A reappraisal of amyloidosis in Behçet’s syndrome

M. Melikoğlu, M. R. Altiparmak¹, İ. Fresko, R. Tunç, S. Yurdakul, V. Hamuryudan and H. Yazıcı

Departments of Rheumatology and ¹Nephrology, Cerrahpaşa Medical School, University of Istanbul, Istanbul, Turkey

Abstract

Objective. To evaluate the clinical features and outcome of patients with Behçet’s syndrome (BS) and amyloidosis and to assess the associated risk factors.

Method. A chart review was done to determine the frequency of amyloidosis in BS among 4000 patients. Data from 14 BS patients with amyloidosis were compared with data obtained from 718 patients with BS without amyloidosis. Multiple stepwise logistic regression analysis was used to assess the risk factors.

Results. All patients with amyloidosis presented with the nephrotic syndrome or significant proteinuria. The mean time to the onset of amyloidosis was 8.1 yr (range 3–15 yr). The mean duration of follow-up after amyloidosis was 3.4 yr (range 1–11 yr). Seven out of 14 patients were alive at the time of the evaluation.Peripheral and pulmonary arterial involvement and arthritis were associated with amyloidosis ($P < 0.05$).

Conclusion. Amyloidosis in BS is rare and has a 50% mortality rate at 3.4 yr (range 1–11 yr). Peripheral and pulmonary arterial involvement and arthritis seem to be the strongest predictors of amyloidosis in BS.

Key words: Behçet’s syndrome, Amyloidosis.

Behçet’s syndrome (BS) is a multisystem vasculitis with protein manifestations. It is characterized by a heightened state of inflammation, although the factors that initiate and sustain this inflammation are not clear. Secondary amyloidosis [1–4] is known to occur and its reported prevalence has been reported to vary between 0.04 and 3% [1, 4].

We evaluated the clinical features and outcome of BS patients with associated amyloidosis and assessed the risk factors related to its development.

Patients and methods

The multidisciplinary BS out-patient clinic in Cerrahpaşa Medical School in Istanbul, founded in 1977, has about 4000 enrolled patients. A retrospective chart review was done to search for patients with amyloidosis. Fourteen patients who fulfilled the diagnostic criteria of the International Study Group for Behçet’s Disease [5] and who also had amyloidosis were identified. Their clinical features and disease outcome were recorded from the charts. Five of these patients have already been discussed in a previous report [1]. Their outcome data were obtained by telephone if the patient was no longer attending the clinic. Non-attendance was defined as no clinic visits within the previous 3 months. All patients had rectal and/or kidney biopsies and all eventually had significant proteinuria. This was in the nephrotic range ($\geq 3.5$ g/24 h) in 12 of 14 patients. The biopsy specimens were stained with Congo red and the green birefringence of amyloid was sought under polarizing microscopy. The presence of secondary amyloidosis was confirmed by the potassium permanganate method. None of the patients with amyloidosis had any other apparent cause for secondary amyloidosis, such as familial Mediterranean fever or tuberculosis.

The charts of 1000 consecutive BS patients without amyloidosis who were registered at our out-patient clinic between 1988 and 1993 were also reviewed. Information about these 1000 patients was already available in a computer file prepared for a survey of clinical findings for a drug study. Seven hundred and eighteen of these patients had a minimum follow-up period of 3 yr. They constituted the controls, and their clinical features were compared with those of 14 patients with amyloidosis.

Statistical analysis of categorical data was done by the $\chi^2$ test. Multiple stepwise logistic regression analysis was used to evaluate the clinical associates of amyloidosis.
## Results

The demographic and clinical characteristics of the 14 patients are shown in Table 1. Twelve of the patients were male and two were female. The mean age at the onset of BS was 27 yr (range 22–41 yr).

Five of the patients already had kidney involvement when they presented at our clinic. None had been diagnosed as having amyloidosis before his or her presentation. One was a female who presented with acute renal failure with proteinuria due to aminoglycoside use. The others had nephrotic syndrome. In nine of the 14 patients, proteinuria was detected during the follow-up. Proteinuria within the nephrotic range was the initial finding in all except one of the patients. She presented with proteinuria in the non-nephrotic range.

The mean time to the detection of proteinuria after the onset of BS in patients with amyloidosis (n = 14) was 8.1 yr (range 3–15 yr). Amyloidosis was initially suspected in two of the female patients because of proteinuria of <3.5 g/day. Proteinuria was >3.5 g/day in the 12 male patients. The diagnosis of amyloidosis was confirmed by rectal biopsy in 11 patients and renal biopsy in the remaining three.

The mean follow-up time for all 14 patients with amyloidosis, after its onset, was 3.4 yr (range 1–11 yr).

Among the five patients who had amyloidosis at registration, the mean duration of follow-up was 2.9 yr (range 1–9 yr). Two of these five died after 1 yr of follow up. The events leading to death were not clear in these patients, for whom the outcome information was obtained by telephone.

Among the nine patients in whom amyloidosis had its onset after registration in our clinic, the mean duration of follow-up was 3.8 yr (range 1–11 yr). The time to the onset of amyloidosis after the disease onset was 9 yr (range 5–12 yr). Four of these patients died at a mean of 1.5 yr (range 1–2.5 yr) after the onset of amyloidosis. One patient died due to nephritic syndrome and septicemia 1 yr after the diagnosis of amyloidosis. Another developed end-stage renal failure and died after 1 month while undergoing haemodialysis. The specific causes of death were not clear in the remaining two patients, for whom information was obtained by telephone. One patient was lost to follow-up.

Six patients had received no immunosuppressive therapy or colchicine before the onset of amyloidosis. Six patients had received immunosuppressive therapy and two had been treated with both immunosuppressives and colchicine for varying lengths of time because of active involvement of major organs other than the kidneys. Two patients had received colchicine alone. Because of the associated amyloidosis, immunosuppressive therapy was continued in two of these patients even though they were clinically silent apart from the proteinuria. In two patients, immunosuppressive therapy was initiated solely because of the onset of amyloidosis (patients 3 and 7 in Table 1). All patients had been given colchicine after the diagnosis of amyloidosis.

### Table 1: Demographic and clinical characteristics of the patients with BS and amyloidosis

<table>
<thead>
<tr>
<th>Age at onset of BS (yr)</th>
<th>Time to amyloidsis (yr)</th>
<th>Clinical features</th>
<th>Follow up after onset of amyloidosis (yr)</th>
<th>Dead or alive</th>
<th>Renal status</th>
<th>M, male; F, female; ARTH, arthritis; CRF, chronic renal failure; DVT, deep venous thrombosis; EN, eye involvement; GU, genitourinary; HD, haemodialysis; LE, lost to follow-up; OF, ophthalmoplegia; PAA, peripherial arterial aneurysm; PERA, peripherial arterial retraction; PRO, proteinuria in the non-nephrotic range; STERNA, superficial thrombophlebitis; VCI, venous cava inferior syndrome.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>9</td>
<td>Alive</td>
<td>Dead</td>
<td>1.5</td>
<td>M, male</td>
<td>F, female; ARTH, arthritis; CRF, chronic renal failure; DVT, deep venous thrombosis; EN, eye involvement; GU, genitourinary; HD, haemodialysis; LE, lost to follow-up; OF, ophthalmoplegia; PAA, peripherial arterial aneurysm; PERA, peripherial arterial retraction; PRO, proteinuria in the non-nephrotic range; STERNA, superficial thrombophlebitis; VCI, venous cava inferior syndrome.</td>
</tr>
<tr>
<td>1.5</td>
<td>9</td>
<td>Alive</td>
<td>Dead</td>
<td>1.5</td>
<td>M, male</td>
<td>F, female; ARTH, arthritis; CRF, chronic renal failure; DVT, deep venous thrombosis; EN, eye involvement; GU, genitourinary; HD, haemodialysis; LE, lost to follow-up; OF, ophthalmoplegia; PAA, peripherial arterial aneurysm; PERA, peripherial arterial retraction; PRO, proteinuria in the non-nephrotic range; STERNA, superficial thrombophlebitis; VCI, venous cava inferior syndrome.</td>
</tr>
<tr>
<td>1.5</td>
<td>9</td>
<td>Alive</td>
<td>Dead</td>
<td>1.5</td>
<td>M, male</td>
<td>F, female; ARTH, arthritis; CRF, chronic renal failure; DVT, deep venous thrombosis; EN, eye involvement; GU, genitourinary; HD, haemodialysis; LE, lost to follow-up; OF, ophthalmoplegia; PAA, peripherial arterial aneurysm; PERA, peripherial arterial retraction; PRO, proteinuria in the non-nephrotic range; STERNA, superficial thrombophlebitis; VCI, venous cava inferior syndrome.</td>
</tr>
</tbody>
</table>
Seven of the 14 patients with amyloidosis were alive at the time of the evaluation for this study. The mean period of follow-up after the diagnosis of amyloidosis was 5.4 yr (range 1–11 yr). Four patients currently have normal renal function, two have compensated chronic renal failure and one is undergoing haemodialysis.

A comparison of the clinical features of the 14 patients with amyloidosis and the 718 patients without amyloidosis (controls) is given in Table 2. Pulmonary and peripheral arterial involvement, involvement of the vena cava inferior and arthritis were significantly more frequent in the patients with amyloidosis (*P* < 0.05).

We performed a logistic regression analysis after pooling the data for the 718 patients without and the 14 with amyloidosis. In this analysis the main associates of amyloidosis remained the same. Since vena cava inferior disease was always present with pulmonary arterial involvement among patients with amyloidosis, the analysis could not be done independently for either of these complications alone.

### Discussion

Amyloidosis in BS is an important but a relatively rare complication. Despite the retrospective nature of the present study, the frequency of 14/4000 that we report here is probably not far from the actual state of affairs, in that in a previous study [1] we had shown that a positive rectal biopsy for amyloidosis was not found among 99 consecutive BS patients without proteinuria.

As for the clinical manifestations associated with the development of this important complication, only one study [2] reported that the presence of genital ulceration, thrombophlebitis, arthritis, a positive pathergy test, uveitis and neuropsychiatric involvement was more frequent among eight patients with BS and amyloidosis than among patients without amyloidosis. It was concluded that the male sex, prolonged duration of disease and multiple systemic involvement were the main clinical characteristics of patients with amyloidosis. The starting point of that study was an overview of eight patients with BS and amyloidosis, and our findings agree with its main conclusions.

In the present study, the strongest predictors of amyloidosis were peripheral or pulmonary arterial vessel involvement, findings that are also associated with the most prominent acute-phase response in BS [6]. Recurrent arthritis, which is also associated with the acute-phase response [7], was also an independent risk factor, although its effect was not as strong as that of major vessel involvement.

It is difficult to give a definitive statement about the influence of these manifestations on the development of amyloidosis because there were too few patients in our study for a formal statistical analysis. On the other hand, we also had patients with amyloidosis who had only isolated mucocutaneous involvement. Furthermore, we did not find that the disease duration affected the occurrence of amyloidosis. Similarly, others have reported a range of disease duration of 1–10 yr before the development of this complication [2, 4].

Amyloidosis was less frequent among the female patients in our survey, who also had a milder course of BS with proteinuria in the non-nephrotic range. This is consistent with the observation that, in general, the disease runs a more severe course in males [8].

BS with amyloidosis had a mortality rate of around 50% in our survey. The use of immunosuppressives or colchicine before or after the diagnosis of amyloidosis...
did not seem to affect the clinical course of amyloidosis. Indeed, there is no evidence that colchicine prevents and/or improves the clinical manifestations of amyloidosis associated with BS [1], as is the case with other forms of secondary amyloidosis [9].

In conclusion, BS with amyloidosis has a poor outcome, and the effects of the currently available drug regimens on its onset and course remain unclear. Arterial involvement and arthritis seem to be the strongest associates of amyloidosis in BS.

References