and 11 and 7.1 years, respectively, in RA (Table 1).

Clinical assessment. Assessment of knee disease activity was carried out within 5 days of arthroscopy as described[21]. The sum of the scores of tenderness (0–3), joint swelling (0–3), ballottement of the patella or "bulge sign" (0–2), and range of knee joint flexion (0–3) and extension (0–3) was taken as the clinical index of joint inflammation on a scale of 0–14. The erythrocyte sedimentation rate (ESR, Westergren) was measured during a 2 week period before the arthroscopic examination.

Arthroscopy. Operations were performed under spinal anesthesia with constant joint irrigation with saline, no tourniquet, and within an average operating time of 45 min. Two to 3 portals were routinely used, with anteromedial and anterolateral points of access.

A Dyonics videoarthroscope (4 mm, 115°, 35 mm focal length) and a curved 4 mm full-radius synovial resector were used. Synovial biopsy specimens to represent the different intensities of KJS were taken under direct vision using biopsy forceps.

Table 1. Comparison of clinical and arthroscopic indices between PsA and refractory RA knee joint synovitis (Mann-Whitney U test).

Clinical Characteristics and Arthroscopic Indices	PsA, n = 20	RA, n = 19
Male/female	12/8	4/15
Age, yrs	46.5 ± 2.45	47.6 ± 2.81
Synovitis duration yrs	5.0 ± 1.3	7.1 ± 1.7
ESR	29.6 ± 6.4*	41.2 ± 5.3*
KJS Clinical Index	5.9 ± 0.5	5.7 ± 0.5
Villous VM	4.5 ± 0.3**	1.3 ± 0.3**
Capsular VM	2.1 ± 0.2***	1.2 ± 0.3***
Pannus VM	2.1 ± 0.3	1.5 ± 0.3

ESR: erythrocyte sedimentation rate, VM: vascular marking. * $p < 0.05$; ** $p < 0.001$; *** $p < 0.02$.

An overall visual survey was made of the synovium on the suprapatellar and femoral gutter walls, perimeniscal and intercondylar notch areas, and over the infrapatellar fat pad[21]. The survey was recorded on Super VHS videotape and reanalyzed by the same blind observer, using a computer image analysis system and dedicated software (Spice System, Smith & Nephew, Milan, Italy), allowing direct single-image analysis, magnification, and storage of recorded images.

Normal synovium appears as a glossy transparent layer folding in many reduplications, through which a fine plexus of blood vessels with loose capillary loops can be seen. It may also take the form of slender, translucent villi with a glomerular-like vascular arrangement[16].

The appearance of vascular markings in PsA and RA KJS was assessed and separately scored for the selected anatomical areas[17], reflecting differences in their vascular microarchitecture[22], as follows. Capsular vascular marking (CVM): On smooth surfaced synovium, increased vascularity seen as dilatation, winding, and crowding of discrete vessels was graded 0–3, and the maximum value was noted as the CVM score. Villous vascular marking (VVM): On single synovial villi, increased width of individual capillaries ("widening") and capillary loops wound around themselves ("meandering") were each graded 0–3 (enlarged capillary limbs or convoluted loops lacking or extending to < 1/3, 1/2, or > 1/2 of the villous shape area, respectively) and the sum of their maximum values (0–6) taken as the VVM score. Pannus vascular marking (PVM): On synovium adherent to hyaline and fibrous joint surfaces, density of vessel dilatation or branching of undulating loops was graded 0–3, and the maximum value taken as the PVM score.

Statistics. Statistical analysis was performed with SPSS software. Means (95% confidence intervals) were recorded for data presentation. Clinical and arthroscopic findings were tested for correlations using Spearman's nonparametric test. P values for differences between groups were calculated using the Mann-Whitney test for unpaired samples.

RESULTS

Clinical aspects. PsA and RA mean disease duration, KJS duration, clinical index of KJS inflammatory activity, and ESR values at the time of arthroscopy are listed in Table 1.

The only significant difference between the clinical characteristics of the PsA and RA groups was the higher ESR level in the latter (Table 1).

Mean disease duration was correlated with mean KJS duration in both PsA and RA KJS.

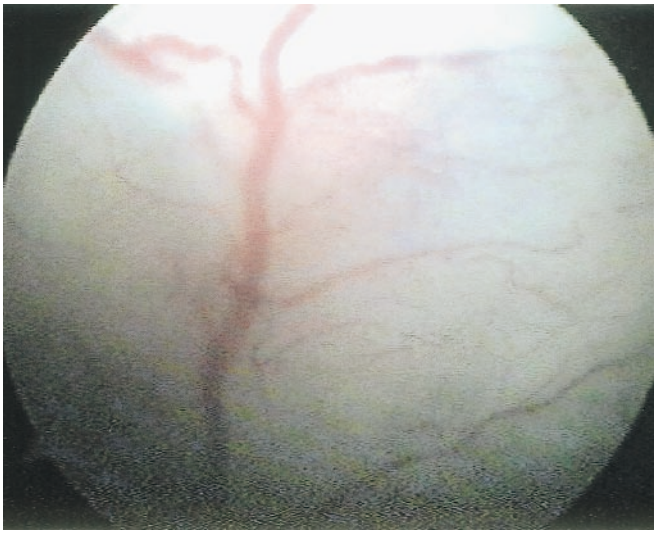
Macroscopic features of KJS. The extent and intensity of synovial hyperemia and granularity was similar in both

groups. Nevertheless, some disease related features were noted. In RA KJS, the greatest inflammatory activity was confined to the area surrounding the cartilage, with a diffusely hyperemic and opaque appearance. In PsA, in comparison to RA KJS, villous proliferation, granulation, fibrous scarring, and pannus propagation appeared to be more inhomogeneously distributed over various parts of the joint, and were also of variable size in each recess and more evident on synovial reduplications and plicae separating suprapatellar and parapatellar recesses, on synovial-cartilage junctions of troclear and intercondylar notch regions, and on alar folds and the ligamentum mucosum surface. Hypertrophic villous formation was also found in 10/10 PsA and 7/7 RA knees with KJS of ≥ 2 years' duration.

In both PsA and RA patients, pannus proliferation was equally distributed between knees with less than and more than 2 years' duration of synovitis.

Vascular marking assessment — morphological features. The prevailing synovial vascular pattern in RA knee joints was shown by straight branching synovial capsular and pannus vessels (Figures 1A, 1C). In general, the majority of villi were opaque, with few visible vessels, showing moderate capillary widening, rare loops, and wide convolutions (Figure 1B).

The typical morphological feature of synovial vessels in PsA was the combination of vessel dilatation and increased tortuosity of capillary loops throughout the separate anatomical areas examined (Figures 2A, B, C). On smooth capsular surfaces, thick vessel crowding and marked enlargement of individual vessels (Figure 2A) usually appeared on the



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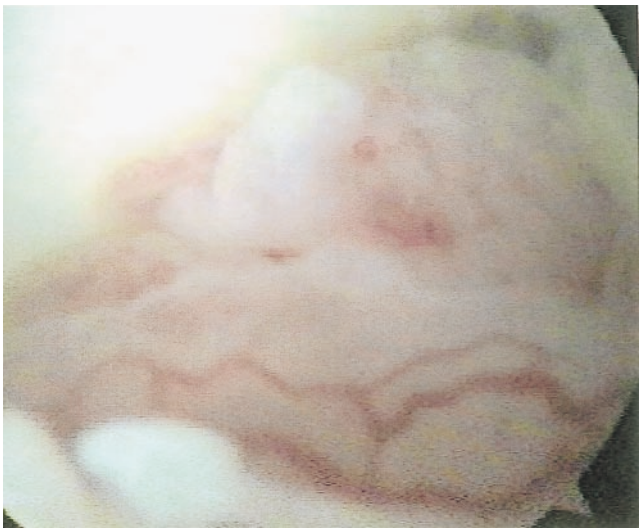

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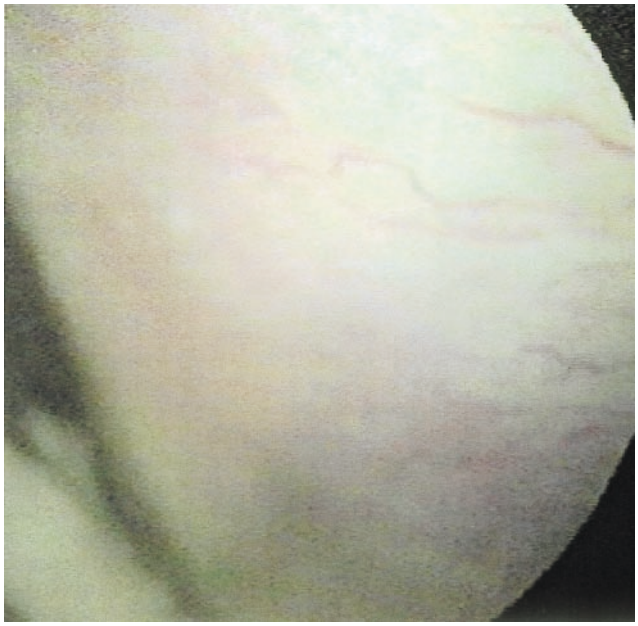

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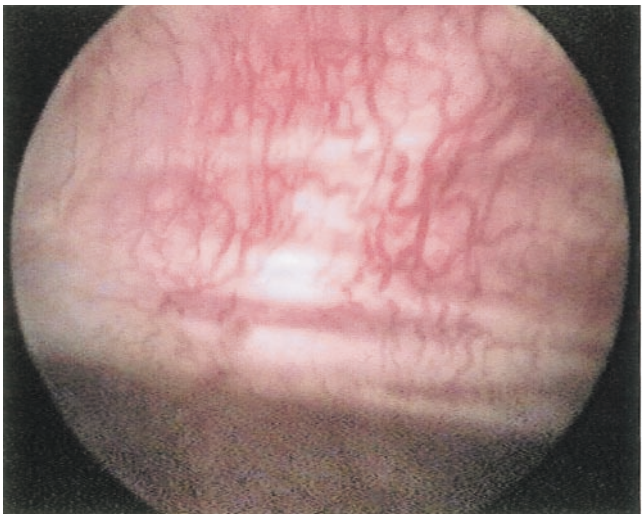
Figure 1. RA knee synovitis: examples of capsular (A), villous (B), and pannus (C) vascular markings from different patients. Note straight branching of synovial vessels (A, C). Opaque polyp-like villi with few visible vessels showing rare loops and wide convolutions (C).



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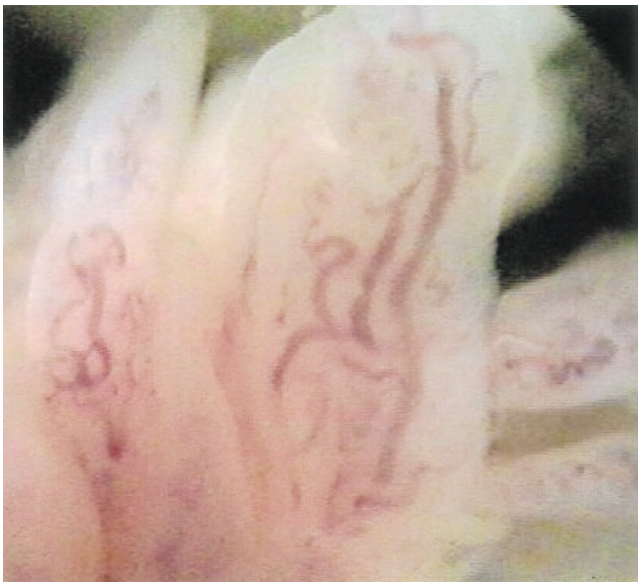

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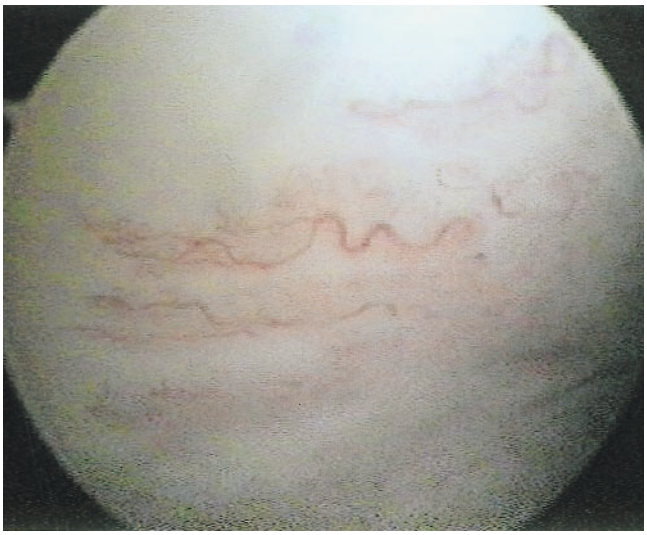

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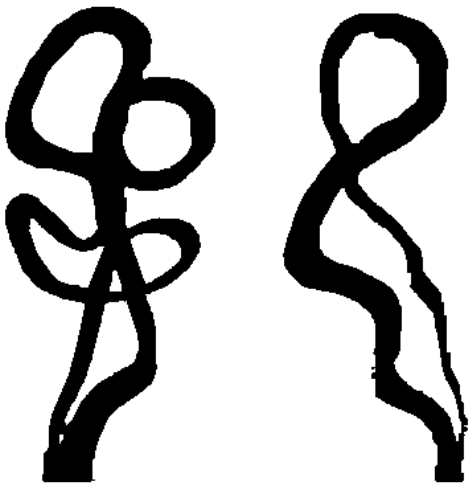
Figure 2. PsA knee synovitis: examples of capsular (A), villous (B), and pannus (C) vascular markings from different patients. Combination of vessel dilatation, crowding, and increased tortuosity (A); capillary widening and meandering with tight convolution (B); undulating vessel loops supported by slender stroma projected onto normal hyaline surface (C).



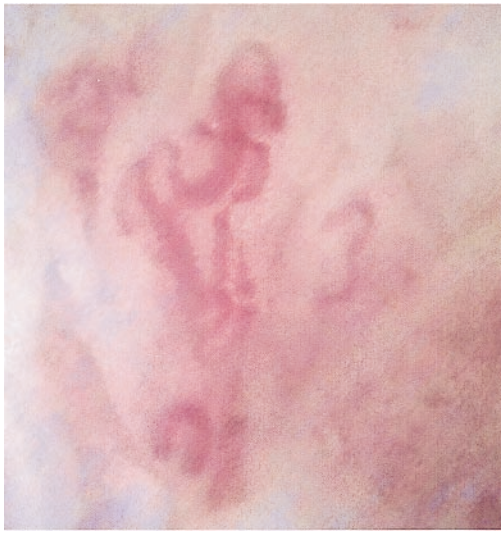


Figure 3. PsA knee synovitis: the typical skin capillary feature of "meandering with tight convolutions" and short-radius undulation of vessels wound around themselves, not involving the whole loop, reproduced with permission from Moll and Wright[3] (left); gross villous vascular changes in psoriatic synovium (right).

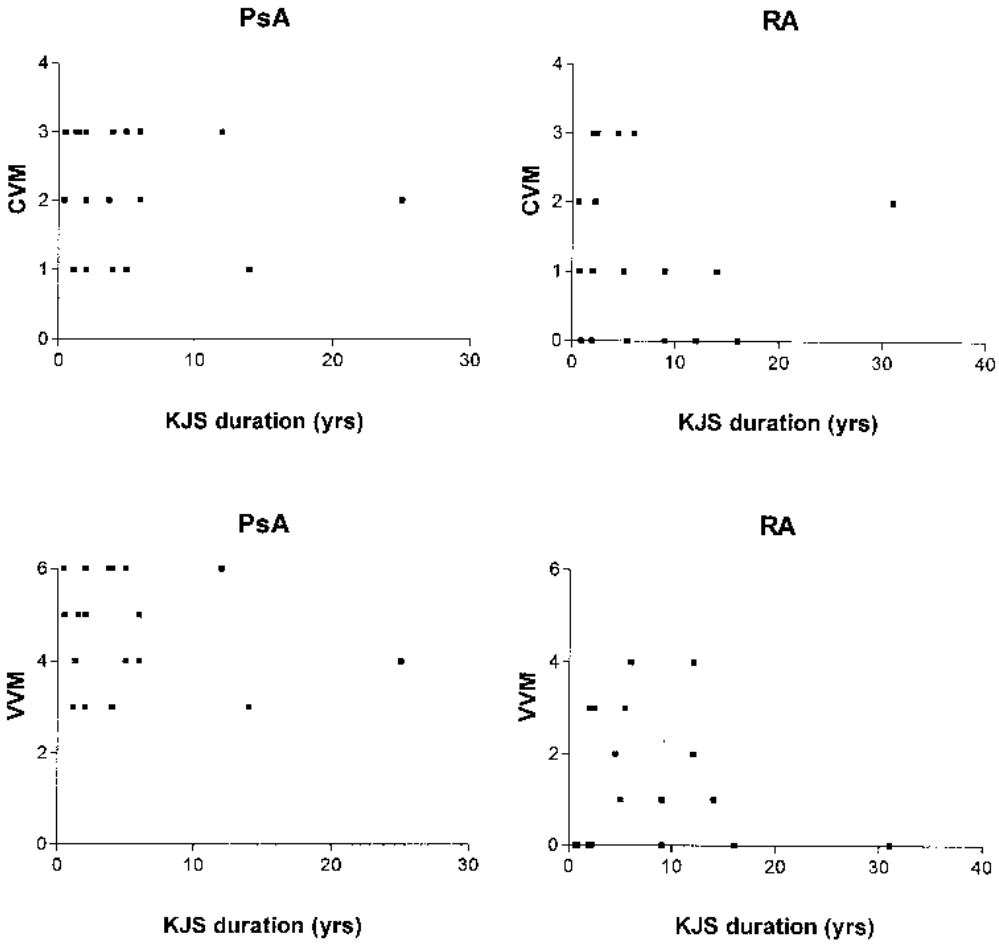


Figure 4. Villous (VVM) and capsular vascular marking (CVM) indices in relation to duration of knee joint synovitis (KJS) in PsA and RA. Correlations between CVM and VVM scores and KJS duration in PsA knees (n = 20; p = NS) and RA knees (n = 19; p = NS) calculated by Spearman rank test.

surface of synovial reduplications, separating the suprapatellar and parapatellar recesses. Enlarged vessels of the capsular vascular network were again found to supply the clearly visible vascular plexus of translucent polyp-like villi (Figure 2B).

One particular feature of the villous vascular markings — observed in 13/20 PsA patients (65%) and 1/19 RA patients (5.5%) — was short-radius undulation of vessels wound around themselves, not usually involving the whole loop — "meandering with tight convolutions." This typical figure (Figure 3) was found to be associated with different degrees of widening, which increased the outlines of the vessel loops.

In PsA KJS, the vascular network of synovium adhering to cartilage (PVM) showed undulating vessel loops supported by slender stroma projected onto normal hyaline surfaces (Figure 2C).

Comparison between KJS groups (Mann-Whitney test). The means of capsular, villous, and pannus vascular marking scores for all synovitis samples assessed by macroscopic examination are listed in Table 1. Compared with RA, PsA KJS had significantly higher scores for all vascular marking indices, other than PVM scores (Table 1). The 13 PsA knees positive for the typical "meandering with tight convolutions" villous feature had a mean KJS duration (2.6 ± 1.77 yrs) that was significantly shorter ($p < 0.017$) than that of the 7 knees negative for the feature (9.4 ± 8.28 yrs).

Correlations between clinical and arthroscopic variables (Spearman rank test). In PsA KJS, VVM and CVM scores were significantly directly correlated with each other ($p < 0.01$), and none of them correlated with ESR (data not shown). None of the VM indices correlated with either KJS duration (Figure 4) or clinical index score.

In RA KJS, VVM score was significantly correlated with the clinical index score ($p < 0.0005$), and none of the VM indices correlated with duration of knee joint synovitis (Figure 4).

DISCUSSION

The standard arthroscopy examination showed increased vascular abnormalities in PsA in contrast to RA knee joint synovitis. Our findings are in agreement with observations of distinct vascular patterns of early KJS in PsA, ReA, and RA[18,19]. We also saw a distinct vascular morphology in the chronic phase of PsA and RA KJS.

Respective macroscopic findings in the synovial villi of scarce vascular markings in RA KJS and marked widening and meandering of villous capillaries in PsA KJS clearly fit previous descriptions of *stratum synoviale* microarchitecture, increased capillary depth, and a greater distance between the capillaries in RA[12,23], and prominent enlargement of blood vessels protruding into the synovial lining in PsA[11]. The high vessel density close to the surface in PsA may be important in the pathogenesis of hemarthrosis and inflammatory joint effusions[24].

Interestingly, using the image analysis system we were able to identify at joint level capillary changes closely resembling those reported 30 years ago in nailfold capillaries[8,25] as being unique to psoriatic and PsA patients[3]. Sharing by the PsA synovium of typical capillary changes such as "meandering with tight terminal convolutions" (Figure 3)[3] and their expression also in the chronic phase of the disease support the role of specific microvascular abnormalities in the pathogenesis of psoriasis and its related arthritis. Since our group of PsA knees with typical villous capillary appearance (Figure 3) had a significantly lower duration of KJS, we confirm the diagnostic utility of arthroscopic vascular surveys in the early phase of KJS[18,19].

We found high intraarticular variation in the macroscopic signs of inflammation in PsA KJS, such as hypervascularity, villous proliferations, and fibrosis[21], as well as in the distribution of early and severe joint damage[26,27], which hinder the use of quantitative systems for scoring the severity of overall joint synovial lesions in PsA knees[28]. In spite of the considered characteristic of the chronic KJS phase, hypertrophic villous formation (Figure 2B) was found in 100% of our cases of refractory PsA KJS of less than 2 years' duration of synovitis, and the degree of villous hypertrophy was similar between PsA and RA KJS, in agreement with recent data[29]. Interestingly, scoring of synovial vessels for separate anatomical areas allowed the detection of important quantitative differences of vascular markings between PsA and RA KJS, with higher significance for the villous vascular marking score (Table 1). Increased vascularity and villous proliferation have already been reported as early[13,19] and interrelated macroscopic features of synovitis intensity[30].

Looking at the relationship of distinct VM scores with the clinical characteristics of KJS, we found the more intense villous VM in PsA than in RA was independent of synovitis duration (Figure 4) and ESR values. Indeed, baseline ESR is not predictive for subsequent musculoskeletal surgery[31], and the macroscopic KJS pattern of villous proliferation[32] has been shown to be highly predictive of a poor longterm response to treatment, unlike local KJS inflammation[33].

Thus vessel abnormalities may represent primary changes in PsA KJS, with inflammation as an overlapping feature, supporting the hypothesis of synovial inflammation as a secondary phenomenon in PsA[4]. Otherwise in RA KJS clinical signs of joint inflammation are not antedated by vascular proliferation[34] and emerge after a threshold of macrophage accumulation[35], later becoming interrelated[36].

A number of questions regarding synovitis in PsA are still not resolved[37]. The features of synovial membrane in PsA[38] — prominent vascular changes just beneath the lining cell layer[9,11], proliferation of larger vessels[11], reduced synovial intimal hyperplasia[10,38,39], and divergent synovial membrane cytokine patterns[39] — all support a distinct pathological process compared with RA KJS[40], recalling a secondary synovitis. The intraarticular predilection sites of villous hypertrophy for highly vascularized areas[22,41] and the strong correlation between villous and capsular vascular markings emphasize rapid vascular growth as the driving mechanism of synovial proliferation in PsA.

Our observations of morphologic and quantitative differences in vascular marking expression in selected anatomical areas of knee joint synovitis in PsA and RA, in both early and chronic disease, suggest possible pathogenetic differences between the 2 types of arthritis. The higher intensity and different clinical relevance of vascular marking scores in PsA compared with RA KJS suggest the potential use of vascular markings as reliable outcome measures for PsA KJS.

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