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Long-lasting remission of Behçet's disease after chlorambucil therapy

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Behçet (1937) drew attention to a syndrome characterized by a triad of symptoms: iritis, aphthous ulceration of the mouth, and ulceration of the genitalia. Although this disease was originally considered to be a rarity, recent reports show that it is more common and widespread than was previously thought, especially in the Middle East, the Mediterranean countries, and Japan. During the last few years, 26 patients seen in the departments of rheumatology, ophthalmology, dermatology, and neurology in our university hospital (Abdel-Fattah, Abdallah, and Fadly, 1969) reflect the relatively high incidence of the disease in Egypt.

The manifestations of Behçet's disease are more complex and protean than the triad of symptoms originally described. Involvement of almost every system has been demonstrated; among these may be mentioned the central nervous system, the joints, the heart, the spleen, the lymph nodes, and the testes (Schotland, Wolf, White, and Dubin, 1963; Nazzaro, 1966; Masheter, 1959; Evans, Pallis, and Spillane, 1957). Arthritis, recurrent thrombophlebitis, and erythema nodosum are now recognized as manifestations of this disease, while eye involvement is considered to be its most serious complication, since blindness is almost inevitable (Mamo and Azzam, 1970). Involvement of the major arteries, such as the thoracic and abdominal aorta, was described by Hills (1967). Obliterative endarteritis of the vasa vasorum of the main arteries, together with microaneurysms

Table I *Patients with Behçet's disease before treatment*

Groups studied	*Case no.*	*Age (yrs)*	*Sex*	*Duration (mths)*	*Eye lesions*				*Mucocutaneous lesions*	
					Iridocyclitis with hypopyon	*Posterior uveitis*	*Neuroretinitis*	*Vascular sheathing*	*Oral ulcer*	*Genital ulcer*
Chlorambucil with steroids	1	18	M	3		+	+	+	+	+
	2	22	M	36			+	+	+	+
	3	29	F	30		+			+	
	4	33	F	42		+	+		+	+
	5	27	M	18	+	+			+	+
	6	42	M	11	+			+	+	+
	7	34	M	18	+			+	+	+
Steroids only	1	24	F	10	+	+			+	+
	2	24	M	24			+	+	+	+
	3	26	M	36	+		+	+	+	+
	4	31	M	10			−		+	+
	5	34	M	10	+	+			+	+
	6	20	F	6			+		+	+
	7	26	F	30			+		+	+

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of the retinal vessels, have also been recorded (Smith, Prior, and Sturman, 1967). These findings suggest that Behçet's disease may be related to other forms of vasculitis with major arterial involvement, such as Takayasu's disease, giant-cell arteritis, and polyarteritis nodosa. Most authors now agree that Behçet's disease is a systemic disorder which may belong to the primary inflammatory connective-tissue group usually referred to as collagen diseases. Like that of other diseases in this group, the aetiology of Behçet's disease is controversial; many theories have been put forward, but none finds universal agreement. The virus theory seems to be the most popular, since some authors have succeeded in isolating a virus from patients with Behçet's disease (Smith and others, 1967; Mortada and Imam, 1964; Moore, 1968,) but the failure of many others to do so has cast doubt on this theory. Oshima, Shimizu, Yokohari, Matsumoto, Kano, Kogami, and Nagaya (1963) and Shimizu, Katsuka, and Oshima (1965) suggested that it might be an autoimmune disease, and this idea was supported by Lehner (1967).

The treatment of Behçet's disease also presents a difficult problem. The methods so far adopted have failed to cure or to achieve long-lasting remission. Heavy doses of corticosteroids result in the temporary suppression of some symptoms but do not prevent the development of severe ocular and neurological lesions (Mamo, 1970).

Interest was therefore aroused by reports of improvement with immunosuppressive therapy. Azathioprine was tried with some success in a few cases (Rosselet, Sosdan, and Zenklusen, 1968), but with inadequate follow-up.

Material and methods

Fourteen patients with classic Behçet's disease selected by the ophthalmology and rheumatology units all showed at least the triad of iritis, and genital and oral lesions, and many also had other manifestations. Table I shows the clinical data recorded before treatment was started. All the patients were receiving systemic steroids.

The patients were divided into two equal groups matched as far as possible for age, sex, and clinical features. Those in one group were given chlorambucil in addition to the steroid therapy, and those in the second (control) group steroids alone.

	Neurological		*Miscellaneous*						
ema um	*Sensory*	*Motor*	*Arthralgia*	*Arthritis*	*Thrombo-phlebitis*	*Vasculitis*	*Spleen*	*Gland*	*Orchitis*
									+
				+	+		+	+	
				+		+			
		+	+					+	
			+						
	+								
				+	+	+			
			+						
				+	+		+		
		+	+						
			+						
			+						
					+				

Chlorambucil 10 to 15 mg. was given in three daily doses after meals, for 1 to 2 months; a maintenance dose, adjusted according to the therapeutic response and evidence of toxicity, was continued for 6 to 8 months. In the meantime the original maintenance dose of corticosteroids was gradually discontinued.

For $3\frac{1}{2}$ years the patients were seen weekly for the first 6 months and then monthly, and at each visit a full clinical study was made including a complete blood count and erythrocyte sedimentation rate. If the total white cell count fell below 3,500/mm.^{3}, the drug was discontinued.

Results

Table II summarizes the effect of steroid therapy alone, and that of chlorambucil combined with steroids, in the two groups studied.

(1) Of the seven patients given chlorambucil and steroids, four have been followed-up for 40 months and the other three stopped attending the clinic after 13, 21, and 23 months respectively. All showed remission in the mucocutaneous lesions, joint symptoms, erythema nodosum, and other manifestations. This remission started from a few weeks to a few months after the addition of chlorambucil to the treatment and has so far been maintained. In all patients it was possible to stop all forms of treatment 6 to 11 months after starting chlorambucil therapy, including the corticosteroids on which they had been maintained before. Complete remission was obtained in cases of posterior uveitis and neuroretinitis. The vascular sheathing seen in some cases remained stationary; iridocyclitis, however, showed deterioration in two-thirds of the cases and partial improvement in only one-third. No further ocular damage or deterioration in visual acuity was recorded. The neurological lesions remained stationary with partial improvement in one case.

(2) Of the seven patients given steroid therapy alone, one stopped attending the clinic after 8 months. All showed improvement in the mucocutaneous lesions, but remission of the oral lesions was achieved in only one case and in the genital lesions in two cases. The rest showed partial improvement, but the lesions recurred on withdrawal of the corticosteroids, which were given in a maintenance dose of 7·5 to 20 mg. prednisolone daily.

Table II *Effect of treatment*

Type of lesion	*Chlorambucil with corticosteroids*					*Corticosteroids only*				
	No. of cases	*Remission*	*Partial improvement*	*No change*	*Deterioration*	*No. of cases*	*Remission*	*Partial improvement*	*No change*	*Deterioration*
Ocular										
Iridocyclitis with hypopyon	3	1	1	0	2	3	1	0	0	2
Posterior uveitis	4	4	0	0	0	2	0	2	0	0
Neuro-retinitis	3	3	0	0	0	5	0	3	1	1
Vascular sheathing	4	0	0	4	0	2	0	0	0	2
Mucocutaneous										
Oral ulcers	7	7	0	0	0	7	1	6	0	0
Genital ulcers	7	7	0	0	0	7	2	0	0	0
Erythema nodosum	4	4	0	0	0	2	2	0	0	0
Neurological										
Sensory	1	0	0	1	0	1		0		1
Motor	1	0	0	1	0	2		1		0
Miscellaneous										
Arthritis	3	3	0	0	0	2	0	2	0	0
Arthralgia	2	2	0	0	0	2	2	0	0	0
Vasculitis	2	1	1	0	0	1	0	1	0	0
Thrombophlebitis	1	0	1	0	0	0	0	0	0	0
Spleen	1	0	0	1	0	0	0	0	0	0
Glands	2	0	1	1	0	3	0	2	1	0
Orchitis	1	1	0	0	0	0	0	0	0	0

The erythema nodosum seen in two cases recurred twice, but went into complete remission when the dose of prednisolone was increased to 15 mg. daily. The arthritic lesions always improved with large doses of steroids, but flared up from time to time. The response in the eye was most unsatisfactory. There was progressive deterioration in visual acuity in spite of the large dose of prednisolone, although the rate of deterioration was slower than the average of 3·6 years from onset of disease to loss of vision recorded by Mamo (1970). In the two patients with neurological involvement, the lesions progressed, and one developed fresh hemiplegia.

Toxic reactions and side-effects

The side-effects of chlorambucil on the white cell count were only temporary, with leucopenia reaching the lowest permissible level of 3,500/mm.^{3} in only two patients. The drug was stopped for 3 weeks and was resumed in smaller doses with no further evidence of toxicity. Drug rashes occurred in two cases but improved with topical steroid therapy. The drug was otherwise well tolerated. The usual side-effects of corticosteroids originally present in these patients were progressively reduced in those receiving chlorambucil as it was possible to withdraw the steroids. In the control cases these side-effects could not be avoided.

Discussion

If an autoimmune mechanism is responsible for the pathogenesis of Behçet's disease, immunosuppressive drugs may be effective in its management. This is also suggested by the results of experimental studies with mercaptopurine previously carried out in related conditions of allergic uveitis in rabbits (Wirostko and Halbert, 1962). Clinically favourable results were obtained with methotrexate in the treatment of a few patients suffering from related allergic and autoimmune ophthalmological conditions, such as cyclitis, uveitis, and sympathetic ophthalmitis (Wong, 1969). Azathioprine has also caused remarkable improvement in patients with uveitis (Moore, 1968). Rosselet and others (1962) have reported favourable results in three patients treated with azathioprine, but Wong (1969) found no appreciable improvement in two patients given methotrexate or in one patient given cyclophosphamide.

Chlorambucil was used in Behçet's disease in 1968 by Mamo and Azzam in Beirut, and by our group in Cairo at the suggestion of Dr. M. I. Hogan, who was visiting the Far and Middle East research centres while working on Behçet's disease. Mamo and Azzam (1970) published their results in eleven patients after a follow-up period of 17 months; our follow-up period of almost 2 years more has allowed a better assessment of the effects.

Our results agree in the main with those of Mamo and Azzam, although the protocol in the two studies was different. In Mamo's work the drug was given to all the patients studied with no control group, each patient serving as his own control. The assessment of the effect of the drug was made individually by comparing the course of the disease before and after treatment.

Our study has allowed us to compare the course of the disease under chlorambucil and steroids with that under steroids alone. All patients treated with chlorambucil went into remission, four of them for 40 months—the longest remission so far recorded in the treatment of Behçet's disease.

The fact that chlorambucil has effected a remission in Behçet's disease does not confirm the autoimmune hypothesis. Although it is likely that chlorambucil is acting through its immunosuppressive properties, other modes of action cannot be excluded. Being a cytotoxic

drug it may be having a direct lethal action on a hidden or a dormant virus. Some authors have actually demonstrated such a virucidal action of immunosuppressive drugs in cancer, and claim that it is the latter rather than the immunosuppression that is responsible for the therapeutic effect (Turk, 1969). We have noticed in our results an observation that may have a bearing on this assumption. In some of our cases a short course of chlorambucil for 2 to 4 months was sufficient to induce a remission, while in others prolongation of the therapy to 8 or 12 months was needed to achieve the same results. Almost all those showing the first type of response were cases of less than one year's duration, while two-thirds of the cases requiring prolonged therapy had had the disease for more than 3 to 5 years. Although the number of cases is too small for any conclusion to be drawn, the possibility arises that chlorambucil may act differently in Behçet's disease according to the chronicity of the condition. The drug may be having a dual effect: virucidal in early cases, requiring a smaller dosage for a shorter time, and immunosuppressive in the late cases, requiring a larger dose for a longer time or maintenance therapy in order to suppress an already self-perpetuating autoimmune tissue reaction. Thus, the response to chlorambucil does not favour autoimmunity as the only mechanism of the disease, but may also suggest an aetiological relation to a virus. It is too early to judge the validity of this hypothesis but it is felt that this new finding should be studied further.

Summary

A controlled study to compare the effect of the immunosuppressive drug, chlorambucil, with that of corticosteroids was carried out in fourteen patients with Behçet's disease. Patients given chlorambucil improved more rapidly; most of the mucocutaneous and joint lesions went into complete remission, and neurological and eye lesions did not progress. In patients not receiving chlorambucil, these lesions progressed with numerous exacerbations. In four patients given chlorambucil, a complete remission of 40 months' duration was obtained, but this was not seen in the control group.

It was noticed that patients who had had the disease for a shorter time improved more rapidly and required a smaller dosage and less maintenance on chlorambucil than the long-standing cases. The significance of this finding is discussed. It is suggested that chlorambucil may be acting as a virucidal agent in early cases and as an immunosuppressive in long-standing cases.

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