

High incidence of malignancy in SAPHO syndrome

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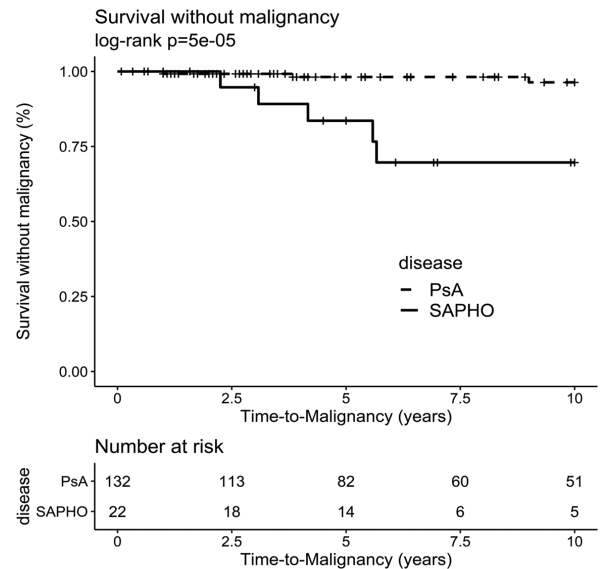
SAPHO syndrome is a rare disease with chronic inflammatory osteoarticular symptoms and dermatological lesions. SAPHO syndrome is sometimes regarded as one of the spondyloarthropathies (1).

Only a few case studies have reported SAPHO syndrome patients with simultaneous or subsequent malignancy (2-4). To clarify the relationship between SAPHO syndrome and subsequent malignancy, we compared the cumulative malignancy rate of SAPHO syndrome with that of psoriatic arthritis (PsA), one of the spondyloarthropathies. This study was approved by the ethics committee of the University of Tokyo (no. 2431 and 11592). We retrospectively examined 22 patients with SAPHO syndrome diagnosed in or outside of our hospital from January 2000 to June 2017. All patients met the inclusion criteria of Benhamou *et al.* (5). 132 patients with PsA from TOSPAR (Todai Spondyloarthritis Registry) were compared as disease controls. As a result, 6 patients developed malignancies after the onset of SAPHO syndrome (27.3%). No significant differences were observed in clinical characteristics (Supplementary Table S1).

Since the average observation period of both SAPHO syndrome and PsA patients was approximately 10 years, we compared the cumulative malignancy-free rate for 10 years after the onset of SAPHO syndrome or PsA (Fig. 1). The malignancy rate among SAPHO syndrome patients was significantly higher than that of PsA patients (log rank $p=5e-05$); this was confirmed by univariate Cox proportional hazards regression modeling (hazard ratio [HR], 6.70; 95% confidence interval [CI], 2.227–20.13; $p=0.00071$). SAPHO syndrome was identified as an independent risk factor for malignancy even after adjusting for onset age of SAPHO syndrome or PsA as covariate (Suppl. Fig. S1; adjusted HR, 5.97; 95% CI, 1.76–20.22; $p=0.0041$). In addition, while the cumulative incidence of malignancy of 50-year-old people in Japan in the next 10 years is 5% for males and 6% for females (6), the incidence of malignancy in this study was much higher (27.3%). Therefore, it is unlikely that the association between SAPHO syndrome and malignancy is fully explained by any confounding by age. Comparing the characteristics of the SAPHO syndrome patients with or without malignancy, a history of allergy was significantly more frequent among patients without malignancy compared with patients with malignancy (20.0% vs. 90.0%; $p=0.017$; Suppl. Table S2). Similarly, SAPHO syndrome patients without a history of allergy had a higher rate of malignancy than those with an allergy history (80.0% vs. 10.0%; $p=0.017$). Except for the age at the onset, no other significant differences in clinical fea-

Fig. 1. Cumulative malignancy-free rate for patients with SAPHO syndrome and PsA.

Kaplan-Meier plot of cumulative malignancy-free rate. At 10 years after disease onset, patients in the SAPHO syndrome group had a higher malignancy rate than those in the psoriatic arthritis (PsA) group.



tures were observed based on the presence of malignancy (Suppl. Table S2, S3). An unknown allergic mechanism may therefore be involved in SAPHO syndrome.

It is uncertain why patients with SAPHO syndrome are more likely to develop malignancy than those with PsA. One possible hypothesis is that chronic inflammation caused by SAPHO syndrome could induce carcinogenesis. The P2X7-interleukin (IL)-1 β axis is reported to be dysregulated in SAPHO syndrome, providing the rationale for the use of IL-1 inhibitors for treatment (7). Inflammation in the tumour microenvironment mediated by IL-1 β has been hypothesised to play a major role in cancer invasiveness, progression, and metastasis (8). Another hypothesis is that the malignancy itself or its treatment including BCG injection could trigger SAPHO syndrome (2, 9). This report is the first retrospective study to statistically demonstrate a risk of malignancy after the onset of SAPHO syndrome. Although our observation is based on a limited number of participants due to the rarity of SAPHO syndrome, our data suggests the possibility that SAPHO syndrome is a heterogenous disease, with subgroups of patients developing allergy or subsequent malignancy.

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