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Synovial histopathology of Behçet's syndrome

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SUMMARY Synovial tissue obtained from 7 patients with Behçet's syndrome and 7 patients with early rheumatoid arthritis could not be distinguished under ordinary light microscopy when examined blind. A wide spectrum of features was seen in both diseases, and it is suggested that these may reflect severity and duration as much as the nature of the arthritis. Electron microscopy also failed to illustrate any distinct features of Behçet's syndrome, but immunofluorescent studies indicated consistent deposition of IgG.

The arthritis of Behçet's syndrome may be the major clinical feature and may precede other manifestations by several years.[1] There have been few reports of the histopathological characteristics of the synovitis. Bisson *et al.*[2] described a wide range of microscopic changes, whereas Vernon Roberts *et al.*[3] noted the replacement of synovial lining cells by granulation tissue with such frequency that they suggested its finding could be of diagnostic value. This observation may have important practical implications because when joint inflammation is a solitary finding the diagnosis may be elusive.

We have compared the synovium from seven patients with Behçet's syndrome with that from an equal number of early rheumatoid patients in an attempt to determine whether the pattern of synvovitis in Behçet's syndrome is sufficiently specific to allow its recognition.

Patients and methods

The patients with Behçet's syndrome had polyarthritis of variable duration. All satisfied the diagnostic criteria of Mason and Barnes,[4] but in 3 patients the investigations were performed when the diagnosis was still obscure. Their principal extra-articular manifestations are outlined in Table 1. The patients with rheumatoid disease underwent synovial biopsy early in the disease and before a diagnosis was established. Only 3 had a positive Rose-Waaler test, but all subsequently developed the features of definite rheumatoid arthritis.[5]

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Table 1 *Distribution of arthritis and extra-articular features of the patients with Behçet's syndrome.*

Patient no.	*Distribution of arthritis*	*Extra-articular manifestations*
1	Knees, ankles, wrists	Orogenital ulcers, uveitis, erythema nodosum, phlebitis, hemiplegia
2	Knees, ankles, elbows, wrists	Orogenital ulcers, uveitis, skin pustules
3	Knees	Orogenital ulcers, skin pustules
4	Knees	Orogenital ulcers
5	Knees, ankles, wrists, elbows	Orogenital ulcers, phlebitis, convulsions
6	Knees	Orogenital ulcers, skin pustules
7	Knees, ankles, elbows	Orogenital ulcers

Samples of synovium were obtained from the suprapatellar compartment of patients' knees with a biopsy forceps combined with arthroscopy in 5 cases and a Holt-Williamson synovial biopsy needle in the remainder. Fragments of synovium for ordinary light microscopy were fixed in formol saline and embedded in paraffin, and sections were stained with haematoxylin and eosin (H and E). Tissue for electron microscopy was fixed immediately in buffered, cold glutaraldehyde, then postfixed in osmium tetroxide and embedded in TAAB resin. Ultrathin sections were examined with a Hitachi HU-12A transmission electron microscope. Specimens for immunofluorescence were collected in isotonic saline, snap frozen, and cut with a cryostat. Sections were stored at −70°C until their examination, when they were washed with phosphate buffered saline, overlaid with the appropriate reagent at room temperature, then washed in Coons saline. Direct immunofluorescence was performed

by using rabbit antihuman IgG, IgA, IgM, and C3 complement, conjugated with fluorescein isothiocyanate (FITC), and indirect immunofluorescence using rabbit antihuman albumin followed by sheep antirabbit IgG labelled with FITC. Control specimens were prepared by preincubation with unlabelled antihuman antibodies before using the FITC conjugates or the omission of the unlabelled antibody when indirect testing was performed. The slides for ordinary and fluorescent light microscopy were examined by observers who were unaware of their identity. Selective features of the H and E stained sections were scored on a 0–3 scale in a manner modified from that described by Vernon Roberts.[6]

Synovial fluid obtained at the time of biopsy was cultured and total white cells estimated on a Coulter

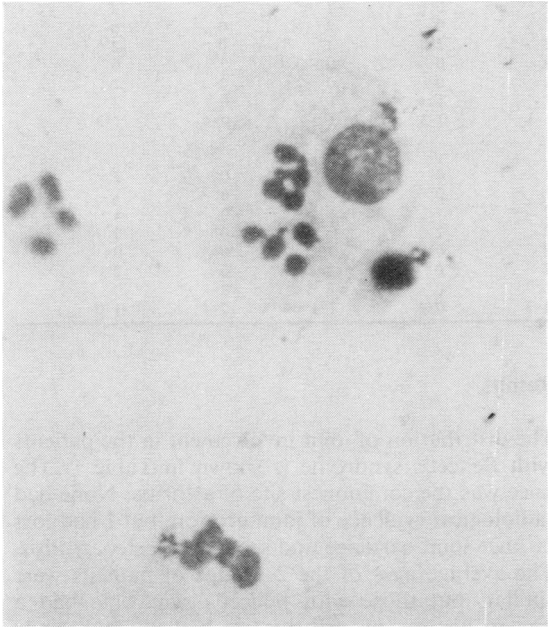

Fig. 1 *Cytosmear of synovial fluid from patient 7 showing a monocyte with intracellular neutrophils (Reiter's cell). May-Grunwald Giemsa. (Original magnification × 1000).*

Table 2 *Details of patients with Behçet's syndrome and rheumatoid arthritis with synovial fluid characteristics at the time of synovial biopsy.*

Patient no.	*Sex*	*Age*	*Duration of arthritis (yr)*	*ESR (mm/h)*	*Synovial fluid*	
					Total WBC ($\times 10^3$/μl)	*Neutrophils ($\times 10^3$/μl)*
Behçet's syndrome						
1	M	53	1	116	19·4	18·6
2	M	40	2	56	9·6	8·4
3	M	45	2	43	32·0	30·0
4	F	54	1	59	2·6	2·0
5	F	27	17	130	6·6	2·9
6	M	50	5	20	12·4	10·3
7	M	25	8	61	6·7	6·0
Mean	2F 5M	42	5	69	12·7	11·2
Rheumatoid arthritis						
8	F	32	2	12	2·5	Not done
9	M	40	0·5	1	Not done	
10	F	51	0·5	26	9·0	7·0
11	F	48	1	24	4·1	3·4
12	F	47	1	32	Not done	
13	F	70	2	110	Not done	
14	M	27	3	17	10·0	9·0
Mean	5F 2M	45	1·5	32	6·4	6·4

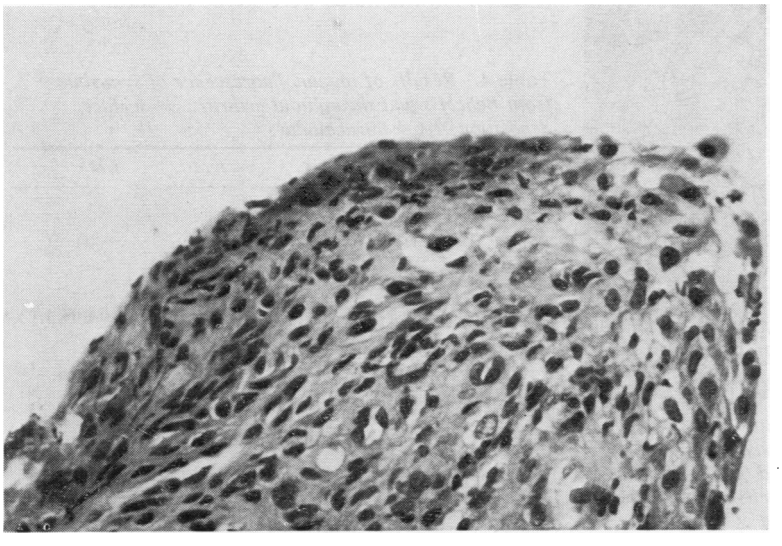

Fig. 2 *Synovium from patient 3 with Behçet's syndrome showing only a remnant of synovial lining cells and dense granulation tissue infiltrated with fibroblasts, polymorphs and chronic inflammatory cells. (Original magnification × 400).*

Table 3 *Light microscopy scores of synovium from patients with Behçet's syndrome and rheumatoid arthritis.*

Patient no.	*Synovial lining cells*			*Subsynovial layer*					
	Hypertrophy	*Hyperplasia*	*Neutrophils*	*Plasma cells*	*Lymphocytes*		*Neutrophils*	*Fibrosis*	*Vascularity*
					Diffuse	*Foci*			
Behçet's syndrome									
1	0	1	0	1	2	0	0	0	1
2	1	2	1	1	1	0	1	0	3
3	Denuded			0	2	0	3	0	0
4	1	2	1	2	2	1	1	0	2
5	0	0	0	0	0	0	0	3	0
6	0	3	1	1	1	0	0	0	1
7	0	1	0	1	1	1	1	0	2
Mean	0·3	1·5	0·5	0·8	1·3	0·3	0·8	0·4	1·3
Rheumatoid arthritis									
8	1	2	1	1	1	0	1	0	1
9	1	1	0	0	1	0	1	0	1
10	1	1	0	2	2	1	1	0	1
11	0	1	0	2	2	2	0	0	2
12	Denuded			1	2	0	3	0	0
13	1	0	0	2	2	0	1	0	2
14	0	1	2	1	1	0	1	3	0
Mean	0·6	1·0	0·5	1·3	1·7	0·4	1·1	0·4	1·0

counter. Differential white cell counts were performed on routine smears prepared with May-Grunwald Giemsa stain. Cytosmears from 4 patients with Behçet's syndrome were stained and examined.

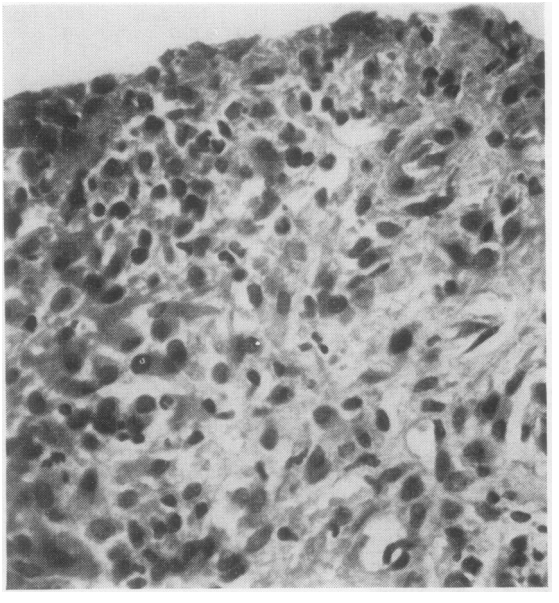

Fig. 3 *Synovium from rheumatoid patient 12 showing residual lining cells in top left hand corner. The immediate subsynovial layer is replaced by granulation tissue containing neutrophils, plasma cells, lymphocytes, and fibroblasts. (Original magnification × 400).*

Results

The distribution of joint involvement in the patients with Behçet's syndrome is shown in Table 1. The knee was the commonest site of arthritis. None had radiological evidence of joint erosion, but I had loss of knee joint cartilage and secondary osteoarthritis. The average ages of the 2 groups of patients were similar, but those with Behçet's syndrome had a longer history of arthritis, a higher erythrocyte sedimentation rate (ESR), and a larger synovial fluid total white cell count (Table 2). Three of 4 samples of Behçet's synovial fluid contained readily observed Reiter's cells in cytosmear preparations (Fig. 1). All the fluids were sterile on culture.

Table 4 *Results of immunofluorescence of synovium from Behçet's and rheumatoid arthritis. s=surface deposition; I/C=intracellular.*

Patient no.	*IgG*	*IgA*	*IgM*	*C'3*
Behçet's syndrome				
1	Not done			
2	+ (s)	+ (s)	± (s)	+ (s)
3	+++ (s)	−	−	−
4	Not done			
5	+ (s)	−	± (I/C)	−
6	+++ (s, I/C)	−	−	++ (s, I/C)
7	± (s)	−	−	−
Rheumatoid arthritis				
8	Not done			
9	−	−	+ (I/C)	−
10	−	−	−	−
11	± (s)	−	± (s)	± (I/C)
12	++ (s)	+ (s)	+ (s)	+ (s)
13	Not done			
14	Not done			

Ordinary light microscopy revealed a wide range of histopathological features in both Behçet's and rheumatoid patients. It was not possible to distinguish the 2 groups, and the histological scores were similar (Table 3). One patient with Behçet's syndrome had replacement of synovial lining cells by granulation tissue, heavily infiltrated with neutrophils and chronic inflammatory cells (patient 3) (Fig. 2). However, a similar appearance was seen in 1 patient with rheumatoid arthritis (patient 12) (Fig. 3). Other specimens were characterised by varying degrees of hypertrophy and hyperplasia of synovial lining cells, hypervascularity, and subsynovial neutrophil, plasma cell, and lymphocyte accumulations. For example, patient 2 had hyperplasia and hypertrophy of lining cells with subsynovial hypervascularity and a moderate subsynovial infiltration of chronic inflammatory cells (Fig. 4). All these features were seen in the rheumatoid patients. One patient with Behçet's syndrome had a normal synovial lining and dense subsynovial fibrosis (patient 5), (Fig. 5).

Electron microscopy reflected the range of changes observed with ordinary light microscopy in greater detail (Fig. 6). There were no features which could be considered distinctive amongst those patients with Behçet's syndrome. None of the samples contained evidence of viral inclusions.

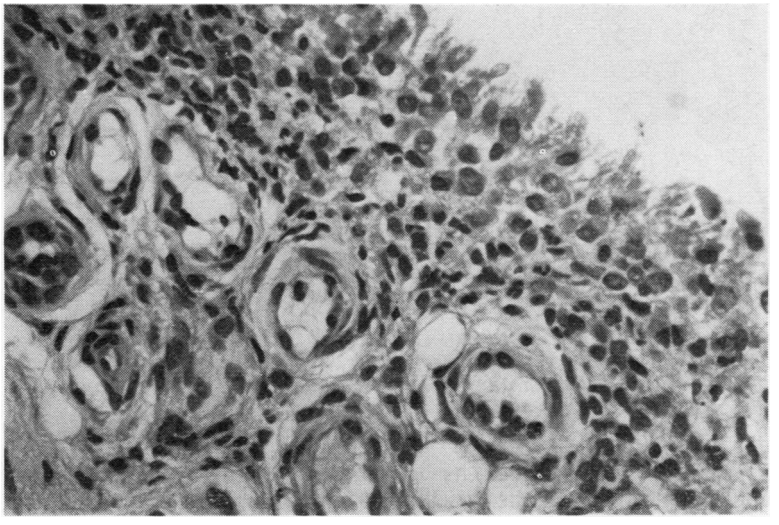

Fig. 4 *Synovium from patient 2 with Behçet's syndrome showing hyperplasia and hypertrophy of synovial lining cells, increased vascularity, and subsynovial infiltration with neutrophils, lymphocytes, and plasma cells. (Haemotoxylin and eosin; original magnification* × *400).*

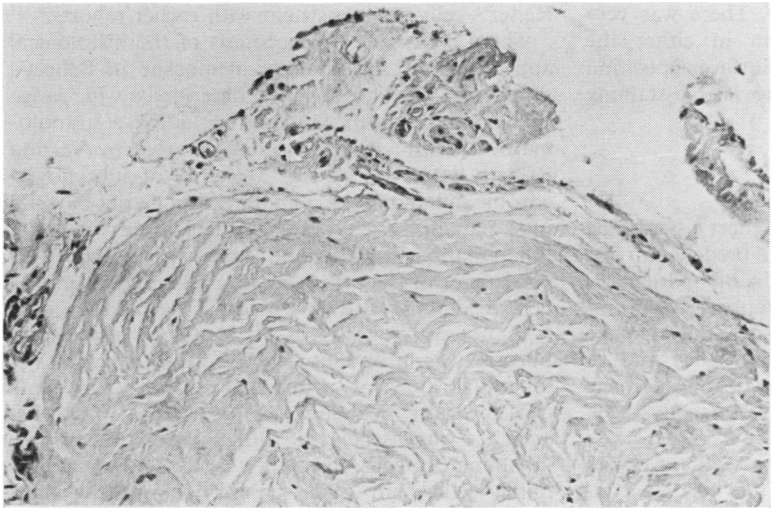

Fig. 5 *Synovium from patient 5 with Behçet's syndrome showing scanty synovial lining cells with dense fibrosis of subsynovium. (Haemotoxylin and eosin; original magnification* × *100).*

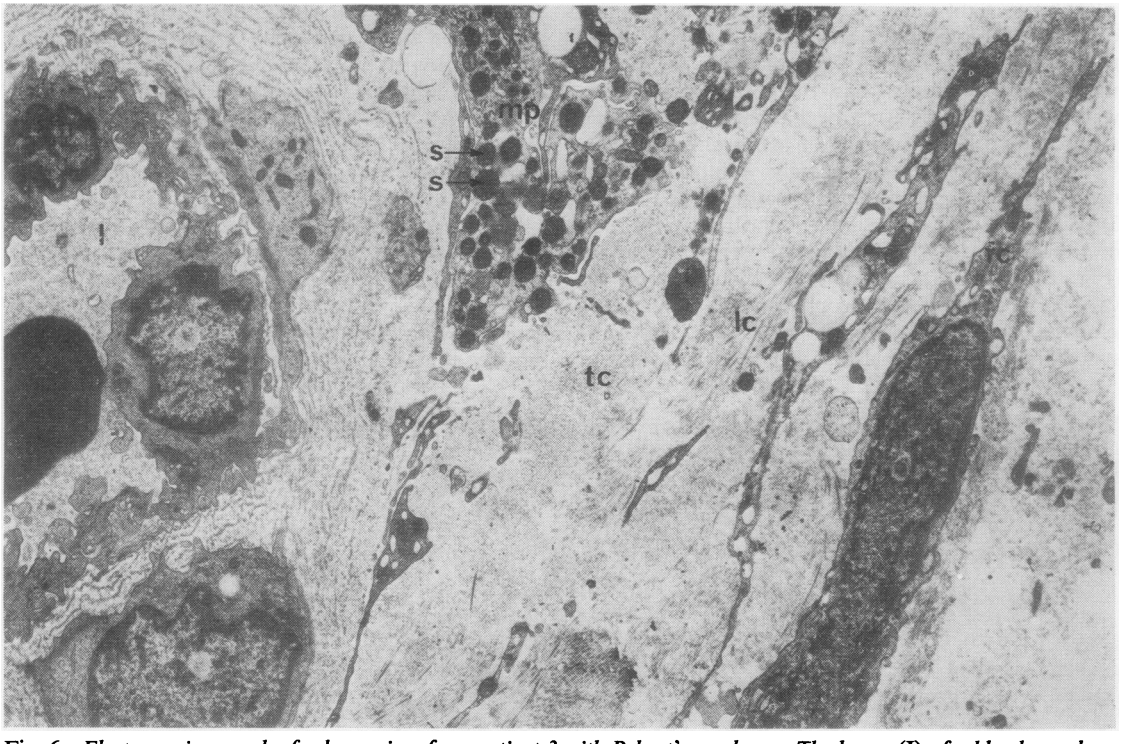

Fig. 6 *Electron micrograph of subsynovium from patient 3 with Behçet's syndrome. The lumen* (I) *of a blood vessel can be seen on the left and a fibrocyte* (*fc*) *on the right. Part of a macrophage* (*mp*) *containing siderosomes* (*s*) *and other lysosomes can also be identified. Collagen fibre bundles cut transversely* (*tc*) *and longitudinally* (*lc*) *occupy much of the intercellular space.* (*Original magnification* × *7500*).

Immunofluorescence revealed deposition of one or more immunoglobulins and complement on the synovial lining surface of the 5 patients with Behçet's syndrome examined. The immunoglobulin was predominantly IgG (Table 4). There was very little intracellular immunoglobulin in either the Behçet's or rheumatoid synovium. Surface deposition was seen on 2 of 4 rheumatoid synovia. No staining was observed in 1 patient.

Discussion

The clinical pattern of arthritis in Behçet's syndrome has been well documented, and a predeliction for the knee joints such as was seen in our patients is characteristic.[7 8] Most previous reports have emphasised that the joint disease does not damage cartilage.[7] Radiological loss of joint space in 1 of our patients suggested that permanent joint damage may ensue. Erosive changes have recently been reported in a few instances.[3]

In the present study examination of the synovial fluid of the patients with Behçet's syndrome confirmed its inflammatory nature. The finding of Reiter's cells in 3 of 4 samples suggests that this may be a frequent phenomenon. The synovial fluid characteristics, including the presence of frequent Reiter's cells, are consistent with earlier reports.[9–11]

There have been few accounts of the histological appearance of the synovial membrane in Behçet's syndrome. The largest series[2] described a wide range of light microscopy findings, including a granulomatous picture similar to that reported by Vernon Roberts *et al.*[3] as well as a picture of subsynovial chronic inflammatory cell infiltration. Serial biopsies of 2 patients suggested that the features of acute inflammation subside and fibrosis increases with persistence of the arthritis.[2] A similar evolution was described in the case reported by Zizic and Stevens.[11] It is noteworthy that in our patients subsynovial fibrosis was pronounced in the subject with the longest history of arthritis. In 1 of 2 patients described by Kennedy *et al.*[12] severe chronic arthritis was associated with subsynovial chronic inflammatory cells and hypertrophy of the synovial lining cells.[13] In other descriptions of the light

microscopic appearance lining cell hypertrophy has been associated with neutrophils in the superficial tissues and lymphocytes and fibrosis in the subsynovium.[9 10] The spectrum of change observed by us was similar to that described by the above authors. The replacement of synovial lining cells by granulation tissue described by Vernon Roberts *et al.*[3] was seen in only 1 of our patients with Beheçt's syndrome. A similar appearance has been described in Reiter's syndrome,[13] and it is notable that we observed an identical lesion in a patient with early rheumatoid disease. As a general rule the synovium of any early arthritis shows a predominence of superficial neutrophils in contrast to the plasma cell and lymphocytic infiltration of chronic joint inflammation.[14] In rheumatoid arthritis and osteoarthrosis the synovial appearance tends to reflect the activity and duration of the arthritis.[15] The influence of these 2 factors may explain why useful diagnostic information is obtained in approximately only 50% of synovial biopsies.[16 17] In Behçet's syndrome this may be especially relevant, since the arthritis may be persistent or episodic and may display fluctuating severity. In our study synovial tissue was obtained when the arthritis was not at its most active except in 2 patients, one of whom showed synovial replacement by granulation tissue. It is possible that differences of disease activity may explain the disparity between our observations and those of Vernon Roberts *et al.*[3] In Reiter's syndrome the synovial histology may be modified in an analogous fashion, since granulation tissue appears to be confined to those with active, early arthritis.[13]

To our knowledge the electron microscopy appearance of the synovium in Behçet's syndrome has been previously described only once.[9] As in our study, the picture was not unique and did not reveal any evidence of cytoplasmic viral particles. A viral aetiology has been evoked by several authors but without substantiation.[18]

It has been claimed that the demonstration of immunoglobulin deposition on or within the synovial membrane enhances the distinction of those patients with rheumatoid arthritis.[19] The finding of IgM and IgG with approximately equivalent frequency has been reported in 69% of well documented rheumatoid arthritis patients but in only 28% of miscellaneous inflammatory joint diseases.[20] In early rheumatoid disease the finding of immunoglobulin and complement in the synovium occurs in 50% of patients,[19] a finding in accord with our small number of observations. The consistent demonstration of IgG deposition in 6 of our Behçet's syndrome patients seemed to suggest that this may be characteristic, but our data are insufficient to allow a confident conclusion.

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