The long-term clinical course of oral ulcers of Behçet's disease

Takafumi Tomizuka 1, Hirotoshi Kikuchi 1, Mai Okubo 1, Kurumi Asako 1, Satoshi Miyata 2, Hajime Kono 1

1 Department of Internal Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8655, Japan
2 Teikyo University Graduate School of Public Health, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8655, Japan

INTRODUCTION

Behçet's disease (BD) is a syndrome of unknown aetiology characterised by four main involvements, namely oral ulcers (OUs), cutaneous involvements, genital ulcers, and ocular involvements. However, the long-term clinical course of BD involvements, including OUs, has not been documented, and the prognostic factors involved in remission require further clarification. In this study, we first proposed remission criteria for the characteristic manifestations of BD (Table 1.). In addition, we constructed a database of detailed clinical information of patients with BD and elucidated the natural history of each clinical BD involvement. For OUs, in particular, we retrospectively examined the various factors involved in their remission.

Table 1. Proposed remission criteria of each involvement of Behçet's disease

Remission is defined as the following conditions that have continued for more than one year

Oral Ulcers	Disappearance
Ocular involvements	Disappearance of uveitis (iridocyclitis and retinal choroiditis). Patients receiving sub-tenon or subconjunctival corticosteroid injections are excluded from remission
Cutaneous involvements	Disappearance of skin symptoms (erythema nodosum-like rash, folliculitis-like rash, superficial thrombophlebitis)
Genital ulcers	Disappearance
Epididymitis	Disappearance
Arthritis	Disappearance
ANB	No meningoencephalitis-like symptoms with fever or headache, and no local signs in the brain, such as hemiplegia and cranial nerve palsy
CPNB	No progression of neuropsychiatric symptoms, including dementia symptoms, and no progression of brainstem atrophy seen on radiology.
Vascular involvements	No morphological changes in aneurysm or arterial stenosis and no exacerbation of deep vein thrombosis.
Intestinal involvements	No abdominal pain, diarrhoea, bloody stools, or ulcers as endoscopic findings.

ANB, acute neuro-Behçet's disease; CPNB, chronic progressive neuro-Behçet's disease

METHODS

We retrospectively studied 155 patients with BD who visited our hospital between 1989 and 2020. We defined remission criteria for each manifestation and examined the changes in the long-term clinical course. Furthermore, classification and regression trees (CART) and multivariable analyses were performed to investigate the prognostic factors of OU; hazard ratios were used to assign scores to prognostic factors deemed significant (OU prognosis score: OuP score).

RESULTS

OUs appeared earliest, with the slowest decline in prevalence observed post-BD diagnosis（Figure1., 2.）. OU presence was the most common factor inhibiting complete remission. Young age at OU onset, never smoker, presence of genital ulcers, positive pathergy test, no usage of tumour necrosis factor inhibitors or of immunosuppressants, and long-term non-treatment or symptomatic treatment for OUs were poor OU prognostic factors（Table 2.）. Results of stratifying the OuP score of OU into four stages with CART analysis (Figure 3). A higher OuP score indicates ease of OU remission, and a lower score indicates difficulty in remission.
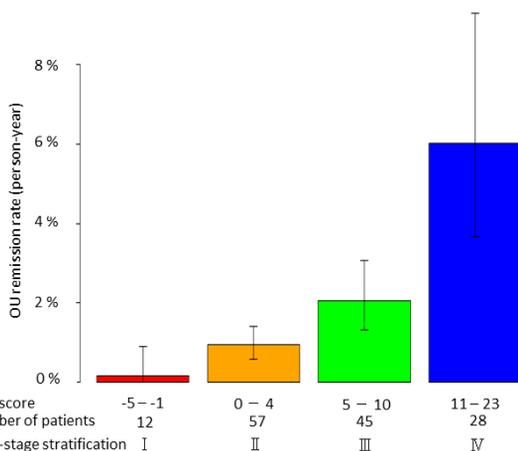
CONCLUSIONS

Remission criteria for each symptom clarified that OU had the greatest impact on complete BD remission. Faster OU remission was associated with earlier OU therapeutic intervention other than symptomatic treatment.
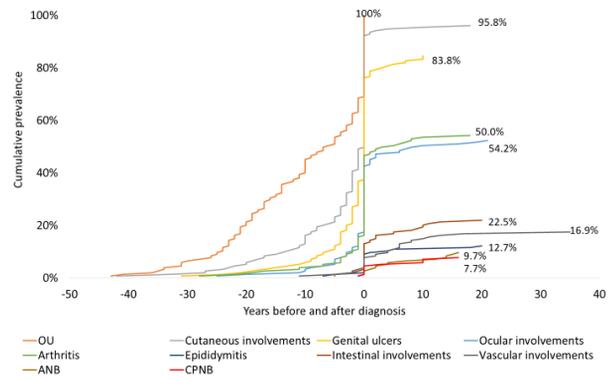
Figure 3. Prediction of OU remission according to the OuP score

Results of stratifying the OuP score of OU into four stages with CART analysis. A higher OuP score indicates ease of OU remission, and a lower score indicates difficulty in remission.
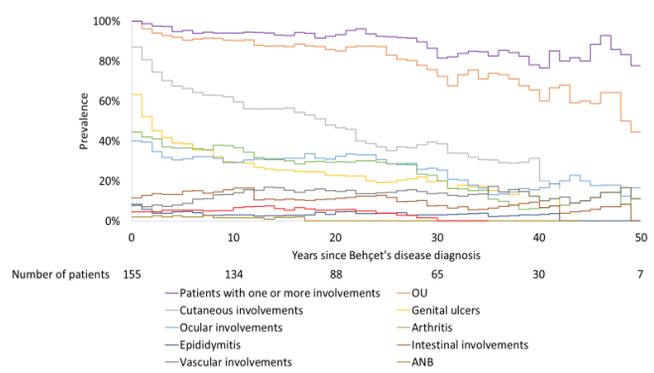OU, oral ulcer; OuP score, oral ulcer prognosis score; CART, classification and regression trees

OuP score	-5 – -1	0 – 4	5 – 10	11 – 23
Number of patients	12	57	45	28
Four-stage stratification	I	II	III	IV

Figure 1. Accumulation curve of each involvement of Behçet's disease relative to diagnosis

Year 0 shows the point of diagnosis of Behçet's disease. The incidence rate of oral ulcers at the time of BD diagnosis is 100%. The increase in incidence rate in negative years indicates that each involvement has already emerged before diagnosis, and an increase after year 0 indicates involvements emerging after the diagnosis of BD. OU, oral ulcer; ANB, acute neuro-Behçet's disease; CPNB, chronic progressive neuro-Behçet's disease

Figure 2. Prevalence of each involvement of Behçet's disease after diagnosis

Number of patients	155	134	88	65	30	7

The vertical axis shows the prevalence in observed cases at that point in time, and the horizontal axis shows the number of years after the BD diagnosis. This prevalence decreases when patients with each involvement reach remission or when the observation period of patients without remission of the involvement by that point ends. OU, oral ulcer; ANB, acute neuro-Behçet's disease; CPNB, chronic progressive neuro-Behçet's disease

Table 2. Results of Cox proportional hazard regression and variable selection and OU prognosis score

Variables	Univariable analysis				Multivariable analysis variable selection (AIC)				OuP score
	HR	95%CI Lower	Upper	p-value	HR	95%CI Lower	Upper	p-value	
Age at OU onset (20.5–44.5 years)	4.08	2.26	7.36	0.000	2.94	1.51	5.72	0.002	3
Age at OU onset (≥44.5 years)	19.97	7.69	51.86	0.000	9.94	3.43	28.8	0.000	10
Past smoker	1.43	0.82	2.49	0.212	1.80	0.99	3.29	0.055	2
Current smoker	2.07	1.10	3.89	0.024	3.13	1.57	6.24	0.001	3
Genital ulcers	0.44	0.24	0.83	0.011	0.49	0.24	1.01	0.053	-2
Pathergy test positive	0.48	0.28	0.84	0.009	0.38	0.20	0.72	0.003	-3
Usage of TNF inhibitors	2.31	1.24	4.30	0.008	2.28	1.12	4.62	0.022	2
Usage of immunosuppressants other than GCs and TNF inhibitors	1.69	1.02	2.78	0.040	1.63	0.94	2.84	0.081	2
Untreated period of OU (1.5–19.5 years)	2.44	1.15	5.17	0.020	3.02	1.34	6.77	0.008	3
Untreated period of OU (<1.5 years)	6.92	3.18	15.05	0.000	6.13	2.58	14.58	0.000	6

The optimal combination of covariates was selected according to a stepwise backward elimination procedure, which achieved the minimum Akaike's information criterion (AIC). A higher hazard ratio indicates ease of remission. Items of the OU Prognosis score (OuP score) are integer-converted forms of hazard ratios of items that were found to be significant in the multivariable analysis.