Clinical Study on Death in Behcet's Disease

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We were able to identify 7 patients who died of Behcet's disease, among 2,200 patients registered at the Behcet's Disease Specialty Clinic of Severance Hospital from November 1983 to October 1992. Six were male and one female. Age of death was 31 to 55 years with the mean age of 39.1. The age of onset was 24 to 54 years with the mean age of 32.6. The mean duration of illness was 6.5 years. The most frequent initial symptom was oral ulcer, with the most common type being the incomplete type in Shimizu's classification. Positive pathergy tests were found in all the 5 patients in whom the test was performed out of 7 patients. Various modalities of treatments such as oral steroid, colchicine, azathioprine, colectomy, and pacemaker insertion were attempted without outstanding therapeutic effects. The causes of death were gastrointestinal bleeding, bowel perforation, superior and inferior vena cava syndrome, aortic regurgitation, cerebrovascular disease, sepsis, and lung abscess.

Key Words: Behcet's disease, Mortality

INTRODUCTION

Behcet's disease occurs worldwide with the incidence particularly high in the Middle East, the Mediterranean coastal region, and Far Eastern countries like Korea, Japan and China (O'Duffy JD, 1981). Behcet's disease is a multifaceted syndrome characterized by oral and genital ulcerations and ocular abnormalities including keratitis, optic neuritis, and uveitis. The disease has multiple systemic associations that include involvement of the gastrointestinal, cardiovascular, and central nervous systems as well as the joints, blood vessels, and lungs. Therefore, the disease may evolve to serious multisystemic illness, potentially resulting in death. Even though the case fatality rate of the disease has been reported to be 3 to 6 percent, no previous studies have addressed the issue of the clinical characteristics of the patients during the course of their illness until the time of death by Behcet's disease. The authors have made such an effort on seven patients who died of

Behcet's disease along with a review of the pertinent literature. In this study, we attempted to delineate the patterns or modes of illness by analyzing tentative clinical features from the initial phase to the times of their deaths.

MATERIALS AND METHODS

From November 1983 to October 1992, among 2,200 patients registered at the Behcet's Disease Specialty Clinic of Severance Hospital, 7 patients had been regularly followed from the initial phase of their disease until around the time of their deaths. We classified the patients according to the classification by Shimizu (Shimizu et al, 1974). Major diagnostic criteria included oral ulceration, genital ulceration, eye lesions and skin lesions while minor diagnostic criteria were arthritic, neurologic, gastrointestinal, and vascular symptoms.

The medical records of the patients were reviewed in order to investigate their personal and clinical characteristics, treatments instituted for the disease processes, responses to the treatments, histopathologic findings, and causes of eventual deaths.

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RESULTS

Classification

According to the Shimizu's classification, the proportion of the different clinical types in the 7 patients were incomplete 3, complete 2, and possible 2 cases respectively (Table 1).

Age and Sex distribution

Six were male and 1 was female. Disease onset occurred most often during the thirties with a mean age of 32.6 years. The range of the age of death was from 31 to 55 with a mean 39.1 years (Table 1).

Duration of illness

The range of duration of illness in 7 cases was 0.5 to 12 years, with a mean of 6.5 years (Table 1).

Duration of treatment following the diagnosis

The duration of treatment in 7 cases of Behcet's disease was 0.1 to 4 years, with a mean duration of 1.4 years.

Major and minor symptoms

Oral ulcer was the most frequent initial symptom in 5 patients, but eventually all seven patients developed oral ulcer. Genital ulcers and skin lesions occurred in 5 patients (71.4%), articular symptoms, gastrointestinal symptoms, and neurologic symptoms in 4 patients (57.1%), thrombophlebitis in 3 patients (42.9%), and ocular symptoms in 2 patients (28.6%) respectively (Table 2).

Pathergy test

Pathergy test was performed in 5 out of 7 patients. The positive test, defined as the development of a papular or pustular lesion 24-28 hours after a needle stick puncture over the skin of the forearm, was found in all 5 patients (Table 2).

Therapeutic responses

Oral prednisolone, colchicine, zinc sulfate, azathioprine, and cyclophosphamide were used as medical treatments. Hemicolectomy and total colectomy as surgical treatments were performed to treat gastrointestinal bleeding in 2 patients. The effects of medical and surgical treatment were as follows; 3 patients partially improved with medical treatment, 3 patients did not improve with medical and surgical treatment, 1 patient remained stationary with medical treatment (Table 3).

Pathologic findings

Extracutaneous surgical pathologic examinations were available in 3 patients who received surgical treatment. The findings are summarized in Table 4.

Causes of death

Among seven patients, 5 died of extracutaneous organ involvements from Behcet's disease; two gastrointestinal tract, two cardiovascular systems and one brain. In two patients, the causes of death were most likely related to immune suppression secondary to medical therapy. Table 5 summarizes individual causes of death.

Table 1. Clinical information on 7 mortality cases with Behcet's disease

Case	Sex	Age of onset (yr)	Age of death (yr)	Duration of illness (yr)	Clinical Type*	Initial major symptom**
1	M	54	55	0.5	P	O
2	M	33	36	3	P	O
3	M	24	32	8	I	O
4	F	26	38	12	I	G
5	M	33	44	11	C	O
6	M	33	38	5	I	G
7	M	25	31	6	C	O

* Clinical types were classified by Shimizu:

P (possible): 1 major symptom

I (incomplete): 3 major symptoms or ocular and 1 major symptom

C (complete): 4 major symptoms

**O; Oral aphthae, G; Genital ulcer

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Table 2. Clinical findings in 7 patients with Behcet's disease

Clinical findings	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Oral aphthae	+	+	+	+	+	+	+
Genital ulcer	-	-	+	+	+	+	+
Skin lesions	-	-	+	+	+	+	+
Ocular lesions	-	-	-	-	+	-	+
Arthralgia	+	-	+	-	+	+	-
Abdominal pain	-	+	-	-	-	+	+
Diarrhea	-	+	-	-	-	+	+
Hematochezia	+	+	+	-	-	-	+
Fever	+	+	+	-	-	-	+
Headache	-	-	+	+	-	+	+
Thrombophlebitis	-	-	+	+	-	-	+
Dyspnea	-	-	+	+	-	-	+
Pathergy test	*	*	+	+	+	+	+

+ : present - : absent * : not tested

Table 3. Therapeutic responses in 6 cases of Behcet's disease

Case	Therapy	Duration of Treatment (years)	Response
1	Prednisolone, Colchicine, Zinc sulfate, Left hemicolectomy, Ileocecal resection	0.5	Not improved
2	Prednisolone, Colchicine, Zinc sulfate, Total colectomy, Ileo-sigmoid colostomy	0.2	Not improved
3	Prednisolone, Dipyridamole, Coumadin	4	Partially improved
4	Coumadin, Captopril, Permanent pacemaker insertion	1	Partially improved
5	Prednisolone, Colchicine, Zinc sulfate	1	Stationary
6	Prednisolone, Colchicine, Zinc sulfate *Azathioprine	2.5	Partially improved
7	Prednisolone, **Cyclophosphamide	0.4	Not improved

* Administered for 28 days (120mg/day)

**Administered for 106 days (150mg/day)

Table 4. Summary of pathologic findings

Case	Biopsy site	Pathologic findings
1	Colon, left	Ulceration with chronic nonspecific inflammation, decreased numbers of goblet cells and intracryptal exudate
2	Terminal ileum & cecum	Ulceration with massive infiltration of atypical lymphoid cells dissecting and destroying muscle layers and encroaching upon the blood vessels and nerves up to the level of serosal fat
3	Aortic valve & wall	Fibrous thickening with mild chronic inflammation

Table 5. Possible causes of death in the 7 cases with Behcet's disease

Case	Cause of death
1	Intestinal bleeding
2	Intestinal perforation
3	SVC & IVC syndrome
4	Valvular heart disease (Aortic regurgitation)
5	Cerebrovascular disease
6	Sepsis
7	Lung abscess

SVC: Superior vena cava

IVC: Inferior vena cava

COMMENT

The diagnosis of Behcet's disease primarily depends on the patient's history and clinical findings, because of the lack of a pathognomonic laboratory test specific enough to confirm the suspicious cases (Callen, 1981). The clinical course of the disease is varied even in an early stage, making it difficult to determine the patient's long term prognosis. In general, male and a younger age of onset seem to contribute separately to a more severe clinical course of Behcet's disease (Yazici et al, 1984). It is known that men with ocular involvement have a poorer prognosis than women (Choi et al, 1991). Young-age patients with ocular involvement were also reported to have poor outcome (Shimizu et al, 1979). Although poor-prognostic factors have been less than clearly defined, involvements of central nervous system (CNS), artery or vein, and gastrointestinal perforation are believed to be associated with poor prognosis (Wong et al, 1984).

This study investigated the clinical characteristics and causes of death in the mortality cases in whom Behcet's disease led to their deaths. We hoped that identification of certain clinical features in these mortality cases could lead to improve therapeutic outcome and to provide a prognostic assessment in the management of Behcet's disease.

From November 1983 to October 1992, among 2,200 patients registered at the Behcet's Disease Specialty Clinic of Severance Hospital, 7 patients had been regularly followed from the initial phase of their disease until around the time of their deaths. This death rate is lower than previously reported. In Japan, the death rate of Behcet's disease was 0.86 percent with 218 recorded deaths (Maeda and Nakae, 1979). Our lower death rate may be attributed to relatively insuffi-

cient public awareness of the disease as a cause of death as well as different cultural attitudes in confirmation of the caused of death such as a very low autopsy rate.

In Korea, the incidence of Behcet's disease in women has been reported to be higher than in men (Eun et al, 1984; Cho et al, 1988). In our study, the mortality cases in men outnumbered those in women. This probably reflects the fact that the prognosis in men is poorer than in women. Consistent with this finding is the more common occurrence of vascular, CNS, or gastrointestinal involvements in men, that are believed to be associated with a poor prognosis. Maeda et al reported the rate of death from Behcet's disease in men to be about twice that in women (Maeda and Nakae, 1979).

The most common age of onset of the disease in this study was in the thirties, while the twenties has been reported by others (Chajek and Fairaru, 1975; Kim et al, 1988; Cho et al, 1988). The mean age at death in our study was 39.1 years, younger than the 45.2 years reported by Maeda et al (Maeda and Nakae, 1979).

The mean disease duration in our cases was 6.5 years. This is quite in contrast to the fact that overall Behcet's disease has a longer period of illness including at least 4.5 years of stable or improving course, as suggested by Yazici et al (Yazici et al, 1974). With these data, we speculate that a large portion of mortalities from Behcet's disease occur in the early or middle stages, while death in the late stages would be less common. Our expired patients apparently had received treatment for a period considerably shorter than usual, implying that the treatment might have been delayed until multisystemic involvement.

The point of interest is the increased reactivity of the skin to scratches or intracutaneous needle punctures following which a self healing sterile pustule appears (Shimizu et al, 1979). This phenomenon, unique to Behcet's disease, is called "pathergy" and occurs in a certain fraction of patients with Behcet's disease. Therefore, the pathergy test is a valuable adjunctive test in the diagnosis of Behcet's disease (Sobel et al, 1973). The positive pathergy test, as defined by the development of a papular or pustular lesion 24-28 hr after a needle stick puncture, is reported to be as high as 88% of patients (Tuzun et al, 1979). However, it is interesting to note that positive pathergy tests tend to be lower in Korea where only 39.6 percent (Yoon et al, 1987) or the highest 47.3 percent (Eun et al, 1984) were reported. In this study, the positivity of the pathergy test in the expired patients who were tested was 100 percent, higher than these two values. Therefore,

this indicates that the positive pathergy test may be utilized as one of the tentative predictors in assessing poor outcome in this country.

Multiple therapeutic modalities have been employed for Behcet's disease. However, any definite statement in regard to therapy would be far from satisfactory, especially because the number of cases in this study is so small. Most of the expired patients showed no clinical improvement despite vigorous treatment. They had already showed manifestations of gastrointestinal, cardiovascular or central nervous system. It can be said that once the disease involves any of these systems, no current mode of management for the disease may be effective, and thus prognosis would be poor. The patients in our study who died of sepsis and lung abscess might have developed infection secondary to immunosuppressive therapy employed to treat such systemic illness. One patient in the study interestingly developed aortic regurgitation as an extracutaneous involvement of Behcet's disease, which is rare in the literature. It remains to be seen, however, whether the disease may have to be considered as a rare cause of aortic regurgitation.

It appears that early diagnosis and prompt treatment of the disease and prudent patient follow-up would lead to improvement of therapeutic outcome in Behcet's disease. This is much to be hoped for in a country like Korea where public or even physician's awareness of the disease has been surprisingly low notwithstanding the high incidence of the disease. In addition, autopsy of our patients, had it been possible, could have provided us with more insight into the causes of their deaths. As in the understanding of the etiology and pathophysiology of the disease, tissue examination of the patients with the disease would be of particular importance in unfolding the mystery still surrounding Behcet's disease.

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