Behçet's disease associated with amyloidosis in Turkey and in the world

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SUMMARY The association of amyloidosis with Behçet's disease has infrequently been reported in published works. Twenty four such cases have been observed in the world, of which 12 are from Turkey, including eight of ours. In all our eight cases renal biopsy showed amyloidosis of type AA. Behçet's disease of male preponderance, long duration, complete type, multiple organ involvement, and positive skin pathergy test were the main characteristics of all 24 cases of Behçet's disease with amyloidosis. We conclude that amyloidosis associated with Behçet's disease is a secondary AA amyloidosis occurring as an intrinsic manifestation of Behçet's disease.

Key words: systemic amyloidosis, AA amyloidosis, renal amyloidosis, nephrotic syndrome.

Behçet's (BD) was first described in 1937 by Hulusi Behçet with a clinical picture of recurrent oral and genital ulcerations and hypopyon iritis.¹ Further studies have shown its systemic character with multiple organ involvement.²⁻⁴ Renal involvement in BD, including non-amyloid renal lesions^{5,6} and renal amyloidosis, has only recently been reported with an increasing frequency. Renal amyloidosis associated with BD was first described in 1964 by Sherf *et al.*⁷ When we reported two cases of amyloidosis with BD in 1977 there were five others in published reports.⁸⁻¹⁰ We subsequently presented two more cases.^{11,12} The total number of cases reported has now reached 24, including our four previous cases and four new cases. We now present the cumulative characteristics of our eight cases and give an overview on this subject.

Patients and methods

Our 368 patients with BD, diagnosed according to the criteria of the Behçet's Disease Research Committee of Japan¹³ and our new criteria,¹⁴ have been followed up regularly in our unit, and physical examination and routine laboratory findings, or

both, relevant to renal involvement or amyloidosis, including complete blood chemistry, renal function tests, and pyelography, have been evaluated further.

Renal biopsy was performed in 13 patients having either proteinuria or any other findings of nephrotic syndrome or renal dysfunction. Renal amyloidosis was found in eight. Biopsy specimens of all patients were stained with Congo red and cresyl violet. Light and polarised light microscopy were used in all and electron microscopy in five. The potassium permanganate (KMnO₄) reaction was performed in all eight.¹⁵

Results

Tables 1 and 2 give the demographic, clinical, and laboratory features of our patients. All were middle aged men. Seven had complete and one incomplete BD. All had recurrent oral and genital ulcerations, and all but one had thrombophlebitis (superficial, deep or major, or both). Three had juvenile onset of BD. The mean duration of BD was 16 years (range 7-27 years). Oral aphthae were one of the initial manifestations in five patients, and skin lesions in the other three. Inferior vena cava syndrome was found in none of our cases. None of the patients had any clinical findings relevant to primary amyloidosis nor any other disease which might cause secondary

Accepted for publication 16 June 1987.

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amyloidosis. Only patient No 5 received colchicine before diagnosis of amyloidosis was made. In this case colchicine treatment for BD was started nine years ago and continued up to the present. Although last year he developed amyloidosis, neither proteinuria nor nephrotic syndrome have developed until now. In patient No 1 colchicine treatment was

first instituted after the diagnosis of amyloidosis 10 years ago and continued until recently when he developed renal insufficiency. Patients 3 and 8 died in hospital a few weeks after admission for renal failure. Patients 4 and 6 died at home not long after the diagnosis of amyloidosis. Patients 3, 4, 6, 7, and 8 had nephrotic syndrome with uraemia. Bence

Table 1 *Demographic and clinical characteristics of our eight patients with Behçet's disease with amyloidosis*

	Patient No							
	1	2	3	4	5	6	7	8
Sex	M	M	M	M	M	M	M	M
Present age (years)	33	46	31	44	43	40	31	42
Behçet's disease								
Age of onset (years)	7	39	16	32	16	23	21	28
Duration of BD (years)	26	7	15	12	27	17	10	14
First symptom	OA	EN	EN	Acne	OA, GU, TP, PA	OA	OA, GU, AG	OA
Type	C	IC	C	C	C	C	C	C
Manifestations								
Oral	+	+	+	+	+	+	+	+
Genital	+	+	+	+	+	+	+	+
Eye	+	-	+	+	+	+	+	+
Arthritis	+	-	+	+	+	+	AG	+
Skin	+	+	+	+	+	-	-	-
Thrombophlebitis	+	+	+	+	+	+	+	-
Pleuropulmonary	+	+	-	-	-	+	-	-
Neuropsychiatric	+	+	-	-	+	-	-	-
Skin pathergy test	+	+	-	+	+	+	+	-
Oedema	-	-	3+	2+	-	1+	3+	3+
Blood pressure	N	N	H	N	H	H	N	N

OA=oral aphthae; EN=erythema nodosum; GU=genital ulceration; TP=thrombophlebitis; PA=peripheral arthritis; AG=arthralgia; C=complete; IC=incomplete; N=normal, H=high.

Table 2 *Laboratory findings of our eight patients with Behçet's disease with amyloidosis*

	Patient No							
	1	2	3	4	5	6	7	8
Urine								
Sp. gravity	1016	1018	1012	1020	1020	1005	1012	1013
Protein (g/l)	1.5	1.5	15	7	trace	4.5	7-10	3
Bence Jones protein	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
Microscopy	N	N	WBC, RBC, Gr. Hy, casts	N	N	N	N	WBC, Hy, casts
Blood								
Urea (mmol/l)	5.64	6.64	37.18	33.20	5.97	35.85	50.46	48.80
Creatinine (mmol/l)	79.65	106.20	424.80	619.50	88.50	504.45	1416	1327
Renal biopsy								
Light microscopy (amyloid)	+	+	+	+	+	+	+	+
AA amyloid (KMnO ₄)	+	+	+	+	+	+	+	+
Electron microscopy (amyloid fibrils)	+	ND	+	+	+	ND	ND	+

N=normal; WBC=white blood cell; RBC=red blood cell; Gr=granular; Hy=hyaline; ND=not done.

Jones proteinuria was not demonstrated in any of them. Amyloidosis was found by light and polarised light microscopy in all renal biopsy specimens stained with Congo red and cresyl violet. Treatment of sections with KMnO_4 resulted in virtually complete disappearance of the affinity of the amyloid for Congo red. This finding indicates that the amyloid was type AA. In patients 1, 3, 4, 5, and 8 amyloid fibrils were demonstrated in glomerular basement membranes by electron microscopy (Figs 1 and 2).

Table 3 shows the comparative prevalence of the main features of our eight patients with amyloidosis and our total of 368 patients with BD.

Discussion

The incidence of amyloidosis appears to be quite high in Turkey¹⁶ and the cases are mostly secondary amyloidosis.¹⁷⁻²⁰ In previous studies we showed that amyloidosis due to familial Mediterranean fever

Fig. 1 Patient No 1. Note the amyloid fibrils in the glomerular basal lamina (Bl). Pedicles (P), slit membranes (→), and endothelium (En) can also be seen.

Fig. 2 Patient No 5. Between endothelium (En) and podocytes (P), amyloid fibrils (→) are dispersed in the glomerular basal lamina. In the middle of the figure part of the basal lamina (lamina densa) is clearly visible.

Table 3 *Comparative prevalence of the main features of our patients*

	<i>Behçet's disease with amyloidosis</i>	<i>Behçet's disease</i>
No of cases	8	368
M:F	All male	1:82
Present age (mean, years)	38.7	33.9
Age at onset (mean, years)	22.7	24.7
Duration of Behçet's disease (mean, years)	16	8.9
Manifestations (%)		
Oral aphthae	100	99.6
Genital ulceration	100	78
Eye	87.5	53
Skin	62.5	75.9
Peripheral arthritis	75	51.1
Thrombophlebitis	87.5	40.3
Neuropsychiatric	37.5	8.1
(+) Skin pathergy test	75	70.5

(FMF) constituted more than one third of the total cases of secondary amyloidosis.^{19 20} We have also shown that the prevalence of secondary amyloidosis associated with infectious and rheumatic diseases is comparable with that of many European countries.^{18 20}

Regional differences in secondary amyloidosis have been mentioned by various authors.²¹ Patients with juvenile onset rheumatoid arthritis and FMF are more prone to develop amyloidosis than adults.^{20 22-24} Long duration, severity of the disease, and male sex have an important role in the development of secondary amyloidosis.^{23 25} There is also a predominance of men with primary amyloidosis and myeloma associated amyloidosis.²⁶ Despite the high prevalence of BD in Japan there is only one report of its association with amyloidosis.²⁷ In Japan

Table 4 *Cumulative data on 24 cases of Behçet's disease with amyloidosis reported so far in published work*

<i>Study No</i>	<i>Authors</i>	<i>Ref.</i>	<i>Year</i>	<i>Country</i>	<i>No of cases</i>	<i>Sex</i>	<i>Present age (years)</i>	<i>Age of onset (years)</i>	<i>Duration of BD (years)</i>	<i>Initial symptom</i>	<i>SPT</i>	<i>OA</i>	<i>GU</i>	<i>Eye</i>
1	Sherf	7	1964	Israel	1	M	19	10	9	PA	+	+	+	+
2A	Nestor	8	1969	Rumania	2	M	23	21	2		+	+	+	+
2B						M	38	29	9		+	+	+	+
3A	Rosenthal	9	1975	Israel	2	M	38	37	1/2	OA, GU	+	+	+	-
3B						M	14	12	2	Leg ulcer	+	+	-	-
4A	Dilşen	10	1977	Turkey	2	M	33	7	26	OA	+	+	+	+
4B						M	46	39	7	EN	+	+	+	-
5	Jimi	27	1979	Japan	1	M	54	35	19			+	-	+
6	Hamza	33	1980	Tunisia	1	M	30	18	12	OA, GU, PA	+	+	+	+
7	Dilşen	11	1982	Turkey	1(3)	M	31	16	15	EN	-	+	+	+
8	Rubiès-Prat	34	1982	Spain	1	M	34					+	+	-
9	Greco	35	1982	USA	1	F	31	<15	>15	OA	+	+	-	+
10	Strouboulis	36	1983	Greece	1	M	38	20	18			+	+	+
11	Aral	12	1983	Turkey	1(4)	M	44	32	12	Acne	+	+	+	+
12	Penza	37	1983	Italy	1	F	13	4	9	OA, GU	+	+	+	
13	Peces	38	1984	Spain	1	M	36	17	19	TP	+	+	+	-
14A	Sözen	39	1985	Turkey	2	M	33	24	9	OA, eye		+	+	+
14B						M	43			OA		+	+	
15A	Yurdakul	40	1986	Turkey	2	M								
15B						M								
16A	Dilşen	*	1987	Turkey	4(8)	M	43	16	27	OA, GU, PA, TP	+	+	+	+
16B						M	40	23	17	OA	+	+	+	+
16C						M	31	21	10	OA, GU, AG	+	+	+	+
16D						M	42	28	14	OA	-	+	+	+

*Present study. Number in parentheses shows total number of our cases.

Blank spaces indicate no data given by the authors.

it appears that secondary amyloidosis is also rather infrequent.²⁸

It is clear from a review of the causes of secondary amyloidosis in the world that chronic non-infectious systemic inflammatory disorders constitute one of the main causes. This group is composed mainly of two subgroups: (a) rheumatoid arthritis and other collagen diseases and (b) seronegative arthritides, either juvenile or adult type. It has been proposed that BD and FMF should be included in the latter group.^{20 29-32}

The main characteristics of our eight cases of BD associated with amyloidosis were as follows: all were middle aged men, three had BD of juvenile onset, the mean duration of BD in this group was twice as long as that of our total group with BD, all but one had complete type of BD. Genital ulceration, eye

involvement, thrombophlebitis, peripheral arthritis, neuropsychiatric manifestations, and positive skin pathergy test were found to be higher in the patients with amyloidosis. Five patients had massive proteinuria and nephrotic syndrome. Five patients were uraemic and three had hypertension. Amyloid deposits were demonstrated in all by renal biopsy. The potassium permanganate method showed type AA amyloid protein in all. None of our patients had any other associated disease which could cause secondary amyloidosis.

A review of the data available on 24 cases of BD with amyloidosis reported so far in published work, including our series, has shown the characteristics given in Table 4.^{7-12 27 33-40}

Apart from one case from Japan²⁷ and one case from the USA³⁵ the other 22 cases of BD associ-

Folliculitis	Acne	EN	TP		PA	NS	NP	Amyloidosis			Associated disease	Proteinuria	Fever	Diarrhoea
			S and/or D	VC				Necropsy	Biopsy	KMnO ₄				
			-	-	+	+	+	+	-					
+		+	+	+	+	+	+	+	-		Staphylococcal septicaemia	Massive	+	+
+		+	+		+	+	+	-	+(Renal)		Staphylococcal septicaemia	Massive	+	-
			-	-	-	-	-	+	-		Chronic bronchitis	Trace		
			+	+	-	+	+	-	+(Rectal)		Septic leg ulcers	8-15 g/24 h	+	-
+	-	+	+		+	-	+	-	+(Renal)	+	-	1.5 g/l	-	-
-	-	+	+	-	-	-	+	-	+(Renal)	+	-	1.5 g/l	+	-
			+		+			+	+(Rectal)			Massive		
-	-	-	-	-	+	-	-	-	+(Renal)		-	6 g/24 h	-	-
+	-	+	+	-	+	+	-	-	+(Renal)	+	-	7-15 g/l	-	-
			+	+	-	+	+	-	+(Spleen, liver, lymph node)		-	4 g/24 h	-	-
			+	-	+	+	+	-	+(Renal)	+	-	28 g/24 h	-	-
+	+		+		+	+	+	+	-			21 g/24 h	+	-
+	+	-	+	-	+	+	-	-	+(Renal)	+		7 g/l	-	-
+			-	-	-	+	-	-	+(Renal, rectal)	+	Draining lymphadenitis, recurrent otitis	350 mg/m ² /h		
-	-	-	-	+	-	+	-	-	+(Renal)		-	5 g/24 h	-	-
			-	+		-		-	+(Rectal)		-	Trace	-	+
						+		-	+(Duodenal)		Chronic myeloid leukaemia	4 g/24 h	+	+
						+		-	+(Rectal)					
						+		-	+(Rectal)					
+	+	+	+	-	+	-	+	-	+(Renal)	+	-	Trace	-	-
-	-	-	+	-	+	+	-	-	+(Renal)	+	-	4.5 g/l	-	-
-	-	-	+	-	-	+	-	-	+(Renal)	+	-	7-10 g/24 h		
-	-	-	-	-	-	+	-	-	+(Renal)	+	-	3 g/24 h	-	

PA=peripheral arthritis; OA=oral aphthae; GU=genital ulceration; EN=erythema nodosum; TP=thrombophlebitis; SPT=skin pathergy test; S=superficial; D=deep; VC=vena cava; NS=nephrotic syndrome; NP=neuropsychiatric.

ated with amyloidosis came from Mediterranean countries. Of the 24 cases, 12 have been reported from Turkey, of which eight belong to our series. Male preponderance was significantly high (M:F=11:1). In two cases amyloidosis was first observed in childhood. Eight out of 20 cases had BD of juvenile onset.

The prevalence of the following were found to be comparatively high in this group: genital ulceration, eye involvement, thrombophlebitis, peripheral arthritis, neuropsychiatric manifestations, and positive skin pathergy test. A severe course, complete type, and multiple system involvement characterised most of them.

Nephrotic syndrome was observed in 13 out of 24 cases. Massive proteinuria was found in 17 cases and mild proteinuria in five. Renal amyloidosis was demonstrated in 18 out of 24 cases either by biopsy or at necropsy. Although no histopathological data were available about the kidney in six cases, four of them had nephrotic syndrome.

This analysis of 24 cases has shown that amyloidosis occurring with BD is a systemic secondary amyloidosis on the basis of the organ distribution, exclusion of primary amyloidosis in all, and proof of AA amyloidosis by the KMnO₄ method in some cases (Table 4). We and other authors, except Nestor *et al*⁸ and Yurdakul *et al*,⁴⁰ agree that amyloidosis is an intrinsic manifestation of BD.

Colchicine therapy has been found to be helpful in the prevention of experimental amyloidosis and of some cases of human amyloidosis (e.g., FMF).^{41 42} Some cases of both primary and secondary amyloidosis have also benefited from colchicine therapy.⁴³ Colchicine has been used successfully in the treatment of FMF and BD.^{42 44 45} As far as we can ascertain from a study of the published work colchicine has been administered in only one case of BD with amyloidosis.³³ In two of our cases of BD with amyloidosis colchicine has helped to slow down the progression of amyloidosis. We therefore propose that colchicine therapy should be started early and continued as long as possible in cases of BD, not only for the general treatment of the disease but also for the prevention of amyloidosis.

We conclude that patients with BD should be screened for amyloidosis and followed up carefully in case of its possible development. We believe that further detailed studies will show a higher prevalence of amyloidosis in BD.

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