Research Article

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The Association between Objective Tongue Color and the Static Blood Findings of Yusho Patients

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ABSTRACT

Objective: Yusho is a 1968 mass food poisoning event caused by the ingestion of rice oil contaminated with dioxins and related organochlorines that induce oxidative stress. Many patients continue to suffer from symptoms. Oxidative stress has been reported to be the pathogenesis for static blood (SB), and we have found many Yusho patients with palmar erythema (PE) and dilatation of the sublingual vein (SV), both signs of SB. Livid tongue is also a sign of SB, and we developed a tongue image analyzing system (TIAS) for the objective recording of tongue color (TC). With TIAS, we previously reported a correlation between the severity of SB and TC(4a*). However, the association between SB and the TC of Yusho patients is unclear. This study was done to clarify the prevalences of PE and dilatation of the SV and used TIAS to determine the relation between PE and dilatation of the SV with the severity of the SB of Yusho patients.

Methods: The data of 132 certified Yusho patients who attended our medical screening was available for analysis. TC was classified by the device-independent international commission on Illumination 1976L*a*b* color space standards at four points. PE was classified into three groups: (A) none, (B) partial, and (C) positive and dilatation of the SV into four, (A) none, (B) slightly, (C) moderate, and (D) markedly.

Results: PE and dilatation of the SV were observed in 63.6% (A,19; B,29; C,84) and 100%(B,61;C,63;D,8), respectively. Adjusted for confounding factors, TC (3b*) was significantly associated with PE (positive) and TC (4a*) with dilatation of the SV (moderate and markedly).

Conclusion: Along with our previous finding of an association the severity of SB and TC, observation of dilatation of the SV could be useful in the development of new strategies for targeting the SB of Yusho patients.

Keywords: Kampo medicine; Palmar erythema; Dilatation of sublingual dilatation; Static blood; Tongue image analyzing system

INTRODUCTION

Yusho is a 1968 mass food poisoning that was caused by the ingestion of rice oil contaminated with dioxins and related organochlorines. Initially, many Yusho patients had acne-like eruptions, blackheads, and pigmentation on the face, anterior region, and vulva. Our Yusho research group has been doing annual medical checkups for its victims since 1969. The main symptoms we have observed are not only the characteristic skin syndrome, but also respiratory symptoms, such as cough with the expectoration of sputum, neurological symptoms including numbness and paresthesia of the extremities, general fatigue, and arthralgia. Although over 50 years have passed since the event, Yusho patients still suffer from many symptoms. Their mean blood concentration of polychlorinated dibenzofurans has remained more than 10 times higher than that of normal individuals 30 and 40 years after the event [1,2]. The ideal curative treatment is to induce the complete excretion of the causative chemicals or to convert the dioxins into harmless metabolites. Several clinical trials with chelating agents or dietary fibers have been done to accelerate the excretion of these compounds [3-7]. Unfortunately, these

attempts to promote the excretion of dioxins have had limited success. Because of the limited success of the clinical trials, alternative treatments have been required. Chloracne is the major skin symptom caused by dioxin intoxication. Dioxin activates the arylhydrocarbon receptor (AHR)–cytochrome p450 1A1 (CYP1A1) system, generates oxidative stress, and induces hyperkeratinization of keratinocytes and sebocytes, leading to chloracne. Because antioxidant phytoextracts are potent inhibitors of AHR-mediated oxidative stress, we screen for phytoextracts that suppress dioxin-induced toxicity via the AHR–CYP1A1 pathway and activate the NRF2–antioxidative pathway. Cinnamomum cassia extract and its major constituent cinnamaldehyde have been shown to have dual activity [8]. Both C. cassia extract and cinnamaldehyde attenuate the AHR–CYP1A1 axis to inhibit oxidative stress [9]. Many Japanese Kampo herbal medicines contain varying doses of C. cassia extract. Among them, keishibukuryogan is the strongest inhibitor of AHR–CYP1A1 signaling [9]. Therefore, we did a clinical trial of the oral administration of keishibukuryogan for the treatment of patients who had high concentrations of polychlorinated dibenzofurans after eating contaminated rice bran oil in 1968 [10,11]. After three months of oral administration, keishibukuryogan significantly attenuated the symptoms of chloracne, general fatigue, cough, and the expectoration of sputum. It also tended to reduce numbness and paresthesia of the extremities [11]. In Kampo medicine, keishibukuryogan is usually used for SB, known as oketsu in Japanese, which is an important underlying pathology related to blood circulation disorders and inflammation in traditional Chinese and Japanese Kampo medicine [12,13]. SB is not restricted to the arterial and venous systems but extends to capillaries [12,13]. Representative clinical features of the SB include PE and dilatation of the SV [14-17]. Recently, we found many Yusho patients with PE and dilatation of the SV. It has been proposed that oxidative stress is one of the pathogenic factors for SB [12,13]. Dioxins and their related organochlorines are well-known environmental pollutants which induce oxidative stress [18]. These compounds bind arylhydrocarbon receptor and generate excessive amounts of reactive oxygen species [18]. In fact, biomarkers for oxidative stress are elevated in the blood and urine of patients with Yusho who were intoxicated by high concentrations of 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PeCDF) [18-20]. Hence, along with the findings of previous study that found keishibukuryogan to be effective for Yusho patients, we speculated that SB might be central to the pathology of Yusho patients. Livid tongue is also part of the diagnostic criteria of SB [21]. However, objective recording of tongue color (TC) is usually difficult for non-specialists. To overcome this problem, a photoimaging tongue image analyzing system (TIAS) has been established and validated [22-24]. We previously reported that TC diagnosis with TIAS would be a useful screening tool for judging the severity of the SB [25]. The purpose of this study was to investigate the prevalence of PE and dilatation of SV and the correlation between PE and dilatation of the SV, with the severity of SB judged by TIAS.

MATERIALS AND METHODS

Patient enrollment

Retrospective analysis was done of the data of 144 certified patients (≥ 20 years) who reported to a medical screening for Yusho in August and September of 2018. Age, sex, height, weight, and BMI (body mass index) were collected from electronic medical records, and history of smoking was taken at the visit. The blood concentrations of 2,3,4,7,8-PeCDF and total PCBs were measured at the Fukuoka Institute of Health and Environmental Sciences using a high- resolution gas chromatography/high-resolution mass spectrometer equipped with a new large -volume injection system (SGE Ltd.,Victoria, Australia) [26]. PE was classified into three groups (Figure 1): (A) none, (B) partial (on the pad of the thumb, the pad of the little finger, or limited to the base of the fingers), and (C) positive (when it extended over the entire finger). Dilatation of the SV was classified as previously reported [27] (Figure 2). (A) none, (B) slightly, (C) moderate, and (D) markedly.

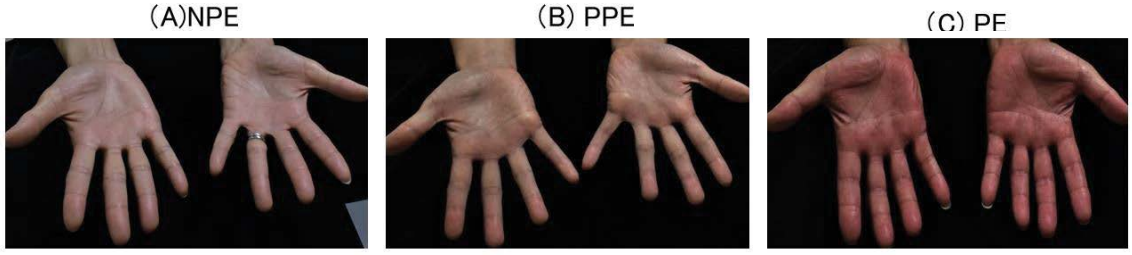

Figure 1: Classification of palmer erythema: (A) none, (B) partial (on the pad of the thumb, the pad of the little finger, or limited to the base of the fingers), (C) When it extends to the entire finger (positive).

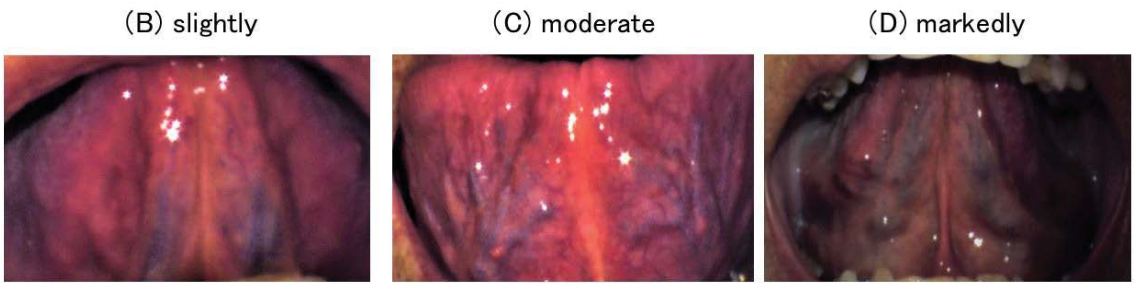

Figure 2: Classification of dilatation of the sublingual vein: (A) none, (B) slightly, (C) moderate, and (D) markedly. All of the patients in this study had dilatation of the sublingual vein, thus there were no group (A) patients.

This study was done after obtaining approval from the Ethics Committee of Kyushu University Hospital (approval number: 28-130). Written informed consent was obtained from all participants prior to study placement.

TIAS analysis of tongue color

TC and the sublingual vein were photographed by the TIAS system, which has been validated in previous studies [22,23]. TC was measured by the device-independent international commission on Illumination (CIE) 1976L*a*b* color space standards (L* indicates the bright component, a* the red component, and b* the blue component) at four points: (1) tongue edge, (2) tongue posterior, (3) tongue middle, and (4) tongue apex [24]. Because coating does not grow on the edge of the tongue, the color of the edge can be considered the color of the tongue body. In contrast, the color at the other three points is a mixture of the coating and the body of the tongue. By calculating the tongue body to tongue edge ratio (<1.0), we have shown that the color of the tongue reflects the body of the tongue, not the coating.

Statistical analysis

Wilcoxon rank sum test was used for comparison of age, BMI, and PeCDF, and $\chi 2$ test was used for comparison of the male / female ratio and smoking. The TC values obtained by TIAS are expressed as mean value ± standard deviation. The Kruskal-Wallis test was used for comparison of the PE and dilatation of the SV groups. For the logistic regression analysis of this study, we divided the PE patients into none to partial (groups A and B) and positive (group C) groups, because group (C) is the only group of the original three recognized as having signs of SB [21]. Further, we divided dilatation of the SV into slightly (group B) and moderate to markedly (groups C and D) groups in the same way because moderate to marked dilatation of the SV is easier for non Kampo practitioners to distinguish. For both categories, logistic regression analysis was done to determine the odds ratio (OR), 95% confidence interval (95% CI), and p-value, adjusted for age, sex, smoking history, and PeCDF value (median value 24.6). Furthermore, ROC analysis was done for items for which a significant difference was obtained by logistic regression analysis, and the area under the curve (AUC) was calculated. In addition, for items for which significant differences were obtained, the relation of outcomes of the PeCDF group is shown. All statistical analyzes were performed using JMP (Ver. 14, SAS Institute Japan Ltd.), and $p < 0.05$ represents a significant difference.

RESULTS

The exclusion of participants who could not flip their tongue vertically (n=10) or who lacked TIAS data (n=2) left the data of 132 patients available for analysis (Figure 3). PE was significantly associated with sex and BMI (P=0.002, 0.027) (Table 1), and dilatation of the SV was significantly associated with a history of smoking (P=0.038). (Table 2). PE was significantly associated with TC (1b*, 3b*, 4L*, 4a*, and 4b*) (P=0.002, <0.001, 0.015, 0.043, 0.011) (Table 3). Dilatation of the SV was significantly associated with TC (4a*) (P=0.048). (Table 4) Logistic regression analysis. adjusted for sex, age, smoking history, and PeCDF (cutoff value of median 24.6),

Table 1: The comparison of background factors among three groups in palmar erythema.

	NPE (n=19)	PPE (n=29)	PE(n=84)	*P-value*
Sex (Male/Female)	6/13	7/22	49/35	P=0.002
Age (years)	69.7±11.5	67.4±11.8	64.7±11.1	P=0.114
BMI(kg/m^2)	21.7±3.0	22.3±2.4	23.6±3.4	P=0.027
Smoking (%)	2(10.5)	3(10.3)	21(25.0)	P=0.128
PeCDF (pg/g lipid)	182.3±239.9	91.0±139.0	63.7±142.7	P=0.293

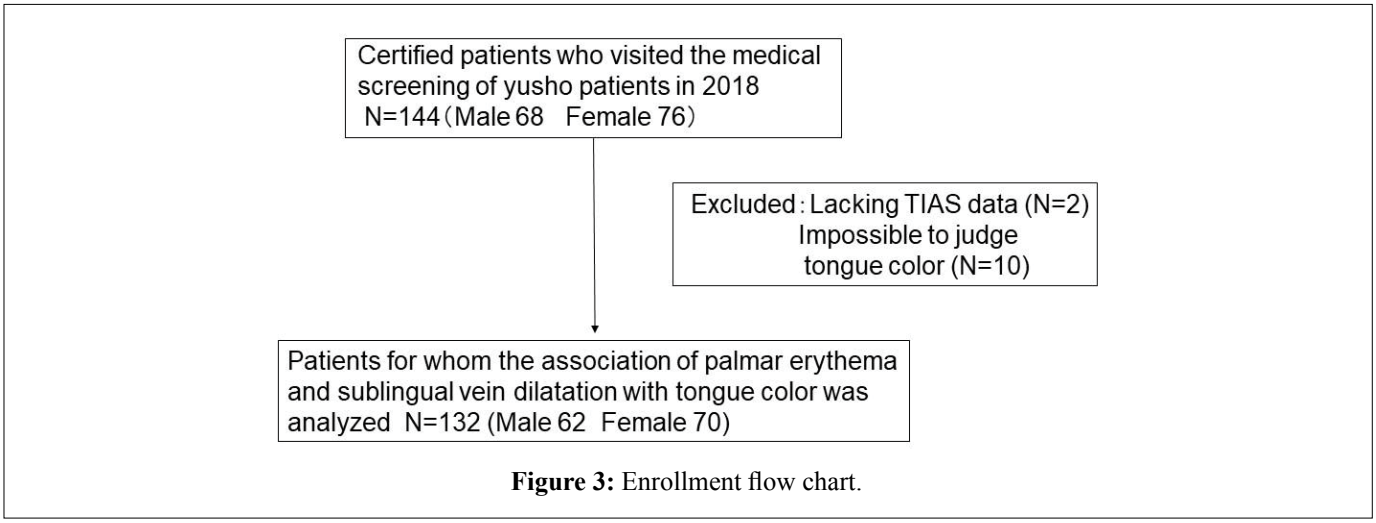

Figure 3: Enrollment flow chart.

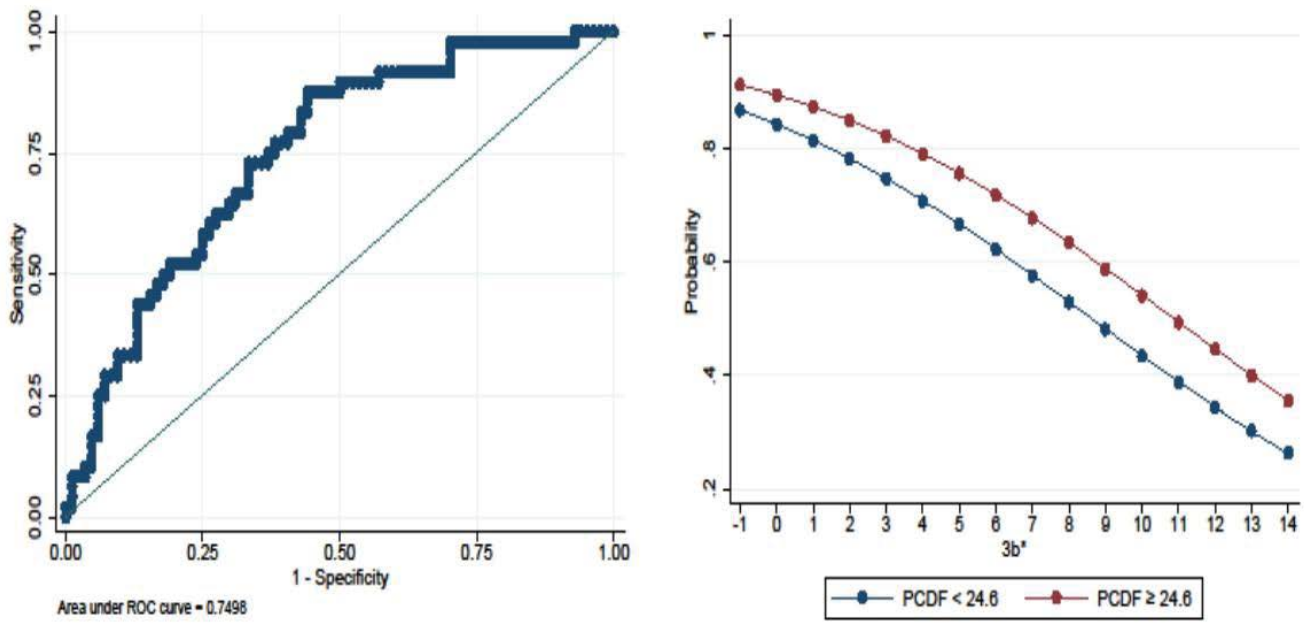

Figure 4a: ROC curve of tongue color(3b*) of patients with palmar erythema **4b** Association between PeCDF concentration and the tongue color(3b*) of patients with palmar erythema.

Table 2: The comparison of background factors among three groups in dilatation of sublingual vein.

	Slightly (n=61)	**Moderate (n=63)**	**Markedly (n=8)**	***P-value***
Sex (Male/Female)	29/32	29/34	4/4	P=0.971
Age (years)	65.2±11.4	66.8±11.4	65.4±12.2	P=0.663
BMI(kg/m^2)	23.1±3.4	23.1±3.2	22.9±2.9	P=0.994
Smoking (%)	8(13.1)	14(22.2)	4(50.0)	P=0.038
PeCDF (pg/g lipid)	105.5±205.0	74.3±120.1	41.9±56.7	P=0.534

Table 3. Comparisons of tongue color among three groups in palmar erythema groups.

	NPE(n=19)	PPE(n=29)	PE(n=84)
1L*	52.55±4.79	47.39±10.13	49.23±7.93
1a*	35.20±5.82	36.64±6.80	36.06±6.22
1b*	**9.34±3.11**	**9.32±3.37**	**7.27±3.05**
2L*	46.52±25.91	44.49±9.81	46.04±11.03
2a*	26.51±7.38	27.91±6.64	27.10±7.27
2b*	9.41±4.52	9.09±4.55	8.38±5.50
3L*	56.44±3.71	54.05±5.42	54.60±4.48
3a*	31.97±4.83	31.55±4.51	31.84±5.04
3b*	**8.38±2.61**	**7.33±1.82**	**5.77±2.93**
4L*	**55.10±4.03**	**51.67±7.87**	**51.12±5.65**
4a*	38.12±4.69	38.73±5.11	40.55±5.56
4b*	**10.63±2.34**	**10.48±2.96**	**9.00±2.81**
2L*/1L*	0.88±0.54	0.98±0.30	0.95±0.27
2a*/1a*	0.77±0.24	0.78±0.21	0.76±0.18
2b*/1b*	1.06±0.49	1.11±0.69	1.26±1.89
3L*/1L*	1.08±0.08	1.19±0.26	1.14±0.23
3a*/1a*	0.92±0.12	0.88±0.13	0.89±0.13
3b*/1b*	0.96±0.32	0.84±0.25	0.86±0.56
4L*/1L*	1.05±0.07	1.12±0.19	1.06±0.20
4a*/1a*	1.10±0.19	1.08±0.14	1.14±0.16
4b*/1b*	1.31±0.77	1.20±0.33	1.19±2.17

found a significant association between TC (3b*) and PE. TC(4a*) was significantly associated with dilatation of the SV. (Tables 5 and 6).

The ROC curve of the TC (3b*) of patients with PE gave an AUC of 0.7498, showing no significant association between PeCDF concentration and TC (3b*). (Figures 4a and 4b). Further, the ROC curve of the TC (4a*) of patients with dilatation of the SV gave an AUC of 0.6629, showing no significant association between PeCDF concentration and TC (4a*). (Figures 5a and 5b).

DISCUSSION

This is the first study to use TIAS for the objective evaluation of the relation of TC to the PE and dilatation of the SV of the tongue of a population of patients sickened in the Yusho incident. PE is a well-known physical finding that commonly consists of a symmetric, non-painful, non-pruritic, slightly warm, non-scaling erythema that most frequently involves the entire of the palmar surface. PE is a finding that reflects vasodilation of the skin. Fussy small erythema also frequently occurs in the thenar and hypothena eminences of the palm. It reflects dilation and expansion of capillaries and arterioles, and the local skin temperature is high. PE can develop in either primary or secondary forms as a result of an underlying systemic disease [28]. Although the pathogenesis is not fully understood, the impaired degradation or increased production

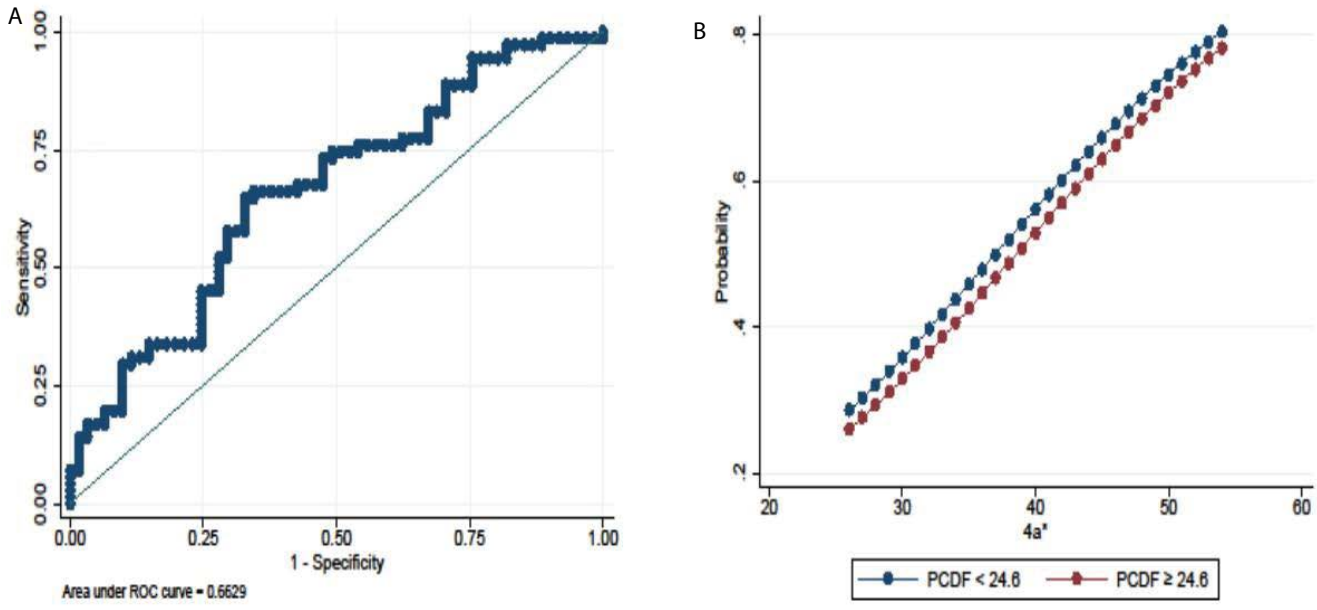

Figure 5a: ROC curve of tongue color(4a*) of patients with dilatation of the sublingual vein **5b** Association between PeCDF concentration and tongue color(4a*) of patients with dilatation of the sublingual vein.

Table 4: Comparisons of tongue color among three groups in dilatation of sublingual vein groups.

	Mild (n=61)	Moderate (n=63)	Severe (n=8)
1L*	49.9±7.30	48.39±9.12	51.97±6.88
1a*	35.59±5.23	36.92±7.19	32.93±4.66
1b*	7.97±2.69	8.34±3.65	5.84±3.59
2L*	44.5±17.13	47.28±9.74	43.5±12.88
2a*	28.35±8.50	26.2±5.63	26.19±4.79
2b*	8.85±5.19	8.07±4.20	12.35±9.58
3L*	54.97±4.02	54.4±5.14	55.81±4.98
3a*	31.46±4.68	32.41±5.05	29.59±4.43
3b*	6.5±2.53	6.58±2.99	5.67±4.14
4L*	52.8±4.12	50.72±7.55	52.91±5.71
4a*	**38.60±4.21**	**41.02±6.00**	**39.34±7.04**
4b*	9.12±2.49	10.1±3.03	8.65±3.69
2L*/1L*	0.90±0.36	1.01±0.29	0.83±0.23
2a*/1a*	0.8±0.22	0.73±0.17	0.80±0.12
2b*/1b*	1.21±0.84	1.16±0.77	1.32±5.79
3L*/1L*	1.12±0.16	1.17±0.29	1.09±0.13
3a*/1a*	0.89±0.11	0.90±0.15	0.91±0.13
3b*/1b*	0.85±0.30	0.82±0.41	1.44±1.27
4L*/1L*	1.08±0.15	1.07±0.23	1.03±0.12
4a*/1a*	1.10±0.14	1.13±0.18	1.20±0.15
4b*/1b*	1.25±0.62	1.44±0.86	-0.98±6.49

Table 5: The association of tonguecolor to palmer eryhthema.

	Odds ratio	95% CI		*P-value*
1L*	0.99	0.95,	1.04	0.770
1a*	1.01	0.95,	1.08	0.679
1b*	0.87	0.76,	1.00	0.056
2L*	1.01	0.98,	1.04	0.632
2a*	0.98	0.93,	1.04	0.475
2b*	0.96	0.89,	1.04	0.341
3L*	0.97	0.89,	1.05	0.473
3a*	1.03	0.95,	1.11	0.496
3b*	**0.81**	**0.69,**	**0.95**	**0.009**
4L*	0.96	0.90,	1.03	0.251
4a*	1.07	0.99,	1.15	0.071
4b*	0.89	0.77,	1.04	0.135
2L*/1L*	1.38	0.42,	4.59	0.597
2a*/1a*	0.30	0.04,	2.27	0.242
2b*/1b*	1.05	0.81,	1.36	0.727
3L*/1L*	0.93	0.17,	4.90	0.927
3a*/1a*	1.01	0.05,	22.35	0.995
3b*/1b*	0.66	0.29,	1.52	0.332
4L*/1L*	0.69	0.09,	5.13	0.718
4a*/1a*	4.30	0.30,	60.88	0.281
4b*/1b*	0.99	0.76,	1.29	0.948

*Adjusted for sex, age, smoking history, and PCDF (cutoff value of median)

Table 6: Association of tonguecolor to dilatation of sublingual vein.

	Odds ratio	95% CI		*P-value*
1L*	0.98	0.93,	1.02	0.308
1a*	1.04	0.98,	1.10	0.250
1b*	1.03	0.91,	1.16	0.657
2L*	1.01	0.99,	1.04	0.389
2a*	0.96	0.91,	1.02	0.185
2b*	0.98	0.91,	1.05	0.551
3L*	0.98	0.91,	1.06	0.567
3a*	1.04	0.96,	1.12	0.326
3b*	0.99	0.87,	1.14	0.928
4L*	0.94	0.88,	1.01	0.080
4a*	**1.09**	**1.02,**	**1.17**	**0.017**
4b*	1.15	0.99,	1.32	0.063
2L*/1L*	2.75	0.76,	9.91	0.121
2a*/1a*	0.17	0.02,	1.28	0.086
2b*/1b*	0.99	0.78,	1.25	0.901
3L*/1L*	2.76	0.47,	16.08	0.259
3a*/1a*	1.34	0.08,	23.22	0.840
3b*/1b*	0.96	0.44,	2.11	0.928
4L*/1L*	1.02	0.15,	6.87	0.985
4a*/1a*	4.36	0.40,	47.95	0.228
4b*/1b*	0.99	0.80,	1.23	0.955

*Adjusted for sex, age, smoking history, and PCDF (cutoff value of median)

of angiogenic factors appears to be essential. The hormone estrogen can induce vascularization [29] and is known to cause PE in pregnant women and patients with cirrhosis. Because estradiol is metabolized in the liver, increased levels of estrogen are associated with hepatic decompensation in cirrhosis [30]. One study reported that almost none of their patients with fibrosis F0-1 had PE, while PE was seen in about 25% of the patients with stage F3 in chronic hepatitis and in 70% of the patients with stage F4 (cirrhosis) [31].

This showed PE to be a sign of cirrhosis and indicated that it is a skin manifestation of hepatic dysfunction. It has been reported that mortality from liver disease is higher in men than in women and that liver cancer is higher in female than in male Yusho patients [32]. Dioxin also causes hepatotoxicity by affecting metabolic pathways in the liver [33]. Therefore, the finding of a higher frequency of PE in Yusho patient may reflect potential liver dysfunction. We previously reported a significant relation between erosive gastritis and TC (3b*) by TIAS, confirmed with endoscopic findings [24], which suggests that a detailed gastrointestinal history interview would be necessary for Yusho

patients with PE. In addition, in Kampo medicine the middle of the tongue represents the spleen[TM], and stomach[TM], which control digestion and absorption. Researchers have reported a "skin-intestine correlation", and our results of TC and PE suggest such a relation between the skin and intestine.

It is notable that analysis of the data of all Yusho patients who had dilatation of SV and remarkable dilatation of the SV of the tongue showed a significant relation with TC (4a*). We recently reported a relation between the severity of SB and TC (4a*) [25]. This suggests that moderate to marked dilatation of the SB may be associated with severe SB. Although about 20% of the veins behind the tongue cannot be judged well [17], marked dilatation of the SB of the tongue would be an objective sign of the severity of SB that would be easily understood by doctors who are not familiar with Kampo medicine. Although we previously reported he usefulness of keishibukuryogan for Yusho patients [11], we feel that moderate to marked dilatation of the SB would be a useful indication for its prescription. Further, when TC (a) is seen in the apex of the tongue, "fever in heart[TM]" is indicated. In Kampo, the body's internal organs are roughly divided into five zang-gans, liver [TM], heart [TM], spleen [TM], lung [TM] and kidney [TM]. The heart [TM] has the function of circulating blood, maintaining the level of awareness, and adjusting the rhythm of arousal and sleep. Orengedokuto has been used for removing "heat" and "poison" and for inflammation, hypertension, gastrointestinal disorders, and liver and cerebrovascular diseases [34,35]. Moreover, Furue et al recently reported that orengedokuto inhibits Benzo[a] pyrene-induced reactive oxygen species (ROC) production [36]. Therefore, we think that when keishibukuryogan lacks effectiveness, medical practitioners might change to or add orengedokuto. Although the pathogenesis of SB remains unknown, oxidative stress is assumed to be involved at least in part [12,13]. The blood concentrations of 2,3,4,7,8-PeCDF were significantly higher in Yusho patients than were those of normal healthy controls [37]. Dioxin and its related compounds aryl hydrocarbon receptor and generate oxidative stress, therefore, we expected that the blood concentrations of 2,3,4,7,8-PeCDF would be correlated with SB, however, this was not the case. The blood concentrations of 2,3,4,7,8-PeCDF had nothing to do with PE, dilatation of SV, or TC alteration in the present study. One of the reasons is the difficulty of detailed clinical scoring of PE and dilatation of the SV, although we cannot exclude the possibility that concentration-independent effects of dioxins may be related to the SB of Yusho patients.

There are several limitations in this study. The number of patients was small. We did not measure blood or urinary markers to test for oxidative stress. Although chloracne, general fatigue, increased blood sugar, and hyperlipidemia have been reported to be correlated with the concentration of 2,3,4,7,8-PeCDF [38,39], we did not include clinical symptoms of Yusho patients in the present analysis. In addition, we did not calculate a SB score. Further, we estimated TC by TIAS, but did not estimate PE in the same way, thus our results need to be further validated.

CONCLUSION

The static blood conditions PE and dilatation of the SV were observed in a high number of our Yusho patients. Along with our previous finding of an association the severity of SB and TC, observation of dilatation of the SV could be useful in the development of new strategies for targeting the SB of Yusho patients.

DATA AVAILABILITY

Data to support the findings of this study are available upon reasonable request to the corresponding author.

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AUTHOR CONTRIBUTIONS

MK, CM, DO, and TN analyzed the data. MK wrote the paper. GT and MF assisted in the interpretation of the data. All authors contributed to the design and methodology of the study. All authors have read and approved the final manuscript.

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