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Impact of Diabetes on Patient Outcomes in Breast Cancer Patients

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Keywords

Breast cancer · Diabetes · Prognosis · Glycemic control · Insulin resistance

Abstract

Background: Diabetes and the etiology of breast cancer are clearly associated. However, the impact of diabetes on prognosis is not yet understood. Therefore, we conducted a retrospective cohort study to examine the relationship between diabetes and patient outcomes in breast cancer patients. ***Methods:*** We investigated 332 Japanese women with breast cancer who underwent curative surgery at our hospital. Patients without sufficient clinical information including hemoglobin A1c (HbA1c) and those with an observation period of less than 1 year were excluded. ***Results:*** Among the patients examined, 106 had diabetes at the time of their breast cancer diagnosis. Among the 296 patients with invasive breast carcinoma, 36 patients developed distant metastases during the mean observation period of 45 months. Sixteen patients died due to breast cancer, while 13 died of other causes. Multivariate analysis revealed that diabetes, tumor size, and estrogen receptor (ER) status were independent factors related to distant metastasis-free survival (DMFS) ($p = 0.038$, $p < 0.001$, and $p = 0.006$, respectively). Kaplan-Meier curve analysis revealed that diabetes negatively affected the outcomes of ER-negative breast cancer patients both in DMFS and overall survival ($p = 0.045$ and $p = 0.029$, respectively). Meanwhile, patient outcomes did not differ according to the level of HbA1c in diabetes patients. ***Conclusion:*** Patients with diabetes had a significantly shorter DMFS, and the negative effect of diabetes on patient outcomes was more evident in ER-negative breast cancer. Our data indicates the importance of primary prevention of diabetes for breast cancer patients.

Introduction

The number of breast cancer patients has been increasing all over the world and the mortality rate is still on the rise [1]. Diabetes is a risk factor for developing breast cancer or other types of cancer [2, 3]. Meta-analyses indicate that patients with diabetes tend to develop breast cancer, particularly postmenopausal women [4, 5].

The activation of insulin and insulin-like growth factor (IGF) is the supposed mechanism of how diabetes triggers breast cancer development [6]. In other words, insulin hypersecretion and IGF production caused by increased insulin resistance may play a role in carcinogenesis in diabetes patients. IGF-1 promotes the proliferation of breast epithelial cells and the risk of breast cancer increased when the serum level of IGF-1 was high and IGF-binding protein 3 as well as IGF-1 regulator were low [7]. Since estrogen regulates IGF-1 and IGF-binding protein 3, these factors are considered risk factors for breast cancer in premenopausal women [8]. Moreover, insulin might promote carcinogenesis by upregulating insulin receptors in epithelial cells in the breast [9]. Metformin, an oral medication for diabetes, may reduce the risk of estrogen receptor (ER)-positive breast cancer, suggesting that diabetes involves breast cancer development [3].

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Table 1. Clinicopathological factors according to diabetes status

	Diabetes	Control	*p* value
N	106	216	
Age, mean (range)	67.6 (28–89)	61.5 (30–89)	<0.001
BMI, mean (range)	26.8 (17.3–45.1)	23.8 (16.1–35.3)	<0.001
HbA1c			
>7%	46	0	
≤7%	60	216	
Tumor size			
pTis	8	18	0.844*
pT1–2	80	181	0.040**
pT3–4	16	17	
Lymph node metastasis			
Yes	43	66	0.074
No	63	150	
ER			
Positive	85	158	0.176
Negative	14	41	
Unknown	7	17	
PgR			
Positive	71	137	0.611
Negative	28	62	
Unknown	7	17	
HER2			
Positive	14	28	0.974
Negative	85	172	
Unknown	7	16	
Administration of chemotherapy			
Yes	45	71	0.092
No	61	145	

BMI, body mass index; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2. * pTis versus pT1–4. ** pT1–2 versus pT3–4.

While the association between diabetes and the etiology of breast cancer has been investigated in a number of studies, how diabetes affects the prognosis of breast cancer patients is relatively poorly understood. In a meta-analysis by Zhao et al. [10] and another cohort study of Asians including other cancers [11], patient survival was poor in those with diabetes. In contrast, other reports have indicated no difference in breast cancer-related deaths between patients with and without diabetes [12, 13]. Therefore, we conducted a retrospective cohort study to reveal the impact of diabetes on the outcomes of patients with breast cancer.

Patients and Methods

Patient Selection

We retrospectively investigated breast cancer patients who underwent curative surgery at Asahi General Hospital between 2006 and 2018. Patient selection criteria are shown in online supplementary Figure 1 (see www.karger.com/doi/10.1159/000524513 for all online suppl. material). We analyzed their hemoglobin A1c (HbA1c) levels assessed at the time of breast cancer diagnosis, within 6 months prior to the start of treatment. The decision to measure HbA1c was made by the attending physicians. Such data were available for 322 patients, all of whom were Japanese women. Patients with an observation period of less than 1 year and those with stage IV breast cancer were excluded. Patients were offered standard systemic adjuvant treatments for breast cancer. However, patients who did not receive recommended treatments for reasons such as patient refusal or general condition were not excluded in the current study as this was a retrospective observational study. Similarly, whether or not they received adequate treatment for diabetes varied among patients. We defined a body mass index (BMI) over 30 as high and HbA1c values greater than 7.0% as high. This study was carried out with approval from the Ethics Committee of Asahi Chuo Hospital (no. 2019071612), and all data were collected after obtaining written informed consent from the patients.

Statistical Analysis

Statistical analyses were performed using JMP 11.2.1 statistical software (SAS Institute Inc., Cary, NC). Associations between clinicopathological parameters and the presence of diabetes were evaluated using Pearson's χ^2 test. For comparisons of mean values, unpaired data were examined with the two-sided Student's *t* test. A Cox proportional hazards model was constructed in an attempt to discover factors related to distant metastasis-free survival (DMFS) and overall survival (OS). Being a continuous variable, a mean age of 63 was employed as a cut-off value for distinguishing between high and low. For the full-model analysis, we first selected variables according to their clinical significance. We chose age, BMI, the presence of diabetes, tumor size, lymph node metastasis, ER, human epidermal growth factor receptor 2, and administration of chemotherapy. Kaplan-Meier curves were estimated and the log-rank test was applied for comparisons of the survival distributions of the two populations. A *p* value below 0.05 was considered a statistically significant difference.

Results

Diabetes and Other Factors

Of the 322 patients, 106 (33%) had diabetes. Among the patients with diabetes, therapeutic drugs for diabetes were given in 80 cases and insulin therapy had been introduced in 20. A comparison of clinicopathological factors according to the presence of diabetes is shown in Table 1. Patients with diabetes were significantly older and had a higher BMI and larger tumors. There was no difference in the nature of the tumor, such as ER status, or administration of adjuvant chemotherapy.

Clinicopathological Features Relating to Patient Outcomes

Next, to evaluate the risk of developing distant metastasis of breast cancer, we further analyzed 296 patients with invasive breast carcinoma. During the mean observation period of 45 months (range: 2–147), 36 pa-

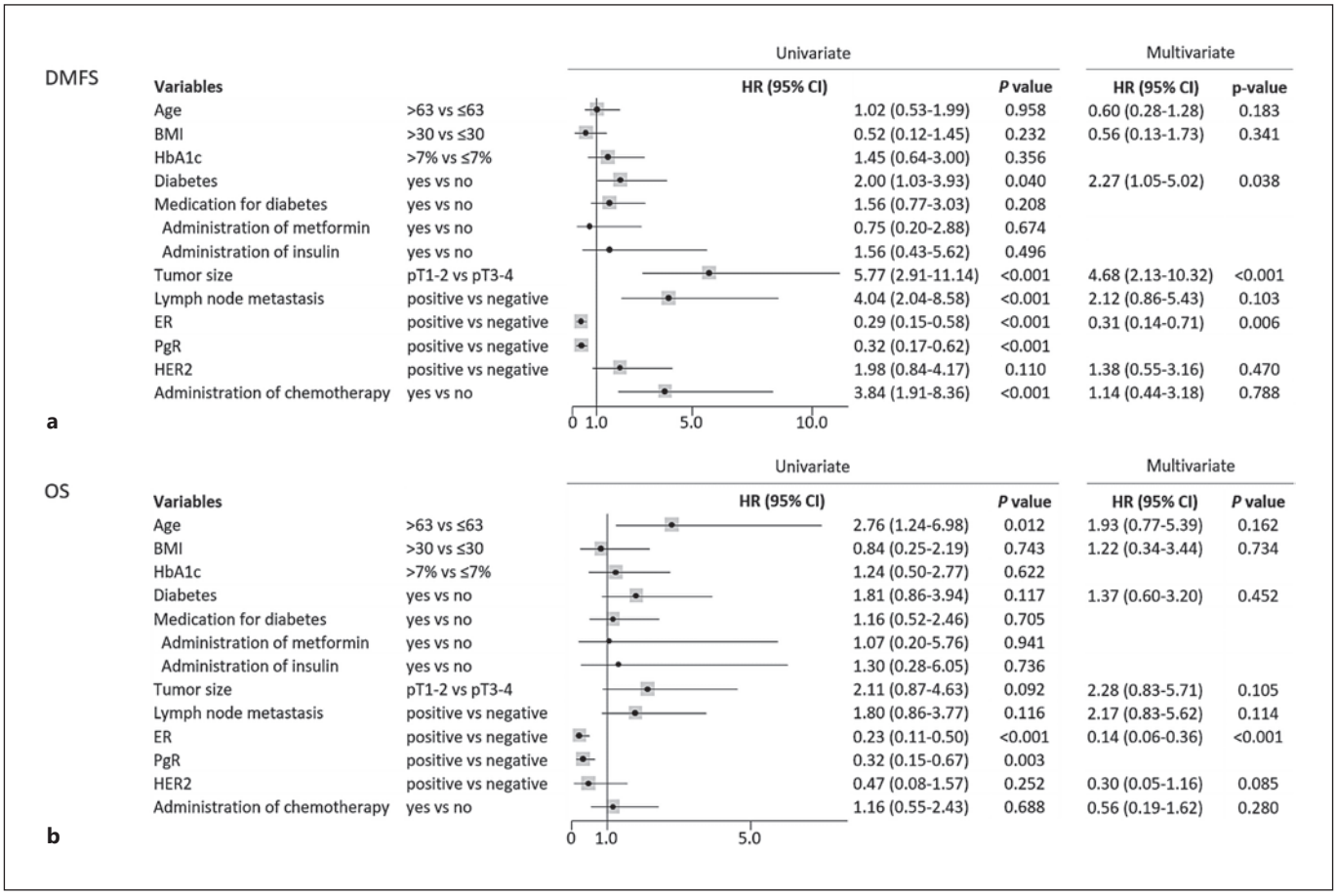

Fig. 1. Association between clinicopathological features and patient outcomes. Factors relating with DMFS (**a**) and OS (**b**) were analyzed employing the Cox proportional hazards model. Forest plots are also shown for HRs in the univariate analysis. BMI, body mass index; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; CI, confidence interval.

tients (12%) developed distant metastasis. Among the 36 patients, 16 (5%) died due to breast cancer. Thirteen patients died of other causes: other cancers in 5 cases, infectious disease in seven, and myocardial infarction in one.

We examined factors relating to DMFS employing the Cox proportional hazards model and found that diabetes ($p = 0.040$), tumor size ($p < 0.001$), lymph node involvement ($p < 0.001$), ER status ($p < 0.001$), progesterone receptor status ($p < 0.001$) and administration of chemotherapy ($p < 0.001$) were significantly associated in univariate analyses (Fig. 1a). In a multivariate analysis, diabetes, large tumor size, and negative ER status remained as independent factors related to shorter DMFS ($p = 0.038$, $p < 0.001$, and $p = 0.006$, respectively). Age ($p = 0.012$), ER status ($p < 0.001$) and progesterone receptor status ($p = 0.003$) were significantly associated with OS in univariate analyses (Fig. 1b). In a multivariate analysis, only ER status ($p < 0.001$) remained as an independent factor among the variables examined.

Next, we drew Kaplan-Meier curves of DMFS and OS according to diabetes status (Fig. 2). Consistent with the aforementioned univariate analysis, the log-rank test revealed that patients with diabetes had significantly shorter DMFS ($p = 0.036$) but not OS ($p = 0.115$). Since ER status was also an independent factor for DMFS and OS, we further divided these results by ER status. Consequently, the presence of diabetes strongly affected the outcomes of ER-negative breast cancer patients; both DMFS and OS were significantly shorter ($p = 0.045$ and $p = 0.029$, respectively), while there were no statistical differences in ER-positive patients.

Diabetes Control and Patient Outcomes

Finally, we focused on the level of HbA1c as a marker reflecting the control status of diabetes. We assessed HbA1c at the time of breast cancer diagnosis. When DMFS and OS were compared between the HbA1c-high and -low groups in diabetes patients ($n = 98$), there were no significant differences (Fig. 3) and the trend remained even after dividing by ER status (online suppl. Fig. 2).

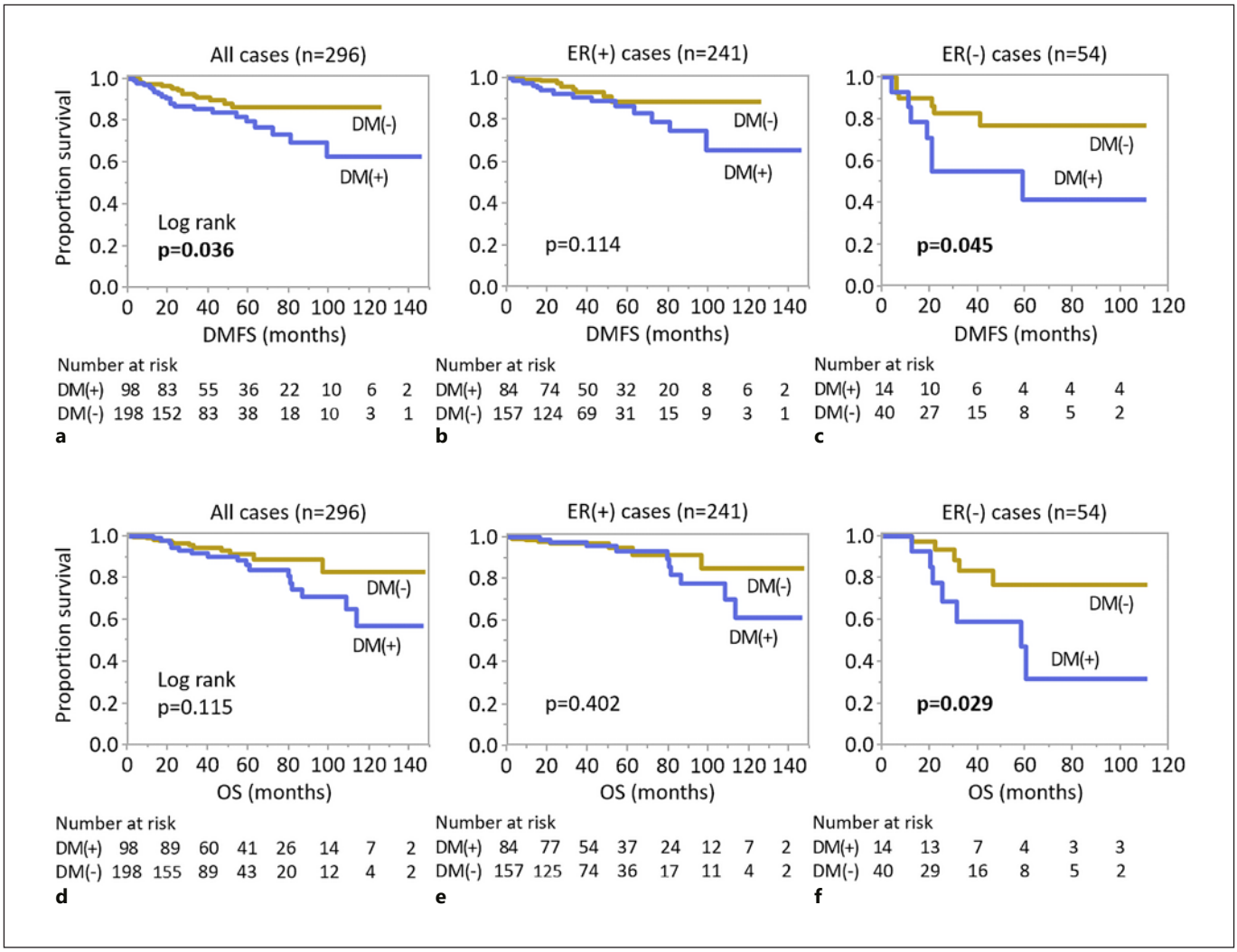

Fig. 2. Kaplan-Meier curves of 296 patients with invasive breast cancer according to diabetes status. Kaplan-Meier curves of DMFS (**a–c**) and OS (**d–f**) according to diabetes. The blue curve indicates patients with diabetes, and the brown curve indicates those without diabetes. Data are shown for all patients (**a**, **d**), ER-positive patients (**b**, **e**), and ER-negative patients (**c**, **f**), respectively.

Discussion

In the present study, the presence of diabetes was an independent factor associated with DMFS, while no correlation was found between diabetes and OS. One reason for observing no difference in OS might be that patients with diabetes had relatively more comorbidities and some died due to causes other than breast cancer. Indeed, our cohort included some deaths due to gastrointestinal perforation, infectious disease, and other cancers. Furthermore, when we divided patients according to ER status, diabetes was a poor prognostic factor only for those with ER-negative breast cancer. An ER-negative tumor itself is a poor prognostic factor, and insulin resistance, for instance, as described below, may contribute more to breast cancer progression in such high-risk patients.

In contrast, we also posit that treatment for diabetes may somewhat regulate the progression of ER-positive breast cancer. Metformin, frequently used in treatments for diabetes, increases the expression of hormone receptors [14, 15]. In addition, metformin reportedly enhances the effects of hormone therapy through induction of apoptosis and other mechanisms [16, 17]. Sonnenblick et al. [18] reported that disease-free survival was improved in metformin-treated patients with hormone receptor-positive breast cancer. No difference was observed in prognosis by metformin administration in this study, but we could not obtain full details of the diabetes treatment details. We believe that whether metformin treatments for diabetes may have a positive impact on patient outcomes in ER-positive breast cancer merits further investigation.

Interestingly, patient outcomes did not differ in relation to the level of HbA1c. While it is logical to assume

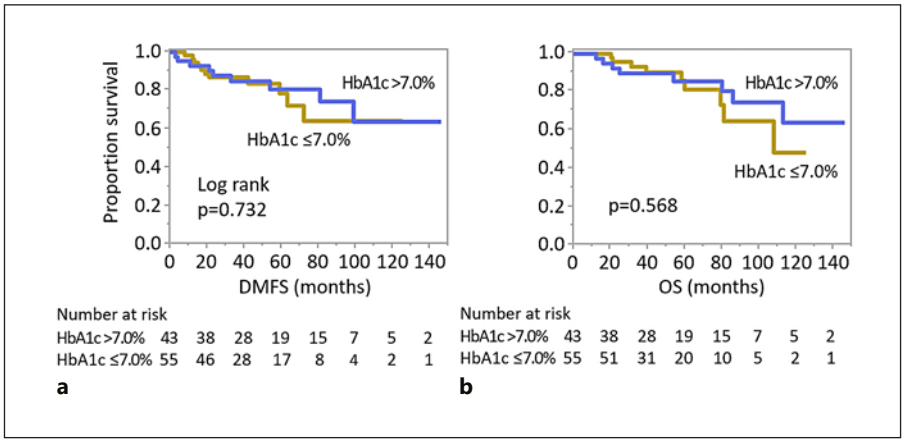

Fig. 3. Patient outcomes with diabetes according to HbA1c. Kaplan-Meier curves of DMFS (**a**) and OS (**b**) according to HbA1c in patients with diabetes. The blue curve indicates patients with high HbA1c (>7.0%), and the brown curve indicates those with low HbA1c (≤7.0%).

better control of diabetes may improve patient outcomes, the relationship between glycemic control and prognosis in breast cancer patients with diabetes has not been fully investigated. Yen-Lin et al. [19] reported that high HbA1c was associated with more breast cancer-related deaths. However, there are a variety of controversial points in their study, such as more inclusion of more advanced cancers in the diabetes group and the lack of details on the timing of HbA1c measurement and systemic therapies. In a study by Erickson et al. [20], poor glycemic control at baseline was associated with poor OS, but there was no difference in breast cancer event-free survival. In the current study, we assessed HbA1c at the time of breast cancer diagnosis, and did not monitor for subsequent changes. Some patients were found to have asymptomatic diabetes during the presurgical examination and started treatment for diabetes thereafter. Additionally, some patients may have had significant weight changes due to presurgical chemotherapy or long-term hormonal therapy. Such expected changes, including HbA1c, should also be assessed in further studies.

Various background factors may affect the prognosis of breast cancer even if blood glucose is controlled. A number of studies suggest that the presence of insulin resistance and hyperinsulinemia may favor breast cancer progression. Breast cancer patients with high blood insulin levels have a poor prognosis [21, 22], and high levels of IGF-1 in the blood, which is produced in the liver, have similar effects to insulin. They are also at high risk for breast cancer occurrence and development [23]. Insulin receptor promotes breast cancer development in a mouse model of type 2 diabetes [24]. High insulin receptor expression is seen in breast cancer tissues [25] and its negative impact on patient outcomes with breast cancer has been observed in some studies [26, 27]. In relation to insulin resistance, a recent study employing HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) revealed insulin resistance was associated with poor prognosis in African American women with breast cancer [28]. Focusing on metabolic health assessment factors such as insulin levels in serum and insulin resistance might be crucial in further examinations to examine the impact of diabetes on patient outcomes with breast cancer [29].

There are some limitations to the current study, as well as the timing of HbA1c evaluation as aforementioned. Since this was a retrospective study, there was a selection bias for patients and some clinical data were missing. HbA1c should have been examined in all patients, regardless of condition and the presence of diabetes. Systemic treatments for breast cancer and diabetes were not standardized. Moreover, a longer observation period would be ideal, considering the effect of diabetes on survival. In order to reach a conclusion, especially on whether or not there was a contribution of HbA1c in the prognosis of diabetes patients with ER-negative breast cancer, further studies with a larger sample are warranted.

Conclusions

Patients with diabetes at the time of breast cancer diagnosis had a significantly shorter DMFS, and negative effects on patient outcomes were more evident in women with ER-negative breast cancer. Our data do not necessarily indicate that good control of diabetes was of less importance but confirm the importance of primary prevention of diabetes in breast cancer patients. The relationship between diabetes and breast cancer prognosis merits further analysis by employing metabolic health evaluation factors such as insulin resistance.

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Statement of Ethics

This study has been approved by the Ethics Committee of Asahi Chuo Hospital (no: 2019071612). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

A. Tobe, K. Kobayashi, and M. Hirano designed the study. A. Tobe and M. Hirano treated the patients and provided clinical information. A. Tobe and Y. Horimoto analyzed the data and wrote the paper. K. Kobayashi, N. Kamisada, and M. Hirano reviewed and revised the paper.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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