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Cell-mediated immune functions and immunoregulatory cells in Behçet's syndrome

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SUMMARY

Lymphocyte responsiveness to mitogens (phytohaemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM)), T-cell subsets (Tμ and Tγ) and short-lived suppressor cell activity were investigated in the peripheral blood of seven patients with Behçet's syndrome and compared to normal individuals and patients with systemic lupus erythematosus (SLE).

Amongst patients with Behçet's syndrome, responses to mitogens PHA and Con A were normal or slightly reduced; numbers of circulating Tγ cells were unaltered whereas Tμ cells were reduced ($P < 0{\cdot}05$) compared with normal individuals. This was in contrast to SLE where a marked reduction in responses to PHA and Con A was found with reduced Tγ cell but normal Tμ cell numbers. Although the mean suppressor cell activity in the Behçet's group was significantly reduced, all patients had values within the normal range, in contrast with SLE where the reduction was much more marked and most patients had values below the normal range.

In conclusion, the pattern of alteration in Tμ and Tγ cells in Behçet's syndrome is distinct from that in SLE, and the reduction of short-lived suppressor cell activity is only mild in Behçet's syndrome but marked in SLE.

INTRODUCTION

Behçet's syndrome is a chronic inflammatory multisystem condition of unknown aetiology, clinically characterized by recurrent oral and genital ulceration with inflammatory ocular disease, and in some cases associated with arthritis, vasculitis, inflammatory bowel disease and neurological manifestations.

Autoimmunity has been suspected of playing a part in the pathogenesis of the disease on the evidence of circulating antibodies to fetal oral mucosal tissues (Lehner, 1967, 1969), specific cell mediated immunity to mucosal antigens demonstrated by inhibition of leucocyte migration (Sanefuji, 1969) and lymphocyte cytotoxicity for oral epithelial cells (Rogers, Sams & Shorter, 1974). Other authors have, however, described disturbances in local defences, namely in the salivary immunoglobulin secretory system, and abnormalities of coagulation and fibrinolytic systems, that may also be of pathogenetic importance (Abdou *et al.*, 1978).

Recent evidence indicates that immune responses are controlled by suppressor and helper cells (Cantor & Boyse, 1977; Waldman & Broder, 1977) and alterations in such immunoregulatory systems may be involved in the pathogenesis of autoimmune conditions (Bresnihan & Jasin 1977; Hodgson, Wands & Isselbacher, 1978a; Strelkauskas *et al.*, 1978). Assessment of immunoregula-

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tory systems in Behçet's syndrome is therefore relevant, particularly in view of some clinical similarities of this syndrome with two other entities, systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD), where alterations in suppressor cell function and putative immunoregulator cells have been described (Bresnihan & Jasin, 1977; Sagawa & Abdou, 1978; Moretta *et al.*, 1979; Hodgson, Wands & Isselbacher, 1978b).

Two approaches were used in this study: (1) Quantitation of Tμ and Tγ cells in the peripheral blood of patients with Behçet's syndrome. These T-cell subsets are characterized by the presence of an Fc receptor for IgM (Tμ cells) or IgG (Tγ cells) and have been shown to have immunoregulatory properties *in vitro* in relation to immunoglobulin synthesis by pokeweed mitogen (PWM)-stimulated B cells, Tμ cells providing a helper effect and Tγ cells a suppressor effect (Moretta *et al.*, 1977). (2) The analysis of short-lived suppressor-cell activity in peripheral blood mononuclear cells. This assay measures the change in mitogen responsiveness observed in a cell population after 24 hr *in vitro* incubation. With cells from normal individuals there is an increase in responsiveness, which is attributed to the death or inactivation of short-lived suppressor cells. Abnormal results suggesting deficient suppressor-cell activity are found in autoimmune disease (Bresnihan & Jasin, 1977). Results were compared with healthy subjects and with a group of SLE patients studied simultaneously.

MATERIALS AND METHODS

Patients. Seven patients with active Behçet's syndrome presenting to the Rheumatology Clinic were studied. Diagnosis was based on standard clinical criteria (Shimizu *et al.*, 1979) plus exclusion of other systemic disorders. One patient was studied on two occasions before and during treatment with levamisole when a clinical remission had occurred. Clinical and laboratory details are shown in Table 1. Six patients with SLE fulfilling the ARA criteria (Cohen *et al.*, 1971) and one with mixed connective tissue disease were investigated simultaneously. All patients had active disease at the time of the study. The control group consisted of 24 healthy individuals with a mean age of 37 ± 13 SD years (nine females and 15 males).

Peripheral blood mononuclear cells (PBMC). These were isolated by conventional Ficoll–Hypaque centrifugation, washed thrice and resuspended in complete medium (RPMI 1640, 15% fetal calf serum, glutamine and antibiotics).

T cells and T-cell subpopulations. T cells were counted and separated after rosetting with amino-ethyl isuronium bromide-treated sheep red blood cells (RBC) (Kaplan & Clarke, 1974, as in Victorino & Hodgson, 1980a). Tμ and Tγ cells were enumerated after 20 hr incubation of isolated T cells, by rosetting with ox RBC, treated with subagglutinating doses of rabbit IgM anti-ox or IgG anti-ox (Gupta & Good, 1977; Victorino & Hodgson, 1980a).

Lymphocyte transformation studies. PBMC were incubated in triplicate in microtitre plates, using 1×10^5 cells per well, and stimulated with doses of phytohaemagglutinin, PWM or Con A (Sigma Chemical Co., St Louis, Missouri) as described in the text. Cells were cultured for 114 hr before harvesting (conditions as in Victorino & Hodgson, 1980a) with 1 μCi of ^{3}H-thymidine present for the last 18 hr.

Short-lived suppressor cell assay. One hundred microlitres of the PBMC suspension at 1×10^6/ml were placed in the wells of microtitre plates. Some of these cells were stimulated immediately with Con A by adding 20 μl of solution containing 15 μg/ml, 25 μg/ml and 50 μg/ml of Con A dissolved in RPMI, or RPMI alone as a baseline control. Others were stimulated with the same doses after having been preincubated for 24 hr without stimulation. Experiments for each set of conditions were done in triplicate. Both groups of cells were kept in culture conditions as indicated above for 90 hr after challenge with the mitogen and for the last 18 hr 1 μCi of ^{3}H-thymidine was added. Viability in both groups of cells was assessed prior to harvesting by trypan blue exclusion and was greater than 95%. Cells were harvested and counted as specified above.

The suppressor activity was expressed as a suppressor index (SI) given by the formula: SI = (Δ c.p.m. 24 hr/Δ c.p.m. 0 hr) where Δ c.p.m. 24 hr = (c.p.m. of cells stimulated after 24 hr preincubation minus c.p.m. of control unstimulated cells) and Δ c.p.m. 0 hr = (c.p.m. of cells stimulated immediately minus c.p.m. of control unstimulated cells).

Table 1. Characteristics of patients with Behçet's syndrome

Patient	Age	Sex	Duration of disease (years)	Main clinical features	ESR (mm/hr)	C1qBA*	MRFBA†	Treatment at time of study
1	23	F	2	Oral and genital ulcers Erythema nodosum Vasculitis	78	Neg.	Neg.	Tetracycline 250 mg bd.
1	23	F	2	Oral and genital ulcers Erythema nodosum Vasculitis	20	Neg.	Neg.	Levamisole 150 mg twice/wk.
2	29	F	3	Oral and genital ulcers Skin pustules Cutaneous hyperirritability	25	n.d.	n.d.	Colchicine 0·5 g bd.
3	28	M	2½	Oral and scrotal ulcers Skin pustules Arthritis	30	n.d.	n.d.	Nil
4	32	F	2	Oral ulcers Vasculitis, uveitis Pseudocerebral mass	5	n.d.	n.d.	Prednisolone 10 mg/day
5	28	M	2	Oral ulcers Pan uveitis Vasculitis	12	n.d.	n.d.	Nil
6	34	F	3	Oral and genital ulcers Cutaneous vasculitis	28	100	50	Nil
7	42	F	7	Oral and genital ulcers Erythema nodosum Uveitis Cutaneous hyperirritability	23	70	50	Prednisolone 10 mg/day

n.d. = Not determined.

* C1qNA = C1q binding assay ($n = <40$ ng equivalent of heat-aggregated IgG).

† MRFBA = Monoclonal rheumatoid factor binding assay ($n < 40$ ng equivalent of heat-aggregated IgG).

The reproducibility of the assay was studied in a normal individual assessed serially in whom the following indices were obtained: 2·0; 2·0; 2·1; 1·8; 2·0; 2·2 and 2·4.

Other laboratory tests. Immune complexes were detected by a C1q binding assay and a monoclonal rheumatoid factor technique (Pussell *et al.*, 1978).

RESULTS

Total T cells

The proportion of peripheral blood mononuclear cells that were T cells did not differ between the three groups (controls 71·2% ± 1·5 SEM, Behçet's syndrome 68·1% ± 2·0, SLE 69·3% ± 2·3). The absolute number of T cells in peripheral blood was less in SLE due to overall lymphopaenia (controls 2,208 ± 118 SEM per 10^{-9} litre; Behçet's syndrome 2,125 ± 298 per 10^{-9} litre; SLE 1,321 ± 230 per 10^{-9} litre).

Numbers and proportions of Tμ cells are shown in Fig. 1. These were both significantly reduced in Behçet's syndrome whereas in SLE the proportions were unaltered, although the numbers were reduced due to lymphopaenia.

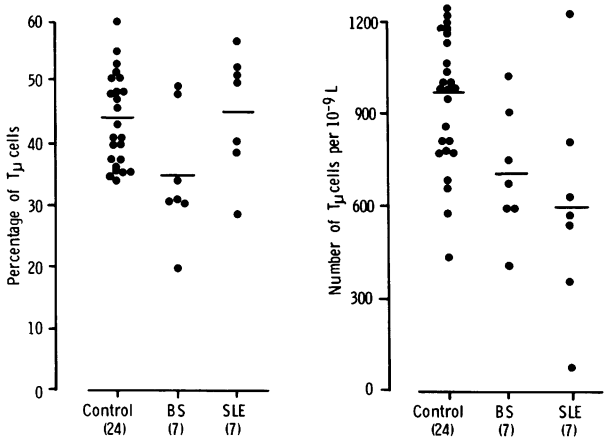

Fig. 1. Percentage of T cells belonging to the Tμ class and absolute numbers of Tμ cells in the peripheral blood in control subjects, Behçet's syndrome (BS) and systemic lupus erythematosus (SLE). Mean marked by bar.

Finally, the numbers of proportions of Tγ cells in Behçet's syndrome did not differ from normals but a marked decrease in proportions and numbers was found in SLE (Fig. 2).

Mitogen responsiveness

As can be seen in Table 2, mitogen responses to PHA and Con A were significantly reduced in SLE. In Behçet's syndrome a slight reduction in responses to Con A and PWM was found but levels of statistical significance were attained for only two of the doses (Con A 250 μg/ml and PWM 40 μg/ml).

Short-lived suppressor-cell activity

The mean of suppressor indices in Behçet's syndrome was lower ($P < 0{\cdot}05$) than that in the control group although all values fell within the normal range (Fig. 3). In contrast, the mean of suppressor indices amongst patients with SLE was markedly decreased when compared to normals ($P < 0{\cdot}001$) and they were also significantly lower than in the Behçet's disease group ($P < 0{\cdot}01$). Results shown refer to the dose of Con A 25 μg/ml. Similar results were obtained with the two other doses.

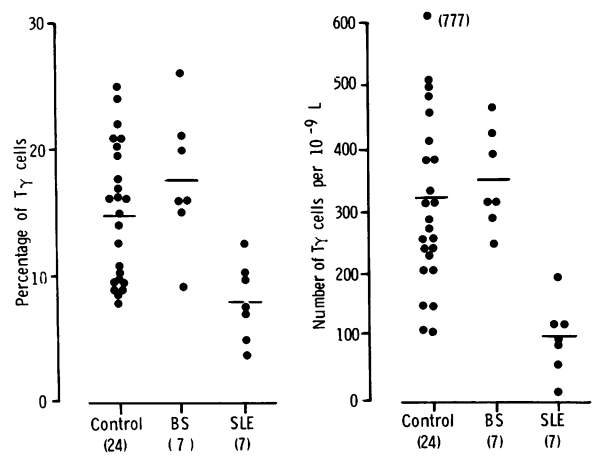

Fig. 2. Percentage of T cells belonging to the Tγ class and absolute numbers of Tγ cells in the peripheral blood in control subjects, Behçet's syndrome (BS) and systemic lupus erythematosus (SLE). Mean marked by bar.

Table 2. Mitogen responsiveness in healthy controls, Behçet's syndrome and SLE

Dose of mitogen (μg/ml)	Mean ^{3}H-thymidine incorporation in c.p.m. ± SEM*		
	Control group	Behçet's disease $n=7$	SLE $n=5$
Con A 250	126,735 ± 14,950 $n=17$	80,416 ± 12,971 $P<0.05$	60,196 ± 8,528 $P<0.001$
Con A 50	49,936 ± 5,162 $n=20$	35,692 ± 5,261 n.s.	14,611 ± 3,125 $P<0.001$
Con A 15	21,638 ± 2,712 $n=17$	17,452 ± 3,344 n.s.	3,814 ± 1,385 $P<0.001$
PHA 100	94,949 ± 8,795 $n=20$	103,010 ± 14,790 n.s.	56,517 ± 4,978 $P<0.001$
PHA 25	55,524 ± 5,944 $n=21$	56,808 ± 10,526 n.s.	19,696 ± 2,303 $P<0.001$
PHA 2·5	33,382 ± 5,802 $n=15$	27,764 ± 5,462 n.s.	6,917 ± 2,560 $P<0.001$
PWM 40	98,782 ± 8,840 $n=18$	82,548 ± 8,149 n.s.	82,813 ± 12,322 n.s.
PWM 4	67,638 ± 9,337 $n=19$	40,710 ± 6,118 $P<0.05$	55,586 ± 9,663 n.s.
Unstimulated cultures	5,177 ± 486	7,778 ± 1,615	1,733 ± 484

n.s. = Not significant.

* Means of experiments in triplicate for each subject studied.

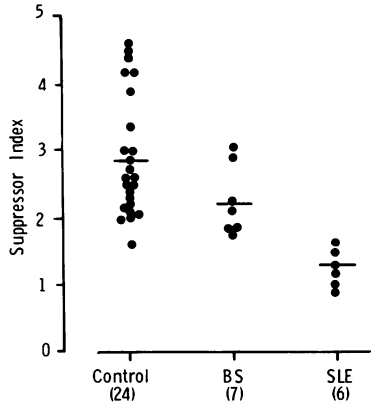

Fig. 3. Suppressor index in control subjects, Behçet's syndrome (BS) and systemic lupus erythematosus (SLE). Mean marked by bar.

Serial study in one patient

In one patient (Na1) with Behçet's syndrome, T-cell subsets and mitogen responses were studied on two occasions. The first was when she had severe disease with orogenital ulcerations, iritis and arthritis, and the second when a clinical remission was achieved during levamisole treatment. Table 3 shows that when remission occurred, the mitogen responsiveness increased as well as the percentage of T cells that were of Tμ class.

Table 3. Serial study of T-cell subsets and mitogen responses in one patient with severe Behçet's syndrome treated with levamisole

Immunological* studies	Severe disease before levamisole	Clinical remission during levamisole
T cells (%)	74	72
Tμ cells (%)	20	39·5
Tγ cells (%)	9	18
PBMC responsiveness to mitogens (μg/ml)		
Con A 250	42,967	87,311
Con A 50	28,941	33,092
Con A 15	15,203	16,676
PHA 100	41,473	89,348
PHA 25	10,376	53,521
PHA 2·5	8,801	9,781
PWM 40	70,613	98,134
PWM 4	30,173	77,446
Suppressor index	2·9	1·6

* Details defined in 'Methods'.

DISCUSSION

The immunological abnormalities that underlie the development of autoimmune disorders have been extensively studied, particularly in SLE, and similar studies in Behçet's syndrome may throw some light on the immunopathogenesis of this condition. Although many questions remain unanswered, the production of auto-antibodies, and reduced suppressor T-cell function which may play a primary or permissive role in this, are well established in SLE (Bresnihan & Jasin, 1977; Sakane, Steinberg & Green, 1978; Sagawa & Abdou 1978). Reductions in numbers of circulating T-cells which may have suppressor function, such as Tγ cells and cells carrying the T5/T8 antigens are described (Alarcón-Segovia & Ruíz-Argüelles 1978; Morimoto *et al.*, 1980).

This study confirms the reduction in numbers of circulating Tγ cells in SLE, with a normal proportion of T cells with Tμ characteristics. This contrasted with our findings in Behçet's syndrome, in which neither absolute numbers nor proportions of total T cells, or Tγ cells differed from normal. It is of interest that in some individuals with Behçet's syndrome, normal Tγ cell numbers were found at a time when (by C1q binding and a rheumatoid factor assay) immune complexes were detected in the serum, suggesting that *in vivo* immune complexes do not necessarily block the Fc receptor of Tγ cells and reduce the numbers detectable. The presence of soluble immune complexes in the circulation of patients with Behçet's syndrome is well described, using a variety of assays (Williams & Lehner, 1977; Levinsky & Lehner, 1978; Gupta *et al.*, 1978).

There was a slight but significant reduction in Tμ cells in patients with Behçet's syndrome, both in absolute numbers and as a proportion of total T cells. This pattern is similar to that we have reported in patients with ulcerative colitis and Crohn's disease (Victorino & Hodgson, 1980a) which may be of interest in the light of occasional reports of gastrointestinal ulceration in patients with Behçet's syndrome. Such gastrointestinal involvement is not common, however (Sladen & Lehner, 1979), and was not specifically sought in our patients. The reduction in Tμ cells may explain the slight reduction in lymphocyte responsiveness noted in our patients, and more strikingly seen in other series (Abdou *et al.*, 1978; Knight *et al.*, 1978), as the number of Tμ cells correlated with the *in vitro* thymidine incorporation by lymphocytes from our patients (data not shown) as it does in normal individuals (Victorino & Hodgson, 1981b). In one of our patients studied serially, clinical improvement was associated with a return of *in vitro* lymphocyte responsiveness to normal, and a

rise in the proportion of Tμ cells. This improvement was attributed to levamisole, which has been reported to be beneficial in the treatment of Behçet's syndrome, and therapeutic doses of levamisole given to patients with recurrent oral ulceration have been shown to enhance *in vitro* lymphocyte proliferative responses (Lehner & Wilton, 1979). There is, however, no definite proof that levamisole was the cause of the clinical improvement in the pattern discussed here, or if it were, that such improvement was due to effects on cell-mediated immunity.

Our study confirmed the widely recognized reduction in suppressor-cell activity seen in SLE, using a simple test measuring loss of non-antigen-specific suppressor activity during *in vitro* incubation (Bresnihan & Jasin, 1977). Using this test we found only a slight reduction in suppressor-cell activity compared with normals in Behçet's syndrome, in contrast to the marked reduction seen in SLE.

Thus, using one functional test of suppressor-cell activity, and one marker for a T-cell subpopulation which possesses immunoregulatory properties, we have not found dramatic alterations in patients with Behçet's syndrome. As there are many immunoregulatory systems described, and suppressor activity may reside in a number of different lymphocyte subpopulations, it is still possible that an important defect in immunoregulation occurs in Behçet's syndrome, but the results reported here do not offer evidence in favour of this suggestion.

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