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EFFICACY OF CYCLOSPORIN ON BEHCET'S DISEASE VASCULOPATHY: A COMPARATIVE STUDY OF CYCLOSPORIN AND CORTICOSTEROID ON LONG-TERM PROGNOSIS.

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Behcet's disease is a vasculitis typified by intimal hyperplasia, internal elastic membrane disruption with medial thining, and an advential/periadvential infiltrate of plasma cells and neutrophils. It is more common in the Mediterranean and is seen slightly more often in males. This multisystem vasculitis is characterized by clinical triad of oral ulcerations that recur at least 3 times a year, recurrent genital ulceration and uvietis. Vasculo-Behcet's disease affect veins more often than arteries. Arterial complications occur in about 10 % of those affected, and venous thrombosis occurs in about 30 %. Thirty-five patients with vasculo-Behcet's disease were included in the study. Diagnosis was based on the clinical criteria, namely, recurrent oral ulceration and involvement of the skin, eye or genitalia in addition to positive pathergy test and duplex scan. Twenty patients (group A) were given Cyclosporin (5mg / kg daily for 6 months) and 15 patients (group B) were given corticosteroids (60 mg daily for 6 months). Eighteen patients of group A had complete reversion of the disease process without further vascular complications and 2 patients developed iliofemoral and caval thrombosis although they were on anticoagulation therapy. Seven patients of group B underwent revascularization surgery for peripheral aneurysms and developed anastomotic disruption. Two patients developed aortic aneurysms. One patient had pseudoaneyrysm at the puncture site for angiography. One patient had progressive ocular deterioration ended with blindness. Conclusions. 1-Cyclosporin is acting by suppressing HLA expressions which is an initial step in triggering the immune system to the vessel wall, a mechanism that is different from that achieved by cortiosteroids 2-Cyclosporin should be used as a first option in the treatment of Behcet's disease as the goal of therapy is to minimize systemic complications by the use of appropriate immunosuppressive agents. 3-Patients with complex aphthosis should be monitored for the onset of Behcet's disease through close follow-up and investigations of systemic complaints. 4-Revascularization should be deferred until acneiform eruption subsides because these eruptions signify the disease activity during which operative tasks will carry a high risk of complications.

Keywords: Behcet, cyclosporin, prednisone, vasculopathy.

INTRODUCTION

Behcet's disease is a chronic multi-system disease characterized by oral and genital aphthae, arthritis, cutaneous lesions, and ocular, gastrointestinal, and neurological manifestations [(1)]. It was first described by the Turkish dermatologist Hulusi Behcet in 1937 as "recurrent oral aphthous ulcers, genital ulcers, and uveitis". Because of the lack of a universally recognized diagnostic laboratory test or histologic finding, the diagnosis of Behcet's disease relies on the identification of its more typical clinical features. The recent publication of the consensus adoption of a common set of criteria by an international study group (ISG) representing 12 centers in seven countries should resolve this difficulty[(2).] These criteria requires the presence of oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions or a positive pathergy test. The prevalence of Behcet's disease is higher in

the Middle East and Japan where it is approximately 1 in 1000 [3]. The disease is far less common in northern Europe, the United States, and the United Kingdom. The mean age of onset ranges from the mid 20s to the fourth decade with a slightly higher male to female ratio [4]. Increased serum levels of soluble IL-2 receptor in patients with thrombophlebitis may suggest an immunologic mechanism for vasculitis in patients with Behcet's disease [5]. The treatment of Behcet's disease can be challenging given the variable clinical course and lack of sufficient double-blind studies. Oral colchicine decreased the size, frequency and duration of oral ulcers by up to 50% a drug that inhibits neutrophil migration and phagocytosis. [7]. Clinical improvement in mucocutaneous manifestations was achieved after treatment with cyclosporin [8]. Although azathioprine was proved to prevent ocular complications when given early [9], however, a similar effect of cyclosporin was not clear. The present study emphasized a superior effect of cyclosporin compared to corticosteroid when given early in the course of Behcet's disease.

PATIENTS AND METHODS

We studied 35 patients with Behcet's disease. Diagnosis was made according to the 1990 criteria of the International Study Group for Behcet's disease[2]. Recurrent oral ulceration was present in the form of minor aphthous, major aphthous (Fig. 1 .a.b) or herpetiform ulceration. The ulcers were round or oval, shallow, with a grey-white pseudo membrane encircled by a thin erythematous halo. The usual site of involvement was labial and buccal mucosa and floor of mouth while the dorsum of tongue and palate were very uncommon. The lesions ranged from 1 mm to 2 cm in diameter and involved any region of the mouth. The least common variety was the herpetiform ulceration which consists of numerous (up to 100) lesions 2- 3 mm in diameter distributed throughout the oral cavity. Genital ulcers were often the presenting complaint which brought a male patient to medical attention. Active genital ulcers always accompanied other skin lesions as acneiform eruption while healed ulcers were commonly seen with superficial thrombopholebitis (Fig. 2a,b). Unusual sites of ulcers were also observed in some patients like those with ulcers in the breast or axilla (Fig. 3a,b). However, these unusual sites of ulcers were not associated with active genital ulceration. A variety of cutaneous lesions were observed in the patients including erythema nodosum-like lesions (Fig. 4a), papulopustular eruptions (Fig 4b). All patients were subjected to a detailed history and clinical examination. Immunological tests included antinuclear antibody, antibodies to double stranded DNA, rheumatoid factor, moreover, erythrocyte sedimentation rate and anti streptolysin 0 titer were carried out. A pathergy test, using a disposable 20 gauge blunt needle, was performed on each patient and read by the same author (Fig.5). Skin biopsy of erythema nodosum-like lesions was taken in some patients and examined histopathologically. Patients were divided into two groups. Group A (20 patients, 17 males, 3 females, 22 to 47 years of age, mean 31.3 years) were given cyclosporin, 5mg / kg daily. Adverse effects were monitored and reduction of dose to 2.5 mg / kg daily if serum creatinine rises above 25% of the baseline level. Further elevation of serum creatinine despite the dose reduction indicates discontinuation of cyclosporin. Group B (15 patients, 13 males, 2 females, 19-41 years of age, mean, 30 years) were treated with prednisone 60 mg daily. Patients were clinically examined at monthly intervals and blood pressure levels were recorded.

RESULTS

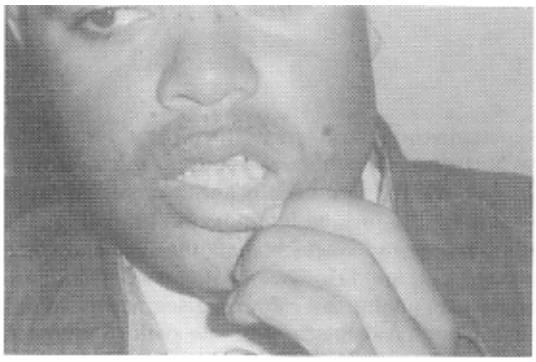
On analyzing the order of appearance of the common clinical features, oral ulcers where the first symptom in the majority, genital ulcers were second, and these were closely followed by cutaneous lesions. Oral ulcers were typically painful, single in 85% of patients, lasting between 1 and 4 weeks and healed without scarring. Genital ulcers usually occurred on the vulva or scrotum and root of the penis, painful in 6% but asymptomatic in all female patients. Genital ulcers were similar in appearance and clinical course to oral aphthae, however they did not recur as often and healed with scarring. Pathergy test was positive in 43% of patients, all of whom had active disease at the time of testing. Histopathologic examination of erythema nodosum-like lesions showed a leukocytoclastic vasculitis, extravasation of erythrocytes,and fibrinoid necrosis of postcapillary venules, or a lesser degree of neutiophilic vascular reaction with no fibrinoid necrosis surrounded by neutrophilic infiltrate, nuclear dust, and extravasation of erythrocytes. None of the patients tested positive for rheumatoid factor, antinuclear antibody or antibody to double-stranded DNA, however, ESR showed high figures during the disease activity and remained above the normal values during the remission state. In eight patients of group A, the frequency, numbers, size and depth of oral ulcers diminished compared to group B ($p<0.05$). In 10 patients of group A, no oral ulcers were observed during treatment but in none of group B. Two patients of group A and 6 of group B showed worsening of the oral ulcers during treatment. No genital ulcers were observed in 16 of group A but in one of group B. In 18 patients of group A, cutaneous lesions as erythema nodosum-like lesions and acneiform eruption did not show during treatment, however, repeated attacks of cutaneous eruptions were recorded during treatment in group B especially in those who needed surgical intervention for vascular complications. During treatment, pathergy tests turned negative in 8 patients of group A but in one of group B. One patient of group B showed progressive ocular deterioration ended with blindness. In 18 patients of group A, no vascular involvement were observed during treatment and the subsequent two years of follow-up as well. Two patients developed venous thrombosis at the third month of therapy and they responded well to

conservative therapy without embolization. (Table 1), summarizes the vascular complications in group B compared to group A. Seven patients of group B developed peripheral aneurysms, three patients developed femoral aneurysms for which excision and interposition of either PTFE or saphenous vein graft was done (Fig.6). Several months later, two patients developed leakage at the proximal end of interposition graft and demanded external iliac-popliteal bypass through a lateral route to avoid the former incision. Two patients developed popliteal aneurysms for which excision and interposition graft was done in one and femoro-posterior tibial bypass was done in the other (Fig.7). One patient developed posterior tibial artery aneurysm (Fig.8) for which excision and interposition vein graft was done and one patient developed peroneal artery aneurysm for which excision and ligation was done (Fig.9), because the thrombosed and recanalized saphenous vein hampered its use as interposition graft (Fig. 10). One patient had pseudoaneuysm at the puncture site for angiography (Fig. 11). Two patients developed aortic aneurysms involving the infrarenal segment, extending to the right common iliac artery in one patient and occluding the inferior mesentric artery in the other. None of the patients of either group has required discontinuation of cyclosporin or prednisone because of adverse effects of the drug. Gingivitis and hypertrichosis were the most common side effects observed in group A, however, transient fatigue and increased body weight were observed in group B during treatment.

Table(1): ***Clinical and therapeutic findings in patients with Behcet's disease.***

Clinical finding	*Group A (n=20)*		*Group B (n=15)*	
	* Before	** After	Before	After
Pathergy test positively	8	-	7	6
Oral ulcer				
Improved		8		-
Cured		10		-
Worsend		2		6
Genital ulcers.				
Cured		16		-
Ocular deterioration				
Light perception		-		1
20 / 200				
Vascular involvement				
Deep vien thrombosis		2		-
Femoral aneurysm		-		3
Politeal aneurysm		-		2
Posterior tibial aneurysm		-		1
Peroneal aneurysm		-		1
Aortic aneurysm		-		2
Pseudoaneurysm		-		1

* Before = Before treatment
** After = After treatment



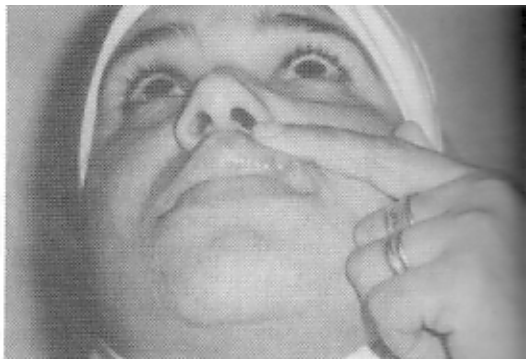


Fig. (1 a, b): Aphthous ulcers of the lip.

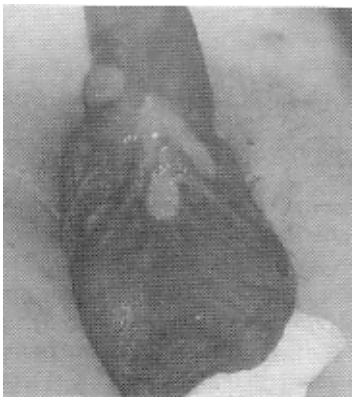


Fig. (2a): Active genital ulcers of the scrotum and root of the penis..

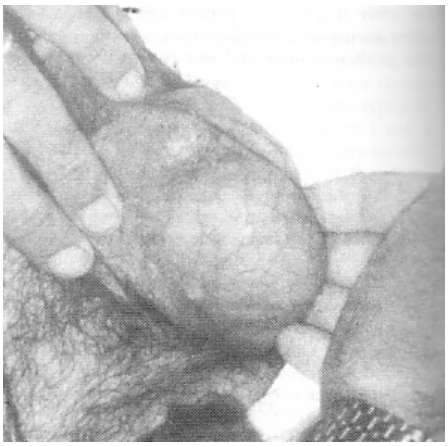
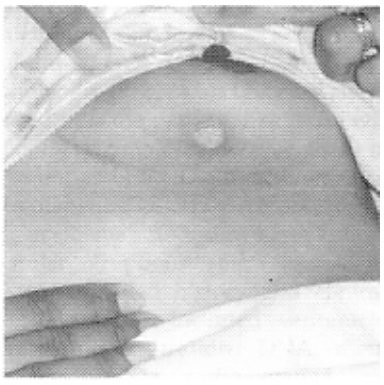


Fig. (2b): Healed genital ulcers of the scrotum.



Fig, (3a): Active ulcer of the breast.

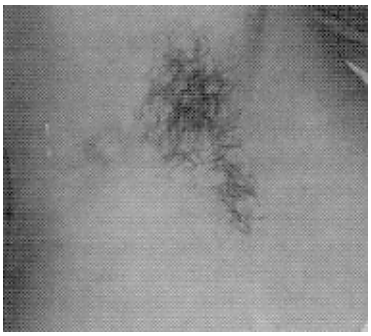


Fig. (3b): Active ulcer of the axilla

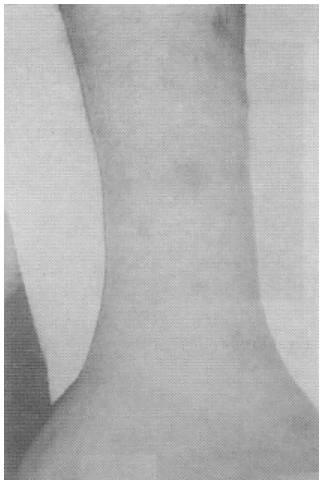


Fig. (4a):Erythema nodosum - like lesion of the leg.

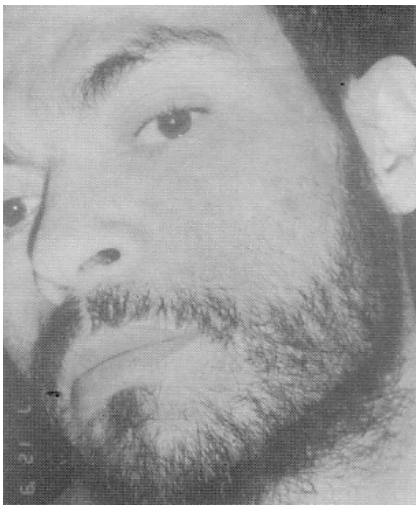


Fig. (4b):Acneiform eruptions of the face.

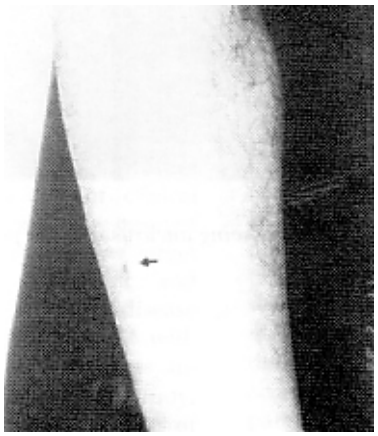


Fig.(5):A positive pathergy test i.e. occurance of pustular lesion 24 hours after cutaneous trauma with needle stick..

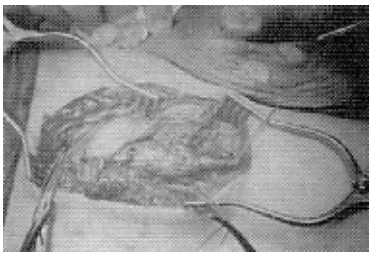


Fig .(6a):An aneurysm of the common femoral artery and extending to the superficial femoral artery..

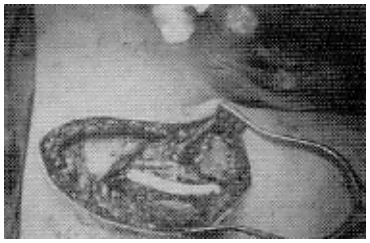


Fig. (6b):After excision of the aneurysm and interposition of PTFE graft..

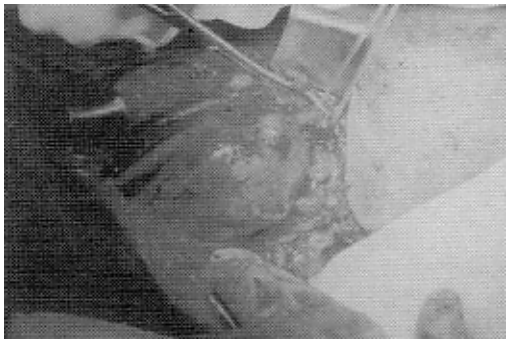


Fig. (7a): An aneurysm of the right popliteal artery for which excision and interposition vein graft was done.

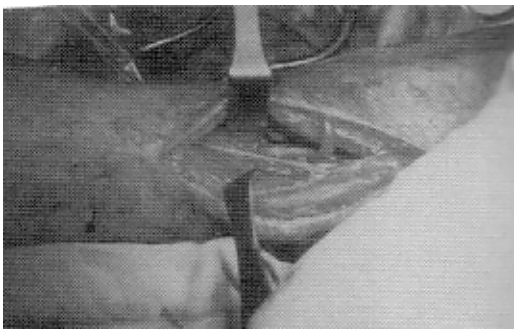


Fig. (7b): Femoro-posterior tibial bypass for popliteal aneurysm.

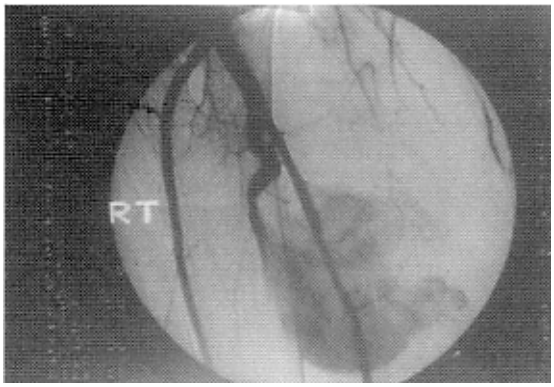


Fig. (8): Digital subtraction angiography showing aneurysm of the posterior tibial artery..

Fig. (9a):Peroneal artery aneurysm..

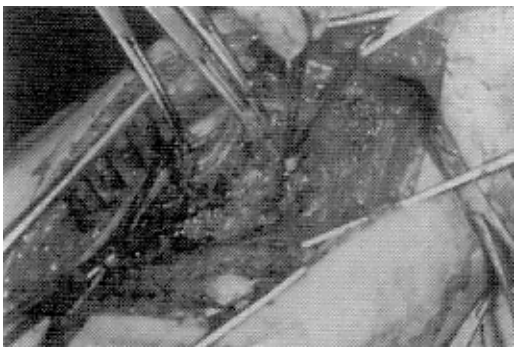


Fig. (9b): Excision and ligation of peroneal artery aneurysm..

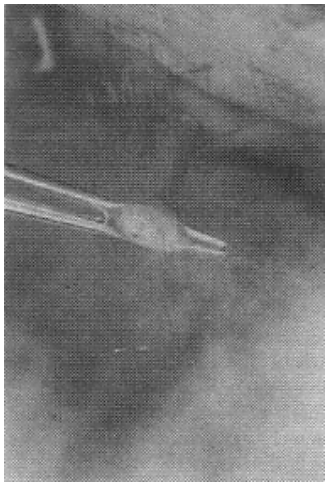


Fig.(10): Thrombosed, recanalized long saphenous vein following attacks of superficial thrombophlebities.

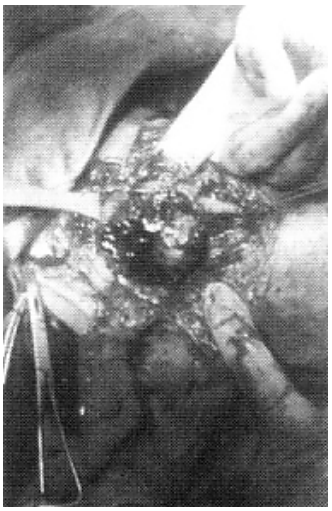


Fig.(11): Pseudoaneurysm of the femoral artery at the puncture site of angiography..

DISCUSSION

Although Behcet's disease was first described in 1937, it remains largely ignored in medical practice. The difficulties in diagnosis are caused by the variability of clinical manifestations, the frequent long delay between the onset of the disease and the appearance of lesions in a new target organ, and the absence of specific pathologic and immunologic features[10]. The etiology of the disease remains unknown. The disease has been associated with HLA - B51[11] which implies that HLA - linked genes are involved in increased susceptibility. In the present study, The observation that many of the patients are residents of certain provinces and that they noticed quiescence of the disease when they moved for a period of I to 3 months away from these provinces, raises the possibility that the disease initiation is a combination of genetic propensity and an exogenous stimulus which may be viral or bacterial. The detection of streptococcus anhemolyticus fragments in the blood of a high percentage of patients with Behcets disease, suggests a possible bacterial role in the initiation of the disease process[12] . The finding that more than 90% of the patients in the present series were males fits with the usual figures, which incriminate a preponderance of young males[13]. Pathergy test, the occurrence of a pustular lesion 24 hours after cutaneous trauma by a needlestick, was found to be positive in 15 of 35 patients which seems to be an important diagnostic marker. Although a similar figures of the test positivity were reported in Turkish patients [14], however, a lower incidence of positive tests were found in British patients[15] and Indian patients[16]. We used a blunt needle in this test as it has been shown that sharp needles elicits a positive result less frequently and with lesser intensity than when blunt needles are used [17]. The mechanism of pathergy test is thought to be small vessel vasculitis [18] or enhanced neutrophil chemotaxis [19].

Several lesions have been described in Behcet's disease as pyoderma gangrenosuin like lesions, palpable purpuric lesions of necrotizing vasculitis, erythema nodosum-like lesions, abscesses, and papulopustular eruption. In the present study acneiform eruptions were a prominent feature in patients with active disease and almost always associated with active genital ulcers. The International Study Group used the follicular acneiform eruptions as one of the diagnostic criteria of Behcet's disease [2], however, because acneiform and folliculitis-like lesions are non-specific, particularly in adolescents, many believe these should not be included [20]. The finding that most of the laboratory tests and immunological studies were negative apart from the elevated erythrocyte sedimentation rate accompanying the disease activity is in line with other studies [21] which defined abnormal values such as leucocytosis, increased ESR and elevated IgG only in disease exacerbations. Vascular findings in Behcet's disease involve blood vessels of all sizes in both the arterial and venous systems [22]. Several studies confirmed that venous occlusions are more common than arterial and most commonly involve the superior and inferior vena cava [19, 23] however, this was not the case in the current study where only two cases of venous thrombosis were recorded in group A. This could be the result of early initiation of therapy since many of these patients developed repeated attacks of superficial thrombophlebitis before the beginning of therapy in either group. In the present study, arterial aneurysms occurred more often than arterial thrombosis which had been proved by others [24]. We reported two cases of aortic aneurysms but eight cases of peripheral aneurysms which is different from the figures

shown by other researchers[25] where the aorta was the most common site of involvement followed by the femoral and popliteal arteries.

The underlying etiologies of Behcet's disease and its vasculopathy remain unknown. However, systemic vasculitis likely plays a central role. Perhaps the most widely held hypothesis concerning the mechanism of tissue damage in Behcet's disease has been that this is an immune complex mediated disease. Immune complexes, as well as damaged membrane fragments, have been reported in the blood of patients with Belicet's disease[25]. For this reason, systemic corticosteroid administration may be utilized, particularly during the acute attacks of this disorder [10 ,26]. We used prednisone in patients of group B for a period of more than 6 months and despite that vascular and ocular complications continued and even disruption of suture lines following revascularization did occur while the patient was still under steroid therapy. This finding is in line with other studies in which systemic corticosteroids had been used for the treatment of manifestations of Behcet's disease but was not useful in preventing systemic complications.[4,27]. Moreover, prednisone combined with heparin when used in patients with Behcet's disease, relapses and mortality of systemic complications were reported in nearly half of the patients during the therapy [28,29]. T cell aberrations have been noted in patients with Behcet's disease. Sakane group[30] have reported abnormalities of suppressor cell activity and in autologous mixed lymphocyte reaction in the pre-active stage of Behcet's disease. T cells from patients with Behcet's disease were found to produce gamma interferon spontaneously, a finding suggesting a derangement in the normally exquisite T cell regulatory process. Cyclosporin A by its known suppressive effect on T cells, was used in the treatment of Behcet's disease. We used cyclosporin A in patients of group A for a period of 6 months and it effectively abrogated the vascular complications in 90% of patients, markedly improved the mucocutaneous manifestations and totally prevented ocular deterioration. Several studies have shown significant benefit with cyclosporin therapy in Behcet's disease [32 , 33]. Marked improvement in mucocutaneous manifestations have been shown after treatment with cyclosporin in Turkish study [8]. In a lager Japanese study of 96 patients, cyclosporin treatment decreased systemic complications when compared with colchicine [20]. Combination therapy of prednisone and cyclophosphamide [34] as well as azathioprine and cycolsporin [35] were used to decrease adverse effects of high dose of these drugs. It is noteworthy that vascular manifestations are the findings that matters in Behcet's disease to the degree that the International Study Group intensively studied thrombophlebitis, deep vein thrombosis and arterial aneurysms, but did not include them in the final criteria because they lacked sensitivity, despite extremely high specificity. Since most of the recorded mortality in the Behcet's disease are the result of systemic vasculitis, we recommended the use of cyclosporin early in the course of the disease for a duration of 6 months to one year according to the manifestations. Cyclosporin would appear to be an effective alternative medication for the potentially devastating vascular complications of Behcet's disease compared to corticosteroids. The treatment was usually discontinued in patients whose disease appeared to be clinically inactive for at least 6 months. However, we do not seem to have induced a tolerant immune state in these patients as there is no rigid guidelines for further treatment of the patients after termination of therapy; decisions were made individually for each patient depending on his clinical status.

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