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Serum docosahexaenoic acid and cognitive impairment of Japanese residents in a remote island

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Abstract

Backgrounds: Docosahexaenoic acid (DHA), which is mainly derived from marine fish, is suspected to reduce the risk of dementia and cognitive decline. The associations of fish consumption and DHA with the scores of Kana Pick-out test (KPT), a cognitive function test to detect pre-dementia, were examined in a remote island of Kagoshima, Japan.

Subjects and Methods: As a part of an annual health checkup of residents, a questionnaire survey, hair sample collection, and the KPT were conducted in a remote island of Kagoshima during September and October, 2007. Out of 1,188 residents taking a health checkup, 505 (224 men and 281 women, age 30-69), who received all examinations, were analyzed. Among of them, serum samples from 424 subjects were available for a free fatty acid assay. Hair mercury level was analyzed by cold vapour atomic absorption method, and serum free fatty acid level was measured by gas chromatography. Multivariate linear regression analysis was used to calculate the age-, sex-, and education-level-adjusted KPT scores among different levels of mercury and the ratios DHA to arachidonic acid (AA).

Results: The average of KPT score in women (38.1) was higher than that of men (35.0, $p < 0.001$). The scores decreased with age ($p < 0.001$) and lower education levels ($p < 0.001$) in both men and women. After adjusting for the effects of age, sex, and education level, KPT score was positively related to the DHA/AA (p for trend = 0.034) in the subjects under the age of 60 but this tendency was not observed in those aged 60 or older.

Conclusion: The present study suggested a potential benefit of DHA on cognitive function in the subjects under the age of 60 but further studies for the elderly people are required.

Key Words: Cognitive Impairment; Dementia; Docosahexaenoic acid; Fish consumption; Kana Pick-out Test

Introduction

Fish is a major dietary source of n-3 polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA) which is suspected to reduce the risk of cognitive impairment and dementia.¹⁾ It has been hypothesized that DHA is associated with cognitive change on the basis of its abundance in brain tissue, and evidence from animal experiments demonstrating superior learning and memory performance among DHA-fed rodents.²⁾ The antioxidant effect by DHA is a possible mechanism of the improvement of cognitive function since the accumulation of lipid peroxide, induced by free radicals, damages cellular function in the aging process.³⁾

Higher intake of eicosapentaenoic acid (EPA) and DHA from diet reduced cognitive decline among elder men with normal cognitive function during a 5-year follow-up.⁴⁾ Another prospective study showed an inverse association between DHA intake and the risk of Alzheimer disease incidence among elder residents.⁵⁾ Kalmijn *et al.*⁶⁾ also reported that dietary intake of EPA and DHA was inversely related to the risk of impaired overall cognitive function and speed of cognitive processes in middle-aged subjects. On the other hand, n-3 PUFAs intake was not related to a long-term risk of dementia or Alzheimer disease in a Dutch population aged over 55.⁷⁾

A higher plasma phosphatidyl-choline DHA concentration was associated with a decrease in the risk of developing all-cause dementia in the Framingham study.⁸⁾ In the Canadian Study of Health and Aging, however, found no evidence of a reduced risk of dementia or Alzheimer disease among the subjects with higher plasma concentrations of total n-3 PUFAs, DHA, or EPA.⁹⁾ The variations in the numerous studies may be due to various factors including study designs, sample sizes, the heterogeneity of study populations, differences in PUFA intake estimations, the serum assays of PUFAs and the wide variety of the applied cognitive tests.

The Kana Pick-out Test (KPT) was developed in Japan as a tool for evaluating frontal lobe function and screening for mild or slight dementia.^{10,11)} In this test, subjects read a short story in hiragana, Japanese syllabic characters which children first learn, and, while reading, circle characters that comprise five Japanese vowels within two minutes. Since functional activity of sub-genual cingulated gyrus (SGC) was closely related to scores of KPT,¹²⁾ the KPT provides a promising tool for screening to detect early stages of Alzheimer disease with low SGC function, and it is widely used in clinical practice to screen early stage of dementia¹³⁾ and to detect

cognitive dysfunction in patients with Parkinson's disease.¹⁴⁾ Furthermore, the KPT is also considered as a test suitable for evaluating working memory and executive function as well as for prefrontal-area function.¹³⁾

Prevention of the cognitive deficit among elderly people is one of the critical issues in aged society including Japan. However, epidemiological reports from Asian countries, where the fish-consumption is relatively higher than that in European countries, are quite limited. To evaluate a potential protective efficiency of DHA on cognitive decline in Japanese, the present study examined the association between fish consumption and serum DHA, in relation to KPT score among the residents of a southern remote island in Japan, where the migration in this population is relatively small especially among people aged around 40 or above, and their diet including fish does not vary significantly among seasons since the island is located in a sub-tropical region.

Methods

Study subjects and measuring methods

As a part of an annual health checkup of residents in W-town, a remote island in Kagoshima prefecture, a questionnaire survey, hair sample collection, and the KPT, a cognitive function test, were conducted during September and October, 2007. Among 1,188 residents, age 30-69, taking the health checkup, 774 (65%) participated to this study. Furthermore, 523 (68%) subjects (233 men and 290 women) out of 774 underwent the cognitive test. The participation rate for the cognitive test was 68%, 69%, and 66% for <50, 50-59, and 60-69 age-groups, respectively. The KPT scores of 18 out of 523 subjects (3%) were lower than the age-specific cut-off points for suspected cognitive deficit, as described later, and these subjects were excluded from the analyses. Since the purpose of the present study is to examine the preventive effects of fish consumption / DHA intake on cognitive function, we focused on the subjects with normal cognitive function. Thus, the total number of the subjects was 505. This study was approved by the ethics committee of Graduate School of Medical and Dental Sciences, Kagoshima University (the approval number: 31, 86, and 363). A written informed consent was obtained from all subjects.

In the KPT, examinees were asked to pick out five hiragana letters corresponding to the five vowels used in Japanese language i.e. "A", "I", "U", "E" and "O", while reading a short story written in hiragana in 2 minutes. A score of the KPT was calculated by subtracting the number of wrong

letters (other than those 5 vowels) from the number of letters picked out correctly. The maximum correct picking score is 61 in this examination. The age-specific cut-off points for suspected cognitive deficit are as follows: 30, 29, 21, 15, 10, 9, and 8 points for age 20's, 30's, 40's, 50's, 60's, 70's, and 80's, respectively.¹³⁾ For the analysis of the association with KPT score, the study subjects were stratified by age 60, <60 and ≥60, since the age-specific cut-off points indicated that the age-dependent decrease of KPT score was the most significant in the population age 30's-50's, and the magnitude of the decrease is small after that.

Information on fish consumption (the amount and frequency of fish consumption), education levels and lifestyles, including smoking and alcohol drinking habits, was collected using a questionnaire. Regarding the frequency of fish intake, interviewees answered one of the following choices; none, once, 2-3 times, 4-5 times, 6-8 times, or ≥ 9 times per week. The volume of fish per meal was determined according to the number of fillet, 4-5 x 4-5 x 1 cm in size, which corresponds to approximately 25g. The amount of fish consumption per week was estimated by multiplying its volume (25, 50, 75, 100, or 125g) and the frequency of intake (0, 1, 2.5, 4.5, 7 or 9 times).

Serum samples were subjected to a free fatty acid analysis. In brief, 200 µL of serum was transferred into a glass tube with a Teflon-lined screw-cap and 200 µL of internal control (tricosanoic acid; 23:0), 200 mg of potassium hydroxide and 2 mL of methanol were added followed by vigorous mixing. After incubation for 1 h at 80°C, 2 mL of hexane was added, and the mixture was vigorously stirred and subsequently at rest for 5 min at room temperature. The upper layer, unsaponified fraction, was discarded and the saponification by hexane was repeated twice. After that, 0.5 mL of hydrochloric acid and 1 mL of methanol were added to the remaining methanol fraction. The mixture was incubated for 1 h at 80°C and 2 mL of hexane was added followed by vigorous mixing. The upper fraction containing fatty acids methyl ester was collected and 1 µL of the sample was applied for the analysis using the Focus GC Gas Chromatography (Thermo Fisher Scientific Inc., U.S.A) on a capillary column SUPELCOWAX™ 10 (SUPELCO, U.S.A), equipped with an auto-injector, auto-sampler, and flame ionization detector, under the following conditions; the oven temperature was programmed 120 °C for 1 min, and from 120°C to 280°C at a rate of 10°C /min, with holding of the final temperature for 23 min. Total run time for one sample was 40 min. The helium carrier flow rate was 1.8 mL/min. The coefficient of variation

for the inter- and intra-assays of DHA and EPA was ~8% and ~14%, respectively. The measurement was repeated four times for both assays.

Hair mercury level was examined as a surrogate marker of fish consumption since human exposure to mercury is primarily from the consumption of fish and shellfish. To wet-digest hair samples (10 mg, about 3 cm length), 1 mL mixed solution of nitric acid and perchloric acid (1:1 ratio) and 2.5 mL sulfuric acid were added. The specimens were heated at 200°C for 1 h and cooled under running water. The volume was adjusted 10 mL using distilled water. Total mercury level (methyl mercury in hair) was then measured using cold vapour atomic absorption (CVAA) method. For each run, one reagent blank and two referent solutions were analyzed using the same procedure. The coefficient of variation for mercury measurement was ~5%. The measurement was repeated five times.

Statistical analysis

Multivariate linear regression analysis was used to calculate the age-, sex-, and education-level-adjusted KPT scores and their corresponding 95% confidence intervals among different levels of mercury and the ratios DHA or EPA to arachidonic acid (AA). Spearman's correlation coefficients were estimated between fish consumption and hair mercury level. All data analyses were performed by STATA version 9.2 (Stata Corp. LP).

Results

Table 1 shows the characteristics of the study subjects; 224 men and 281 women. There were significant differences in the distribution of all factors except age between men and women (Table 1). The average of KPT score in women was higher than that of men (Table 2). The KPT scores decreased with age ($p<0.001$) and lower education levels ($p<0.001$) in both men and women. There was an increasing trend of KPT scores with alcohol drinking in women ($p=0.013$) but that was not true in men. Smoking was not associated with KPT scores in analysis, adjusting for age and education levels (data not shown).

The subjects aged 60 or older showed a weak negative association between fish consumption and KPT scores but there was no association in the subjects under the age of 60. On the contrary, KPT scores tended to increase with hair mercury levels in the subjects under the age of 60 although this association was not statistically significant. Such a

Table 1 Characteristics of the study population

	Number (%)			P value
	Total (n=505)	Men (n=224)	Women (n=281)	
Mean age (min, max)	55.1 (30, 69)	55.4 (31, 69)	54.8 (30, 69)	0.489
Education level				
Junior-high school	119 (24)	49 (22)	70 (25)	<0.001
High school	214 (42)	101 (45)	113 (40)	
Junior college/ Training schools *	71 (14)	16 (7)	55 (20)	
University	47 (9)	39 (17)	8 (3)	
Unknown	54 (11)	19 (8)	35 (12)	
Brinkman Index †				
0	366 (72)	102 (46)	264 (94)	<0.001
≤ 300	38 (8)	27 (12)	11 (4)	
> 300 - 600	45 (9)	40 (18)	5 (2)	
> 600 - 1000	28 (6)	28 (13)	0 (0)	
> 1000	24 (5)	24 (11)	0 (0)	
Unknown	4 (1)	3 (1)	1 (0.4)	
Frequency of Alcohol drinking(day/week)				
None	188 (37)	25 (11)	163 (58)	<0.001
1	83 (16)	20 (9)	63 (22)	
2-4	27 (5)	13 (6)	14 (5)	
5-6	63 (12)	46 (21)	17 (6)	
Everyday	102 (20)	92 (41)	10 (4)	
Unknown	42 (8)	28 (13)	14 (5)	

* Professional training schools are included.

† Number of cigarettes per day × years of smoking

‡ P values were obtained by Mann-Whitney U test for age and chi-square test for education level, Brinkman Index, and alcohol drinking.

tendency was not observed in the subjects aged 60 or older (Table 3). The information on the frequencies of processed fish, fish eggs, and fish sausages was also obtained but there was no significant positive association between these fish products and KPT scores (data not shown).

Hair mercury concentration was used as a surrogate marker of fish consumption. The median of hair mercury levels for men and women were 4.23 ppm (range: 0.18-32.7) and 2.4 ppm (0.37-10.3), respectively. Spearman's correlation coefficients for their associations among men and women

were 0.176 ($p=0.009$) and 0.236 ($p<0.001$), respectively.

Left over serum samples from 178 men and 246 women were available for a free fatty acid assay (Table 4). Multivariate regression analysis revealed that KPT score was positively related to the DHA/AA ratio in the subjects under the age of 60 (p for trend = 0.034). This association remained even after adjusting the effects of smoking and alcohol drinking habits (p for trend = 0.037). Among the subjects aged 60 or older, however, the score was inversely related to the DHA/AA ratio, and the difference between two groups was marginally

Table 2 Distribution of Kana Pick-out Test scores by age, sex, and level of education

	n	Kana Pick-out Test scores		
		Mean* \pm SE*	Range (min, max)	<i>p</i> value [†]
Age (year)				<i>p</i> for trend
< 50	124	38.4 \pm 1.5	25, 58	<0.001
50 - 59	196	36.9 \pm 0.4	16, 59	
60 - 69	185	35.4 \pm 1.2	11, 58	
Sex				<0.001
Male	224	35.0 \pm 0.6	13, 56	
Female	281	38.1 \pm 0.5	11, 59	
Education level				<i>p</i> for trend
Junior-high school	119	35.6 \pm 0.5	13, 50	<0.001
High school	214	37.1 \pm 0.4	14, 59	
Junior college/ Training schools	71	38.6 \pm 0.5	20, 58	
University	47	40.1 \pm 0.8	20, 58	
Unknown	54	32.6 \pm 0.9	11, 52	

* Age-adjusted mean and standard error

[†] *P* for trend derived from multiple regression model adjusted for age, sex, and education (excluding the unknown category)

significant ($p=0.111$). The KPT score was not associated with EPA/AA ratio in both age groups.

Discussion

Key findings and discussion

In the present study, KPT scores were positively associated with the serum DHA/AA ratio among the subjects under age 60 ($p=0.034$) but not in the subjects aged 60 or above. Similar trend was also observed in the association with hair mercury levels though there was no statistical significance. These findings can be interpreted as evidence for the beneficial effects of DHA on cognitive function among Japanese under age 60. There was no positive association between KPT scores and serum EPA/AA ratio.

Recently, a study in Japan reported that elderly Japanese with a moderately-high level of serum DHA, but not EPA, showed a lower risk of cognitive decline than those with low serum DHA after 10-year follow-up.¹⁵⁾ Similar findings were also reported in other cross-sectional studies.^{16, 17)}

A protective effect of DHA was also suggested for severer status of cognitive decline such as Alzheimer disease.¹⁸⁾ Other studies reported the fish-consumption effect on dementia or Alzheimer disease.^{5, 19)} An international cross-sectional study in developing countries found that higher fish intake was inversely associated with the risk of dementia, using 10/66 protocol developed for dementia diagnosis.²⁰⁾ On the other hand, a longitudinal study conducted in the Netherlands did not observe the inverse association between fish consumption and the risk of dementia or Alzheimer disease.⁷⁾

Although many observational studies indicate that higher level of serum DHA and fish consumption are protective against the risk of cognitive decline, some intervention studies did not confirm this protective effects in cognitively healthy subjects^{21, 22)} and patients with Alzheimer disease.²³⁾ Since intervention periods of these studies ranged from 12 weeks to 40 months, the evaluation of a long-term effect might be necessary.

DHA is mainly derived from marine fish but it can also be

Table 3 Distribution of Kana Pick-out Test scores by fish consumption and total hair mercury

	All		Age 30-59		Age 60-69	
	N (%)	Adjusted mean (95% CI) †	N (%)	Adjusted mean (95% CI) †	N (%)	Adjusted mean (95% CI) †
Fish consumption (g/week)	492 (100)*		311 (100)		181 (100)	
≤ 50	184 (37)	35.3 (33.8, 36.7)	125 (40)	36.5 (34.8, 38.3)	59 (33)	33.3 (30.9, 35.8)
50 - 150	157 (32)	34.8 (33.7, 36.0)	97 (31)	36.6 (35.3, 38.0)	60 (33)	32.0 (30.1, 33.9)
> 150	151 (31)	34.4 (33.0, 35.9)	89 (29)	36.7 (35.0, 38.5)	62 (34)	30.8 (28.2, 33.3)
<i>p</i> for trend ‡		0.369		0.838		0.128
Hg level (ppm)	505 (100)		320 (100)		185 (100)	
< 1.85	100 (20)	36.1 (34.7, 37.4)	68 (21)	38.3 (36.7, 39.9)	32 (17)	32.3 (29.7, 34.9)
1.85 –	103 (20)	36.4 (35.5, 37.3)	72 (23)	38.7 (37.7, 39.8)	31 (17)	32.5 (30.7, 34.3)
2.65 –	101 (20)	36.7 (36.0, 37.5)	64 (20)	39.1 (38.2, 40.0)	37 (20)	32.7 (31.4, 34.0)
3.65 –	100 (20)	37.1 (36.2, 38.0)	66 (21)	39.5 (38.3, 40.7)	34 (18)	32.9 (31.4, 34.4)
≥ 5.22	101 (20)	37.4 (36.1, 38.8)	50 (16)	39.9 (38.2, 41.7)	51 (28)	33.1 (30.8, 35.3)
<i>p</i> for trend ‡		0.246		0.280		0.712

* Information of fish consumption was missing for 3 men and 10 women.

† The mean scores and their corresponding 95% confidence intervals were adjusted for the effect of age, sex, and education using a multivariate regression model.

‡ *P* for trend derived from multiple regression analysis adjusted for the effect of age, sex, and education.

Table 4 Distribution of Kana Pick-out Test scores by DHA and EPA

	All		Age 30-59		Age ≥ 60	
	N	Adjusted mean (95% CI) †	N	Adjusted mean (95% CI) †	N	Adjusted mean (95% CI) †
DHA/AA* ratio	424 (100)		263 (100)		161 (100)	
< 0.278	141 (33)	36.1 (34.8, 37.4)	89 (34)	37.9 (36.4, 39.4)	52 (32)	33.4 (31.1, 35.6)
0.278 –	141 (33)	36.8 (36.0, 37.6)	85 (32)	39.2 (38.2, 40.1)	56 (35)	32.9 (31.5, 34.3)
≥ 0.397	142 (33)	37.5 (36.2, 38.7)	89 (34)	40.4 (38.9, 42.0)	53 (33)	32.5 (30.2, 34.7)
<i>P</i> for trend ‡		0.176		0.034		0.603
EPA/AA ^a ratio	424 (100)		263 (100)		161 (100)	
< 0.345	141 (33)	37.3 (36.1, 38.6)	91 (35)	39.7 (38.2, 41.1)	50 (31)	33.5 (31.2, 35.8)
0.345 –	142 (33)	36.8 (36.0, 37.6)	85 (32)	39.2 (38.2, 40.1)	57 (35)	32.9 (31.5, 34.3)
≥ 0.487	141 (33)	36.2 (35.0, 37.5)	87 (33)	38.6 (37.1, 40.2)	54 (34)	32.3 (30.1, 34.6)
<i>P</i> for trend ‡		0.277		0.394		0.498

* DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; AA: Arachidonic acid

† The mean scores and their corresponding 95% confidence intervals were adjusted for the effect of age, sex, and education using a multivariate regression model.

‡ *P* for trend derived from multiple regression analysis adjusted for the effect of age, sex, and education.

synthesized by humans from dietary alpha-linolenic acid (C18:3). However, the conversion efficiency of alpha-linolenic acid to DHA is quite low; on the order of 1% in infants, and considerably lower in adults.²⁴⁾

Although fish contains various beneficial nutrients, it is also a potential source of dietary intake of methylmercury.²⁵⁾ A few epidemiological studies reported adverse effects of methylmercury, through fish consumption, on cognitive function among adults.^{26, 27)} Carta *et al.*²⁶⁾ compared cognitive function between middle-aged habitual consumers of fresh tuna (median of methylmercury level in whole blood: 41.5 µg/L; controls 2.6 µg/L), and found that methylmercury level was inversely related to the color, word reaction time and digit symbol reaction time. Another study from Taiwan reported that blood methylmercury level was significantly associated with the risk of impairments in remote memory, mental manipulation, and orientation among residents living near a deserted chloralkali factory.²⁷⁾ The mean blood methylmercury concentration in this population was 15.3 µg/L. On the other hand, Weil *et al.*²⁸⁾ found no relationship between blood mercury level and cognitive function among populations with very low blood level of total mercury, around 2-3 µg/L. These observations are consistent with a suggestion by Masley *et al.*²⁹⁾: a higher level of blood mercury, particularly ≥15 µg/L, overwhelms the beneficial effects of n-3 FA. Measuring hair mercury level is a choice for biological monitoring of human environmental methylmercury exposure,³⁰⁾ and hair methylmercury level is highly concentrated, approximately 250 times of blood level.³¹⁾ The medians of hair mercury level in our study population were 2.895 and 3.41 ppm for the subjects under the age of 60 and aged 60 or older, respectively, and these values correspond to 11.6 and 13.6 µg/L in blood. Although the levels of mercury in the present study are much lower than the recognized concentrations for neurotoxicity, the lack of association between DHA/AA and KPT scores in the subjects aged 60 or above could be partially explained by a relatively higher mercury level in this group.

Regarding the KPT, the age-specific cut-off points and the distribution pattern indicated that this test is sensitive to detect the decline of cognitive function in the population age 30's-50's but that may not be effective for the population aged 60 or older because the magnitude of the age-dependent decrease is small, and the most elderly people are deviated to low scores without a peak.^{11,13)} Further studies are necessary to confirm the benefit of DHA among elderly people.

In our study population, there was no positive association between KPT scores and EPA/AA ratio. This finding was

consistent with the result of recent study in Japan.¹⁵⁾ Another study, conducted in the southern island of Japan, reported that serum EPA levels were not related to fish consumption in both men and women.³²⁾ The Canadian Study of Health and Aging, a large longitudinal study, reported that serum EPA level was not related to the risk of dementia or Alzheimer disease.⁹⁾ Other prospective studies from Chicago⁵⁾ and Rotterdam⁷⁾ also found no association between EPA intake and the risk of Alzheimer disease and dementia, respectively.

The absence of the association between serum EPA level and cognitive function is consistent with the fact that brain EPA levels are significantly lower than DHA and AA.^{33,34)} The low EPA level in the brain could be explained by multiple mechanisms such as beta-oxidization,^{35,36)} elongation/de-saturation of EPA into longer n-3 PUFA, and lower recycling rate within brain phospholipids.³⁷⁾ Chen *et al.* reported a rapid and extensive beta-oxidization of EPA in the brain^{35,36)} and a significantly low rate of EPA recycling in brain phospholipids in comparison with DHA and AA.³⁷⁾ These findings indicate that EPA may not play an important role in the brain.

The strengths and limitations of the study

The ratio of DHA or EPA to AA, applied in the analysis, is a better indicator than concentrations of DHA and EPA because dietary intake of n-3 PUFA is known to reduce the amount of AA in phospholipids by diminishing its synthesis and simple physical replacement.³⁸⁾ Furthermore, Hossain *et al.*³⁹⁾ suggested that the cerebral DHA/AA ratio was a good indicator of the host defense capability against oxidative damage.

In general, erythrocytes, in which n-3 PUFA persists for months, are preferable to determine the exposure to DHA/EPA since the regulation of free fatty acids is less stable than that in either in serum lipoprotein particles or in erythrocytes.

A cross-sectional study design was one of the important limitations in the present study. Although we tried to ask long-term lifestyle patterns in the questionnaire, interviewees might answered the recent lifestyle patterns, which could violate the temporality of the causal association. However, for most of the study subjects, aged over 40, their dietary preferences are likely to stay constant.

In the present study, the frequency and the volume of fish consumption in the highest group might be underestimated because of fixed choices in the questionnaire. We assumed that the highest frequency and volume of fish intake were 9 times per week and 125 g per meal, respectively, even though some subjects might have eaten fish more frequently. This

might weaken the association between fish consumption and KPT scores. Furthermore, EPA and DHA content vary widely among species but the information on type of fish was not collected. Although we assumed that the diet in this study area does not change significantly among seasons, the questionnaire survey for the diet was conducted only once. We cannot deny a possibility of seasonal variation of fish consumption.

Conclusion and the implications for future research

A beneficial effect of DHA on cognitive function was confirmed in the present study but it was limited to middle-aged population, under age 60. Although further studies using erythrocytes, in which n-3 PUFA persists for months, are warranted, a prospective study would provide further clarification on the association between DHA and cognitive function in the elderly.

Acknowledgements

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本邦離島住民における血清ドコサヘキサエン酸と認知機能との関連について

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背景：魚介類から主に摂取されるドコサヘキサエン酸（DHA）には、認知症のリスクおよび認知機能低下を予防する可能性があることが報告されている。本研究では、鹿児島の離島地域住民を対象として、早期認知症のスクリーニングとしても用いられるかなひろいテストの得点と魚介類の摂取量および血清 DHA 値との関連を検討した。

対象と方法：鹿児島県の離島において、2007 年 9 月、10 月に住民健康診断を受診した者を対象とし、魚介類の摂取などに関する質問調査、毛髪の採取およびかなひろいテストを健診会場で行った。1,188 名の受診者の中で、すべての検査が実施できた 505 名（男性 224 名、女性 281 名、年齢 30-69 歳）を今回の解析対象とした。さらにその中で血清中の不飽和脂肪酸が測定できた者は 424 名であった。毛髪水銀の測定は冷蒸気原子吸光法で行い、血清中不飽和脂肪酸の測定はガスクロマトグラフィーを用いて行った。年齢、性および教育歴を調整し、かなひろいテスト得点と、魚食量、毛髪水銀値および血清 DHA（アラキドン酸 [AA] との比）などとの関連について多変量回帰分析を行った。

結果：かなひろい得点の平均値は女性 38.1、男性 35.0 で、女性の方が高かった（P 値： <0.001 ）。男女とも、かなひろい得点は年齢とともに減少し（P 値： <0.001 ）、教育歴（年数）と正の関連を示した（P 値： <0.001 ）。これらの要因を調整した結果、60 歳未満では、DHA:AA 比とかなひろいテスト得点に有意な正の関連を認めた（傾向性の P 値： 0.034 ）が、60 歳以上ではそのような傾向は見られなかった。

結論：本研究結果により、60 歳未満の者においては、DHA による認知機能改善効果の可能性が示唆されたが、高齢者における有用性はさらなる検討が必要と思われる。

上行結腸癌に対する右結腸切除により偶然発見された虫垂異物の1例

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A Case of Foreign Body in the Vermiform Appendix Detected Accidentally after Right Colectomy for Ascending Colon Cancer.

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Abstract

We report an 85-year-old man who had a foreign body in the appendix, which was identified in the right colon specimen resected for ascending colon cancer, with a review of literature. The patient underwent right colectomy for preoperative diagnosis of ascending colon cancer of cSS, cN0, cH0, cP0, cM0, and cStage II. In addition to ascending colon cancer, a black resin needle-like foreign body was identified at the tip of the appendix in the resected specimen, histologically showing a foreign body reaction. While a foreign body was not identified in the appendix preoperatively, postoperative review showed a foreign body finding only on computed tomography (CT). Foreign bodies in the appendix have been reported in Japan were generally described as long thin hard substances that can enter the orifice of the appendix; specifically, fish bones accounted for the majority. Imaging diagnosis showed no findings in 50% of patients on plain abdominal radiographs, and the foreign bodies were identified on CT. In addition, there are few reports of asymptomatic foreign bodies in the appendixes as in our case; most patients had acute appendicitis of varying severities and underwent surgery, suggesting a foreign body in the appendix to possibly be a cause of acute appendicitis.

Key words: foreign body of vermiform appendix, gastrointestinal foreign body, asymptomatic

和文抄録

上行結腸癌に対する右結腸切除の切除標本に虫垂異物を認めたので、文献的考察を加えて報告する。症例は85歳、男性。上行結腸癌cSS, cN0, cH0, cP0, cM0, cStageIIの術前診断で右結腸切除術を行った。切除標本の虫垂先端に黒い樹脂製で針状の異物を認め、組織学的に異物反応が認められた。術後にCT所見の見直しを行ったところ、虫垂に異物の所見を認めた。本邦における虫垂異物の報告の多くが虫垂開口部に迷入可能な細長く硬い異物で、具体的には魚骨が過半数を占めた。画像診断では5割が腹部単純X線写真で所見を認めず、CTで指摘されていた。また、本症例のように無症候性虫垂異物の報告は少なく、多くが種々の程度の急性虫垂炎を来して手術が行われており、虫垂異物が急性虫垂炎の原因になり得ることが示唆された。

キーワード：虫垂異物，消化管異物，無症候性

はじめに

虫垂内への異物迷入により虫垂炎をきたすことが以前から報告されている。しかし、無症候性の虫垂異物の頻度は多いことが推測されるが、その報告はほとんどない。今回、われわれは、上行結腸癌に対し右結腸切除を行い、その切除標本内に無症候性の虫垂異物を認めた症例を経験したので、若干の文献的考察を加えて報告する。

症例

患者：85歳男性

主訴：黒色便

既往歴：高血圧、前立腺癌に対し加療中。心筋梗塞にて加療歴あり。

現病歴：黒色便を主訴に前医を受診し、血液検査にてCEAの上昇を認め、大腸癌が疑われた。FDG-PETにて

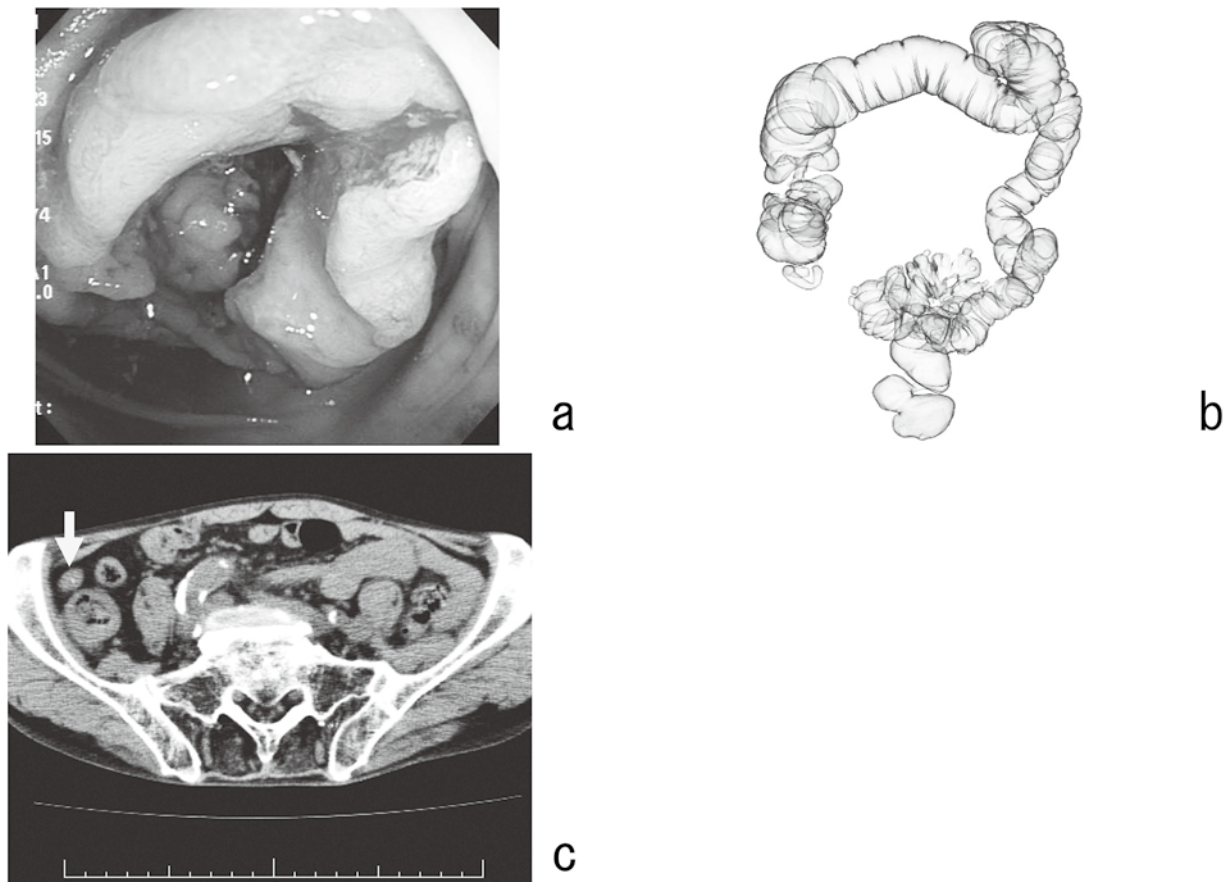


Fig. 1 (a)大腸内視鏡検査：ほぼ全周性の2型の腫瘍を認める。(b) CT virtual colonoscopy：上行結腸にapple core sign様所見を認める。(c) 単純CT：虫垂内に点状の高吸収域を認める。

上行結腸に集積を認めたため、結腸癌が疑われ、精査加療目的に当院に紹介となった。

入院時検査所見：血液生化学検査にて貧血と低蛋白血症を認めるほか、軽度のCRP上昇（1.9mg/dl）を認めた。腫瘍マーカーはCEAの著明な高値（23.9ng/ml）、CA19-9の軽度の上昇（39.9U/ml）を認めた。

大腸内視鏡検査所見：上行結腸に全周性の2型の腫瘍を認めた（Fig.1a）。

腹部CT検査：上行結腸の原発巣に一致する壁肥厚を認めたが、明らかなリンパ節転移は認めなかった。Virtual colonoscopyでは上行結腸にapple core sign様の所見を認めた（Fig.1b）。術後の見直しで虫垂先端部に3スライスにわたって点状の高吸収を認め（Fig.1c）、針状の異物を指摘しえた。

手術所見：以上から上行結腸癌 cSS, cN0, cH0, cP0, cM0, cStageIIと診断し、D2リンパ節郭清を伴う右結腸切

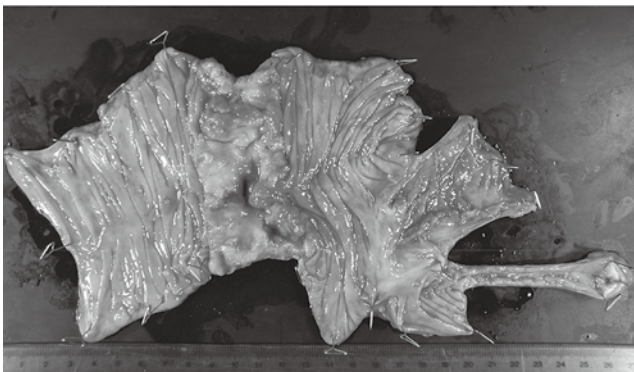
除を施行し、再建は回腸・横行結腸の器械吻合にて行った。術中、腹腔内に目立った癒着は認められず、虫垂周囲の癒着や虫垂の壁肥厚など、急性/慢性虫垂炎を思わせる所見は認めなかった。結腸癌の手術診断はsSS sN0 sH0 sP0 cM0 sStageIIであった。

切除標本肉眼所見：上行結腸に9.0×3.6cm大の2型の進行結腸癌を認めた（Fig.2a）。

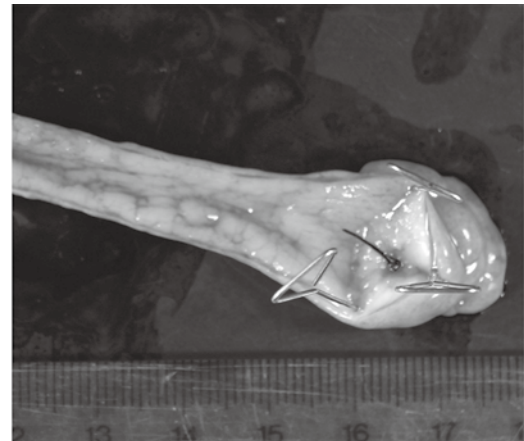
また、虫垂先端部内腔側に約9mm長の異物を認めた（Fig.2b）。異物は黒い樹脂製で針状の形状をしていた（Fig.2c）。虫垂に穿孔や穿通の所見は認められず、肉眼的に虫垂炎の所見は全く認められなかった。

病理組織学的所見：上行結腸癌は高分化～低分化腺癌で、深達度SE, ly1, v1であり、リンパ節転移は認められず、最終病期はStageIIであった。虫垂先端部の異物があった部位には異物反応が認められた。

術後経過：術後経過は良好で第19病日に退院し、現在外来通院中である。



a



b



c

Fig. 2 切除標本：(a)上行結腸に2型の腫瘍を認める。(b)虫垂先端に黒い針状の異物を認める。(c)異物は樹脂製で針状、全長約9mmであった。

Table 1 過去30年間の自験例を含む本邦における虫垂異物の報告55例

報告者	年齢	性別	異物の記載	虫垂穿孔	発見機・主訴	異物発見時の 異物による症状	X線所見	CT所見	術前診断	術前診断	異物の 術前診断	術式	異物誤飲に 関連する既往	文献
吉田	63	男	魚骨	有	右臍(各)部痛	有	描出なし	高吸収	消化管穿孔上行結腸憩室炎	消化管穿孔上行結腸憩室炎	有	虫垂切除		4
高橋	68	女	魚骨	有	右下腹部痛	有	描出なし	高吸収	虫垂穿孔	虫垂穿孔	有	虫垂切除		5
平岡	81	女	魚骨	有	右下腹部痛	有	描出なし	高吸収	虫垂穿孔	虫垂穿孔	有	虫垂切除		6
酒部	48	女	N.D.	有	右下腹部痛	有	N.D.	高吸収	虫垂炎か回盲部腫瘍	虫垂炎か回盲部腫瘍	無	回盲部切除		7
平原	47	男	魚骨	有	右下腹部痛	有	N.D.	高吸収	虫垂穿孔	虫垂穿孔	有	虫垂切除		8
大屋	65	男	魚骨	有	腹痛	有	N.D.	高吸収	虫垂穿孔	虫垂穿孔	有	虫垂切除		9
花本	56	男	魚骨	有	右下腹部痛	有	N.D.	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		10
小沢	30	女	魚骨	有	右下腹部痛	有	描出なし	描出なし	急性虫垂炎	急性虫垂炎	無	腹腔鏡下虫垂切除		11
河俣	49	男	魚骨	有	下腹部痛	有	描出なし	高吸収	虫垂穿孔かS状結腸穿孔	虫垂穿孔かS状結腸穿孔	有	虫垂切除		12
濱田	70代	男	魚骨	有	右側腹部痛	有	N.D.	高吸収	虫垂穿孔	虫垂穿孔	有	虫垂切除、右尿管部分切除		13
中尾	57	男	魚骨	無	腹痛	有	描出なし	高吸収	急性虫垂炎	急性虫垂炎	無	腹腔鏡下虫垂切除		14
池田	51	女	N.D.	無	N.D.	有	N.D.	魚骨	N.D.	N.D.	N.D.	開腹手術(術式N.D.)		15
繁本	55	女	魚骨	有	右下腹部痛	有	描出なし	描出なし	急性虫垂炎	急性虫垂炎	無	虫垂切除		16
伊藤	57	男	魚骨	無	右下腹部痛	有	描出なし	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		17
明石	54	男	魚骨	無	右下腹部痛	有	描出なし	高吸収	盲腸周囲炎	盲腸周囲炎	有	回盲部切除		18
久下	43	男	魚骨	有	下腹部痛	有	描出なし	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		19
北原	69	男	魚骨	有	右下腹部痛	有	描出なし	高吸収	急性虫垂炎	急性虫垂炎	有	回盲部切除		20
二村	30	男	魚骨	無	右下腹部痛	有	描出なし	N.D.	急性虫垂炎	急性虫垂炎	無	虫垂切除		21
大岡	59	男	N.D.	無	右下腹部痛	有	描出なし	N.D.	急性虫垂炎	急性虫垂炎	無	虫垂切除		22
鯉野	48	女	魚骨	有	右下腹部痛	有	描出なし	高吸収	虫垂炎か回盲部腫瘍	虫垂炎か回盲部腫瘍	無	虫垂切除		23
鯉野	59	男	魚骨	無	右下腹部痛	有	描出なし	高吸収	虫垂腫瘍	虫垂腫瘍	無	虫垂切除		24
鯉野	48	女	魚骨	無	右下腹部痛	有	描出なし	高吸収	急性虫垂炎	急性虫垂炎	有	虫垂切除		25
大栗	21	女	魚骨	無	右下腹部痛	有	描出なし	高吸収	絞扼性イレウス	絞扼性イレウス	無	虫垂切除、小腸部分切除		26
山根	47	女	N.D.	無	右下腹部痛	有	描出なし	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		27
綿川	51	男	魚骨	無	右下腹部痛	有	描出なし	N.D.	急性虫垂炎	急性虫垂炎	無	虫垂切除		28
志田	54	男	N.D.	有	下腹部痛	有	描出なし	腫瘍陰影	回盲部慢性腫瘍	回盲部慢性腫瘍	有	虫垂切除、小腸部分切除	脳梗塞	29
火爪	55	男	魚骨	有	右下腹部痛	有	N.D.	N.D.	急性虫垂炎	急性虫垂炎	無	虫垂切除		30
村瀬	48	男	魚骨	有	右下腹部痛	有	描出なし	描出なし	腹腔内腫瘍	腹腔内腫瘍	無	虫垂切除、小腸部分切除		31
飯田	56	男	N.D.	有	右下腹部痛	有	描出なし	描出なし	原発性虫垂癌	原発性虫垂癌	無	右半結腸切除		3
木村	38	男	魚骨、蜜の爪	有	右下腹部痛	有	N.D.	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		32
加藤	50代	男	歯牙	無	下腹部痛	有	高吸収	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		33
寺内	77	男	歯牙	有	右下腹部痛	有	高吸収	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		34
高埜	46	女	義歯	有	右下腹部痛	有	義歯	義歯	急性虫垂炎	急性虫垂炎	有	虫垂切除		35
久保	49	男	義歯	有	右下腹部痛	有	義歯	義歯	急性虫垂炎	急性虫垂炎	有	虫垂切除		36
関根	52	男	N.D.	有	下腹部痛	有	高吸収	高吸収	消化管穿孔	消化管穿孔	有	虫垂切除	統合失調症	37
鎌山	77	男	N.D.	有	右下腹部痛	有	異物陰影	異物像	消化管穿孔	消化管穿孔	有	虫垂切除	右脳梗塞、左脳出血	38
中尾	33	男	歯科補綴物	有	心窩部痛	有	N.D.	腫瘍陰影	虫垂穿孔	虫垂穿孔	有	虫垂切除		39
中島	63	女	植物性異物	有	右下腹部痛	有	N.D.	N.D.	子宮肉腫か右卵巣腫瘍	子宮肉腫か右卵巣腫瘍	無	虫垂切除		40
碓田	80代	女	N.D.	有	右下腹部痛	有	N.D.	腫瘍陰影	急性虫垂炎	急性虫垂炎	無	虫垂切除		41
磯田	81	男	内臓クリップ	有	右下腹部痛	有	内臓クリップ本	内臓クリップ本	虫垂穿孔	虫垂穿孔	有	虫垂切除		42
小濱	56	男	内臓クリップ	有	上腹部痛	有	高吸収	高吸収	急性虫垂炎	急性虫垂炎	無	虫垂切除		43
川嶋	3	男	金属片	無	腹部単純X線	無	高吸収	高吸収	虫垂内かメックル憩室内異物	虫垂内かメックル憩室内異物	有	腹腔鏡下虫垂切除		44
小嶋	40	女	釘	有	左下腹部痛	有	釘	N.D.	右下腹部異物	右下腹部異物	有	虫垂切除	精神発達遅滞	45
近藤	2	男	釘	有	釘の誤飲	無	釘	N.D.	虫垂異物	虫垂異物	有	虫垂切除		46
藤原	2	男	ネジ	無	腹部単純X線	無	ネジ	N.D.	虫垂異物	虫垂異物	有	腹腔鏡下虫垂切除		47
藤田	52	男	ピン	無	右下腹部痛	有	ピン	N.D.	虫垂異物	虫垂異物	有	虫垂切除	アルコール性肝障害	48
杉浦	52	女	待ち針	有	待ち針の誤飲	無	待ち針	待ち針	虫垂異物	虫垂異物	有	大腸内視鏡的除去	精神発達遅滞	49
藤澤	39	女	待ち針	無	待ち針の誤飲	無	待ち針	高吸収	回盲部異物	回盲部異物	有	腹腔鏡下虫垂切除		50
東	35	男	縫い針	無	腹痛	無	縫い針	縫い針	盲腸、虫垂内異物	盲腸、虫垂内異物	有	虫垂切除	シンナー吸入、寛解剤服用	51
高橋	16	男	ホチキス針	無	腹部単純X線	無	ホチキス針	N.D.	急性虫垂炎	急性虫垂炎	有	回盲部切除		52
千賀	4	男	コンデンサー	無	腹部単純X線	無	高吸収	N.D.	虫垂穿孔	虫垂穿孔	有	虫垂切除		53
田澤	29	女	毛髪	有	下腹部痛	有	描出なし	N.D.	急性虫垂炎	急性虫垂炎	無	虫垂切除	異食症	54
竹村	62	男	木片	有	右下腹部痛	有	描出なし	高吸収	消化管穿孔	消化管穿孔	有	虫垂切除		55
自験例	86	男	片状の樹脂製物	無	右結腸切除	無	描出なし	高吸収	上行結腸腫瘍	上行結腸腫瘍	無	右結腸切除		

N.D.: No Description

考察

消化管異物の中で、切除虫垂内に異物が存在する割合は0.05%と報告されている¹⁾。虫垂は入り口が狭く、異物は迷入しにくい²⁾、一旦異物が迷入すると、虫垂は先端方向への弱い蠕動運動を有することにより、迷入した異物は排出されにくいという特徴がある³⁾。

本邦で1984年1月から2013年12月までの30年間について、「虫垂」および「異物」をキーワードに医学中央雑誌で検索したところ、54例の虫垂異物の報告があり、これに自験例を加えた55例を検討した (Table 1)。年齢は2歳から80歳代と幅広く、男女比は40:15と男性に多い。異物の種類は、日本人の食生活を反映し、魚骨が31例 (56%) と最も多く、歯牙・義歯・歯科補綴物の7例 (13%) が続いた。自験例のような外来性・非食餌性異物については、13例 (24%) の報告があった。このうち5例は幼児・小児で、薬物中毒患者が1例³¹⁾、精神発達遅滞が2例、2例は医原性異物であり、通常の成人例において魚骨や義歯等の食餌性または内因性異物が多いのと対照的であった。

自験例では術前に症状がなく、術後に問診を行ったが、記憶しておらず、最終的にその由来は不明であった。

異物誤飲を起こす原因としては、口腔内の器質的疾患、軟口蓋を覆う義歯やアルコール摂取による口腔内知覚鈍麻、早急な摂食による不十分な咀嚼、精神障害、視覚障害などが挙げられている²⁾。また、老齢による認知機能の低下も原因の一つとなり得ると考えられる。自験例ではごく軽度ではあるが認知症があり、軟口蓋を覆う義歯を装着していたこともあり、食餌に混入していたものを異物と認識できずに誤飲してしまったものと思われた。

異物の形状としては、自験例を含め、硬く細長い棒状あるいは一端が鋭利なものが41例 (75%) と最も多い。これは虫垂入口部および内腔が狭いため、このような形状が虫垂異物の特徴であると思われた。

画像診断では、腹部単純X線写真とCTの双方が行われた34例のうち、腹部単純X線写真で異物がみられず、CTで17例 (50%) に発見されていた。6例 (18%) ではCTでも異物の所見を認めなかった。自験例で再度検討したところ、CTのみで虫垂に異物の所見を指摘しえた。

自験例は上行結腸癌に対する手術で偶然発見された無症候性の虫垂異物であった。55例のうち、無症候性の虫垂異物は幼児の異物誤飲4例^{44) 46) 53)}を含む8例 (15%) であり、発見時に無症候性で、後に症候性となったものが3例^{51) ~ 53)}であった。これは無症候性の虫垂異物も後に症候性となる可能性が低くないことを示唆している。一方、無症候性の虫垂異物の報告が少ないのは、そもそも無症候性であるがために虫垂異物が発見されることが少なく、報告されていないためとも考えられる。自

験例が無症候性であったのは、異物が小さく、先端まで入り込んでおり、虫垂を穿孔したり、虫垂内腔を閉塞したりすることがなかったためと思われた。その他の47例 (85%) については種々の程度の急性虫垂炎を来して手術が行われており、これらのことから虫垂異物が急性虫垂炎の原因になりえる可能性が示唆された。

結語

比較的まれな虫垂異物の1例について最近30年間に本邦で報告された虫垂異物の55例の検討を加え報告した。虫垂異物が指摘された場合、無症候性といえども定期的な経過観察が必要である可能性が示唆された。

なお、本論文の要旨は第71回日本臨床外科学会総会(京都)において発表した。

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Sporadic Medullary Thyroid Carcinoma in Grave's disease -Report of a case-

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Abstract

A 60-year-old man who noted numbness and dyskinesia of his left-hand fingers was admitted to a hospital. After anticoagulant therapy and medication with L-3, 4-dihydroxyphenylalanine (L-DOPA) were started, his symptoms didn't improve. He was introduced to our institution with gait disturbance and difficulty of articulating properly. L-DOPA was administered under a diagnosis of multiple system atrophy by magnetic resonance imaging. He was also diagnosed as Graves' disease with hyperthyroidism and expression of TSH receptor antibodies. Cervical ultrasonography revealed diffuse thyroid enlargement with abundant blood flow, which was consistent with Graves' disease. A nodule of 6.3 x 8.3 x 9.2mm was also detected in the middle of the right lobe. The nodule was diagnosed as medullary thyroid carcinoma (MTC) by fine needle aspiration cytology (FNAC). The serum calcitonin and CEA level were elevated. We diagnosed sporadic MTC because lacking of pituitary or adrenal tumor, and family history of MTC. After medication for Graves' disease, total thyroidectomy with central lymph nodes dissection was performed. Histopathological examination diagnosed as a MTC the diameter of tumor was 9 mm in the middle of the right lobe without extra thyroidal extension. Most of the thyroid cancers with Graves' disease have been reported to be papillary thyroid cancer. The case of MTC with Graves' disease is very rare with only 12 cases having been reported. We report the case of sporadic MTC with Graves' disease which accidentally diagnosed by episode of multiple system atrophy.

Key words: thyroid cancer; Graves' (Basedow) disease; CEA; calcitonin; concurrence

Introduction

Graves' disease is the most common cause of hyperthyroidism, usually presenting with nodules of thyroid. In patients with both Graves' disease and nodular thyroid disease, thyroid cancer was detected in 2-6 % after surgical treatment ^{1, 2)}. Medullary thyroid carcinoma (MTC) comprises only 1.4-8.7% of all thyroid cancers ^{3, 4)}. In 73 patients who underwent surgery for Graves' disease in our institution from January 2000 through October 2012, the incidence of differentiated thyroid carcinoma (DTC) was 17.8% (13 cases). Histologically, nine patients had papillary thyroid cancer (PTC), two PTC of follicular variant, one follicular thyroid cancer (FTC), respectively. Only one patient (7.6%) had MTC.

We herein report the case of MTC with Grave's disease and also review the literature of such diseases.

Case Report

A 60-year-old man who noted numbness and dyskinesia of his left-hand fingers was admitted to a hospital. Anticoagulant therapy and medication with L-3, 4-dihydroxyphenylalanine (L-dopa) were started, because magnetic resonance imaging (MRI) revealed cerebral infarction. Electromyogram and orthopedics examination were normal. Two months later, gait disturbance occurred and one more month later, he was unable to articulate properly. He was introduced to our

institution for further examination and treatment. Although L-dopa was administered, his symptoms didn't improve. His temperature was 36.3°C, heart rate 68 beats per minute with blood pressure of 117/77 mmHg. Heart rate was regular and atrial fibrillation was not observed. His body weight and height were 71.1kg and 170cm, respectively. Cervical palpation revealed a soft and non-tender thyroid gland without nodules. No exophthalmos or skin changes were found. There were no clinical features other than left-side-dominant extrapyramidal symptoms and no special family history. T2 image on MRI revealed high intensity in the lateral area of the putamen. L-DOPA was administered under a diagnosis of multiple system atrophy.

Serum levels of free triiodothyronine, free thyroxine, and thyroid-stimulating hormone (TSH) were 6.4pg/ml (normal range 2.3-4.0), 2.51ng/ml (normal range 0.9-1.7), and <0.0164 μ IU/ml (normal range 0.5-5.0), respectively. The value of TSH receptor antibodies (TRAb) was high (35, normal range <1.0). Preoperative calcitonin was 220 pg/ml (reference range, 15-86), CEA was 4.0 ng/ml (reference range, 0-5), and thyroglobulin was 50.9 ng/ml (reference range, 0-32), respectively.

Ultrasonography revealed diffuse thyroid enlargement with abundant blood flow, which was consistent with Graves' disease. A nodule of 6.3 x 8.3 x 9.2mm was also detected in the middle of the right lobe (Figure 1). Enlarged lymph nodes weren't detected. Fine needle aspiration cytology (FNAC) based on Papanicolaou stain revealed hyper-cellular tumor with round or elongated nuclei, quite different from

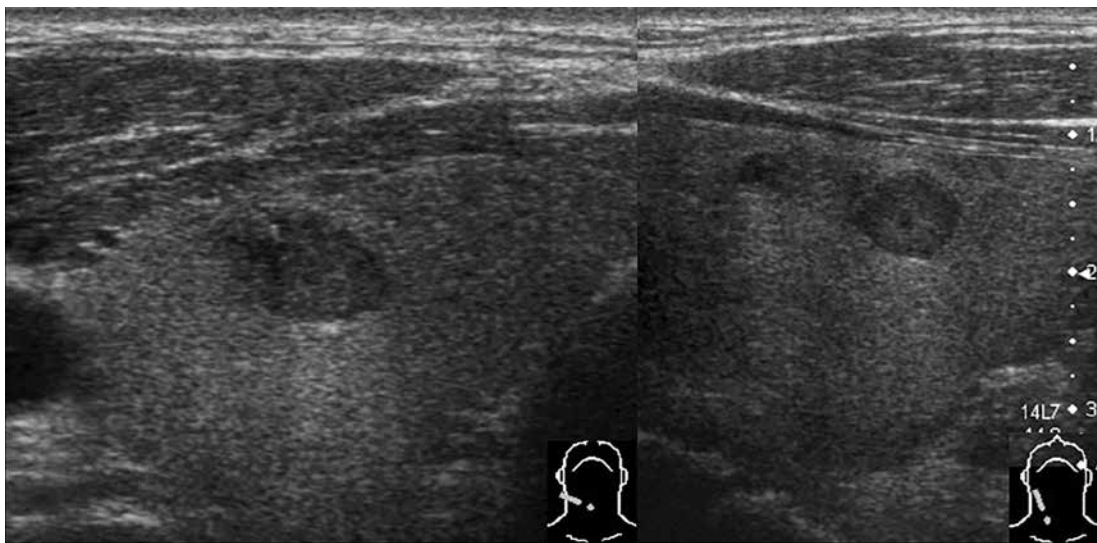


Figure 1: Ultrasonography revealed the presence of a 6.3 x 8.3 x 9.2mm nodule in the middle of the right lobe.

papillary and follicular structures, and an amyloid substance was partly recognized without necrosis (Figure 2). In these findings, the nodule was diagnosed as MTC cytologically.

Computed tomography (CT) of the cervix, chest and abdomen didn't show any metastases or tumors. We diagnosed sporadic MTC because lacking of pituitary or adrenal tumor and family history of MTC. RET gene mutation analysis was not performed because he didn't consent.

Since Graves' disease was probably diagnosed with hyper thyroid state and TRAb positive, thyroid scintigraphy wasn't performed. After medication, total thyroidectomy with central lymph nodes dissection was performed. The diameter of tumor was 9 mm in the middle of the right lobe without extra thyroidal extension (Figure 3). Histopathological examination showed MTC composed of small nests, sheets, and single cells characterized by moderate pleomorphism and hyperchromasia (Figure 4A). Amyloid was present in the background, confirmed by direct fast scarlet staining (Figure 4B). The tumor cells were positive for calcitonin

by immunohistochemistry (Figure 4C). Non-neoplastic thyroid parenchyma was almost normal without features of lymphocytic thyroiditis or hyperplasia. The serum calcitonin was <0.1ng/l at 55 months after surgery.

Discussion

Overt Graves' disease and DTC are relatively rarely associated. It has been reported that the incidence of DTC with Graves' disease ranged from 0.76% to 9.8%⁵⁻⁸). Thyroid nodules with Graves' disease are reportedly only palpable in the range of 15% to 25%^{6,9}). The risk of cancer in palpable thyroid nodules is controversial. The majority studies reported that there was no significant difference in DTC incidence between Graves' disease and other toxic nodular goiter¹⁰⁻¹⁸).

FNAC is a useful tool to evaluate thyroid nodules. The majority of DTC with Graves' disease are PTC, followed by FTC, as in the general population. According to our survey, only 12 cases of MTC combined with Graves' disease have

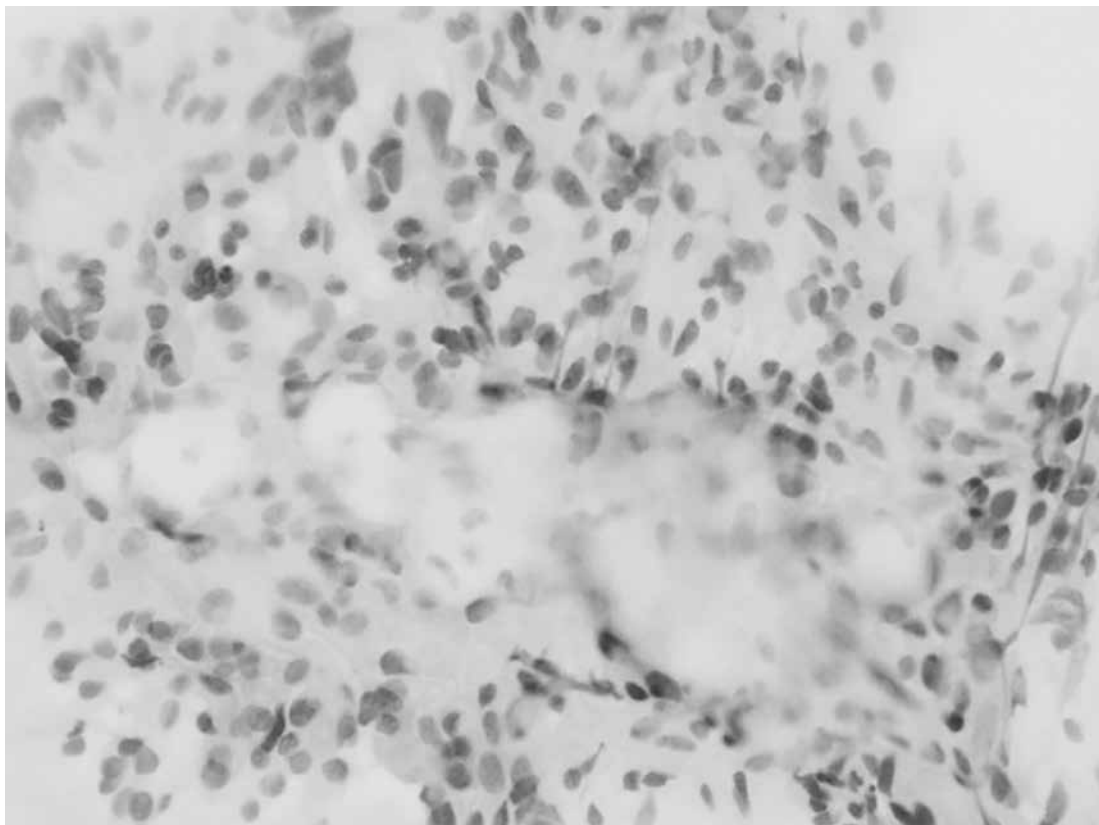


Figure 2: The tumor cells revealed round or elongated nuclei with non-papillary and non-follicular structures, and amyloid substance was recognized without necrosis.



Figure 3: The tumor was 9mm in diameter in the middle of the right lobe without extrathyroidal extension.

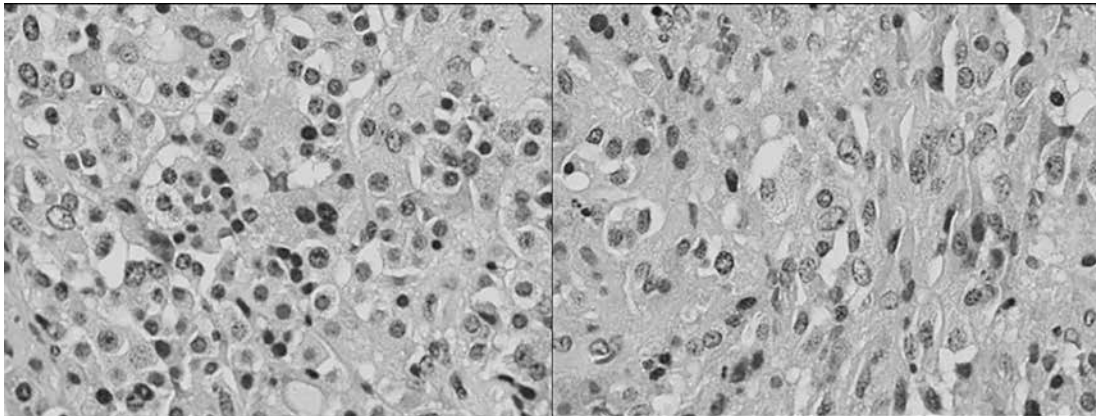


Figure 4A: Histopathological examination showed a medullary carcinoma composed of small nests, sheets, and single cells characterized by moderate pleomorphism and hyperchromasia.

been reported in the literature¹⁹⁻²⁸). Although MTC with Graves' disease is very rare, MTC may be also suspected by FNAC. Immunohistochemical staining against calcitonin and Congo red (direct fast scarlet) staining for amyloid substance should be considered when the cytological diagnosis suggests MTC. FNAC, measurement of serum calcitonin and CEA are useful for the diagnosis of MTC. In the case of a normal upper limit of serum calcitonin or CEA, measurement of calcitonin in wash-out fluid from fine needle aspiration is useful^{29,30}).

The patient was incidentally diagnosed as having MTC with Graves' disease. He had no certain clinical features suggesting multiple endocrine neoplasia such as diarrheal syndrome, flushing or a specific family history. Neither

thyroid nodule nor neck lymph nodes were palpable. Although MTC with Graves' disease is uncommon, FNAC was able to detect such a rare disease. Left-side-dominant extrapyramidal symptoms he first noted numbness and dyskinesia were not improved with the surgical treatment.

In conclusion, meticulous examination by ultrasound is also needed in Graves' disease as well as hormonal examination; and if abnormal nodules are found, FNAC is strongly recommended without overlooking thyroid malignancy combined with Graves' disease.

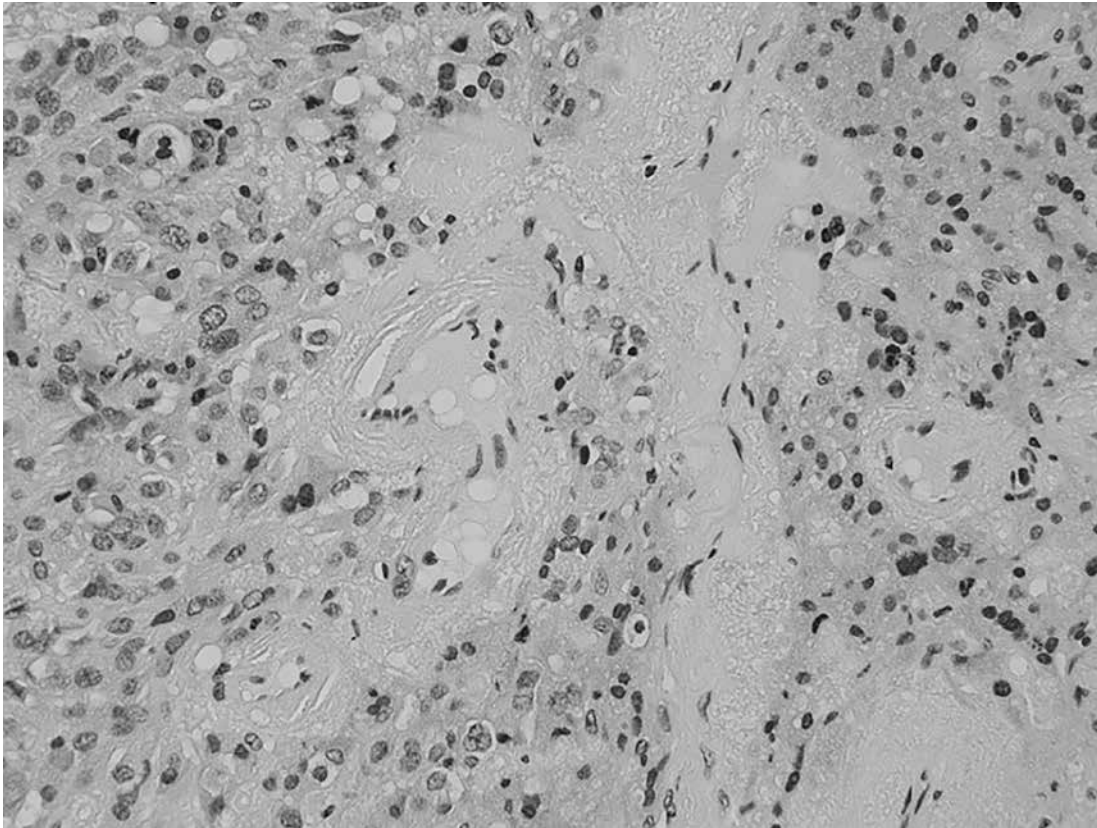


Figure 4B: Amyloid was present in the background, confirmed by Congo red (direct fast scarlet) staining.

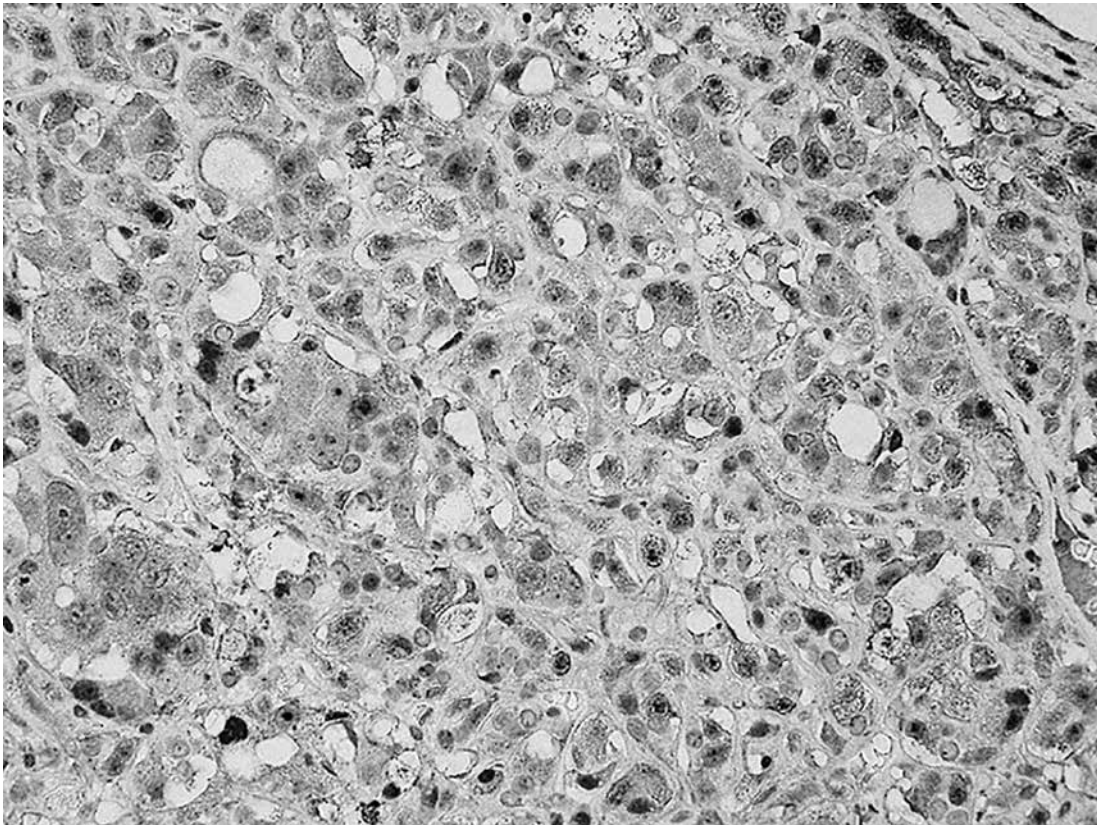


Figure 4C: The tumor cells showed positivity for calcitonin by immunohistochemistry.

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和文要約

症例は 60 歳男性。左手指のしびれ・ジズキネシアを主訴に近医入院。脳梗塞やパーキンソン病を疑われ治療をされるも改善が認められなかった。その後、歩行障害の出現と徐々にろれつが回りにくいことに気付き、当院紹介受診。頭部 MRI 施行され多系統萎縮症を疑われ内服加療となった。採血にて甲状腺機能亢進・TRAb 陽性にてバセドウ病(Graves' disease) の診断となった。頸部超音波検査では、血流豊富で腫大した甲状腺が描出され、バセドウ病が疑われた。また、甲状腺右葉中部に 6.3 x 8.3 x 9.2mm の低エコー結節を認めた。超音波下穿刺細胞診まで施行し甲状腺髄様癌の診断となった。カルシトニン及び CEA の上昇も認められた。家族歴はなく、全身検索も行ったがその他の腫瘍性病変は認めず、散発性甲状腺髄様癌の診断となり甲状腺全摘術、リンパ節郭清を施行した。病理診断にて甲状腺右葉中部に 9x7mm の限局型髄様癌を認めるのみでリンパ節転移も認めなかった。現在まで再発・転移は認めていない。甲状腺髄様癌は全甲状腺癌の中でも 2～3% と稀な疾患で、バセドウ病における甲状腺癌の合併は乳頭癌が一般的に多く、髄様癌の報告はこれまで 12 例のみである。今回我々は、多系統萎縮症の精査の際に偶然バセドウ病を合併した散発性甲状腺髄様癌が診断された、貴重な 1 例を経験したので報告する。

成人紫斑病性腎炎に対するステロイド療法の検討

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Effectiveness of Steroid Therapy for Henoch-Schönlein Purpura Nephritis

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Abstract

Purpose: Steroid therapy has been established for pediatric patients with Henoch-Schönlein purpura nephritis (HSPN). Therefore, adult patients with HSPN have been treated with steroid alone or combined with tonsillectomy. However the effect of steroid therapy with or without tonsillectomy in adult patients remains to be determined. This study aims to evaluate whether steroid therapy with or without tonsillectomy affects the clinical course of adult HSPN patients.

Methods: We retrospectively investigated nine adult patients, including five men, with biopsy-proven HSPN from 2006 to 2012, followed by observation for more than 12 months (range: 19 to 97 months).

Results: The median age of the patients was 36 years (range 20 to 72) at the time of renal biopsy. Three patients received steroid pulse therapy combined with tonsillectomy, and three received steroid therapy. In three additional patients, one was treated with an angiotensin II receptor blocker (ARB) and dilazep, one was treated with a Ca blocker, and the other did not receive any medication. Except for the patient receiving the Ca blocker, eight patients were in remission throughout the observation period. Notably, two of

three patients treated with steroid pulse therapy and tonsillectomy and one of three with steroid exhibited a rapid decrease in urinary excretion of protein, resulting in remission within a year.

Conclusions: All patients receiving steroid therapy with or without tonsillectomy were in remission. These results suggest that steroid therapy alone, regardless of tonsillectomy, is likely effective in adult patients with HSPN.

Key words: Henoch-Schönlein purpura nephritis, tonsillectomy, steroid

緒言：紫斑病性腎炎(Henoch-Schönlein purpura nephritis：以下HSPN)は、IgA型免疫複合体が関与した全身性血管炎のHenoch-Schönlein紫斑病(HSP)に合併した腎炎である。成人HSPは50～80%で腎炎を合併し、小児に比して重症化することが多い¹⁾。しかし、成人HSPNは発生数が少ないため、有効性の証明された治療法は確立されておらず、口蓋扁桃摘出術＋ステロイドパルス療法（以下扁桃摘パルス療法）が有効であったHSPN症例が報告されているにすぎない^{2), 3)}。今回我々は扁桃摘パルス療法を実施した3例を含む成人紫斑病性腎炎9例の臨床経過について検討した。

方法：2006年8月～2012年4月に当院において腎生検を

施行し、HSPNと診断した症例のうち、1年以上経過観察可能であった9例を対象とした。なお本研究は当院臨床研究倫理委員会で承認され【承認番号26-83】、文書同意が得られた症例を対象としている。観察期間は2005年12月～2014年11月とし、腎生検日を観察開始日とした。治療の内訳は①ステロイド療法群6例（扁桃摘パルス療法3例を含む）、②経過観察群3例（アンジオテンシン受容体拮抗剤(ARB)、ジラゼブ塩酸塩等）で、尿潜血陰性化(定性±以下またはRBC 5個/High Power Field未満)と尿蛋白陰性化(定性±以下または0.3g/gCr未満)の両者が得られた状態を寛解と定義した。eGFRは血清Crに基づくGFR推算式（ $194 \times \text{Cr}^{-1.094} \times \text{年齢}^{-0.287}$ (女性は $\times 0.739$))を用いて算出した。

Table 1. Basic characteristics of the patients

	全体 (n = 9)
年齢, 中央値 (範囲)	36.0(20-72)
性別 (男 / 女)	5/4
BUN * (mg/dL)	14.3±5.9
Cr * (mg/dL)	0.78±0.31
eGFR * (mL/min/1.73m ²)	86.7±28.8
IgA * (mg/dL)	453±412
C3 * (mg/dL)	101.5±13.2
CRP * (mg/dL)	1.7±2.8
ASO * (IU/mL)	111.5±130.4
U-TP * (g/gCr)	3.49±4.25
Complication	
Purpura	9
Nephrotic syndrome	3
Arthralgia	4
Abdominal pain	3
ISKDC Grade (I , II , III , IV , V)	1,3,5,0,0

* Values are expressed as mean±SD. U-TP : proteinuria

結果：患者背景は、年齢(中央値)36歳(20-72歳)、男性5例、平均血清Cr 0.78 ± 0.31 mg/dL、平均eGFR 86.7 ± 28.8 mL/min/1.73m²、平均尿蛋白は 3.49 ± 4.25 g/gCrで、平均観察期間は 39.4 ± 23.3 ヶ月であった(Table 1.2)。3例(33.3%)にネフローゼ症候群を認め、うち1例は腎生検後に尿蛋白が増加して、ネフローゼ症候群に至った症例であった。関節痛は4例(44.4%)、腹痛は4例(44.4%)に認められたが、腹痛例の1例からはノロウイルスが検出された。International Study of Kidney Disease in Childhood (ISKDC)分類はgrade Iが1例、grade IIが3例、grade IIIが5例であった。扁桃誘発試験が陽性であった2例及びステロイド抵抗性かつHBV既往感染が疑われた1例の計3例に扁桃パルス療法を施行した。またネフローゼ症候群の1例にステロイドパルス療法、検尿所見および組織所見が軽症であり外来での加療を希望された1例にステロイド内服単独、ステロイド抵抗性の1例にステロイド・Cyclosporin A(CyA)併用治療を施行した。経過観察した3例は組織障害軽度(ISKDC grade II)の早期尿蛋白陰性化例や、積極的な治療を実施できない妊娠・授乳例(ISKDC grade III)、組織障害軽度(ISKDC grade I)の高齢者例で、それぞれARB+ジラゼブ塩酸塩、無投薬、Ca拮抗薬で観察されていた。なお経過観察した3例は全例半月体形成を認めなかった。全9例において観察期間中に急激な腎機能増悪およびHSPNの再燃は認めなかった。

患者背景を比較すると、尿蛋白の多い症例にステロイド療法が施行されており、扁桃パルス療法は扁桃誘発試験が陽性あるいはステロイド抵抗性でかつHBV既往感

染があるために免疫抑制剤の追加にリスクを伴う症例で行われていた。経過観察群に比べステロイド療法群は血清IgA、CRP、尿蛋白、ISKDC gradeが高い傾向がみられた。一方、経過観察群では尿蛋白が 0.43 ± 0.22 g/gCrと少ない傾向がみられた。

ステロイド療法群6例(扁桃パルス療法3例、ステロイド療法3例)と経過観察群3例において治療前後の尿蛋白、血清CrおよびeGFRを検討した(Fig.1)。ステロイド療法群では入院時に尿蛋白増加がなかった1例を除いた5例で治療後に尿蛋白が著明に減少していた。一方、経過観察群ではCa拮抗薬で観察されていた1例で1年後に尿蛋白の増加を認めた。治療前にネフローゼ症候群、血清Cr上昇がみられた1例は、ステロイド・CyA併用治療によって改善がみられたが、ステロイド療法群の2例では血清Crが増悪した。一方、治療前にeGFRの低下がみられたステロイド療法群の1例ではその改善がみられたが、扁桃パルス療法の1例とステロイド療法群の1例ではeGFRは低下した。

全症例における経過および寛解までに要した期間を検討したところ、ステロイド療法群では6例全例に寛解が得られ、3例は1年以内に寛解していた(Table 3)。ステロイド療法群で寛解に1年超を要した3例のうち、2例はネフローゼ症候群をきたしており、腎炎の活動性が高かったことが原因と考えられた。また寛解に13ヶ月を要した1例は、尿蛋白がもともと少なく、外来での加療を希望されたために、治療開始ステロイド量が 0.56 mg/kgと少なかったことが影響したと考えられた。一方、経過観

Table 2. Characteristics of patients at baseline

	ステロイド群 (n = 6)	保存的加療群 (n = 3)
年齢	45.8±20.0	42.7±26.6
性別 (男 / 女)	3/3	2/1
BUN(mg/dL)	14.3±7.32	14.3±2.49
Cr(mg/dL)	0.80±0.35	0.80±0.30
eGFR(mL/min/1.73m ²)	83.9±29.6	92.3±32.6
IgA(mg/dL)	515.0±507.3	331.2±45.0
C3(mg/dL)	102.2±8.2	100.3±21.8
CRP(mg/dL)	2.38±3.26	0.28±0.32
ASO(IU/mL)	82.4±95.5	160.0±188.8
U-TP(g/gCr)	5.0±4.54	0.47±0.19
ISKDC Grade (I , II , III , IV , V)	0, 2, 4, 0, 0	1, 1, 1, 0, 0

Values are expressed as mean±SD.

察した3例では、Ca拮抗薬が投与された1例では寛解が得られず、ARB・ジラゼブ塩酸塩が投与された1例では早期に尿蛋白が陰性化したものの、尿潜血が陰性化するまでに22ヶ月を要した。また無治療の1例も寛解までに87ヶ月と更に長期間を要した。

考察：HSPは紫斑、腹痛、関節痛を三徴候とし、その頻度は紫斑100%、関節炎82%、腹痛63%と報告されている4)。本研究では紫斑は全例(100%)に認められたものの、関節痛・腹痛は共に44.4%といずれも少ない傾向であった。また20-30%の症例に消化管出血を合併し5)、時に急激な転帰をたどる症例も経験されるが、今回の検討では消化管出血を合併した症例はみられなかった。一方、成人HSPN例では15-28%にネフローゼ症候群を呈する6)。今回の検討ではネフローゼ症候群の合併は33.3%とやや高い結果であったが、検尿異常や腎機能障害を認め腎生検を必要とした症例を対象としたためと考えられる。

成人HSPNに対して有効性の証明された治療法は確立されていない。臨床所見が軽症の場合は経過観察となることもあるが、半月体形成率が高い場合やネフローゼ症候群、急速進行性糸球体腎炎を呈した場合にはステロイドパルス療法や免疫抑制剤の併用など積極的な加療が必要となることもある6)。近年、IgA腎症に対する治療法である扁摘パルス療法が有効であった成人HSPN例が報告された2)、3)。HSPNはIgA腎症と同様にIgA型免疫複合体が糸球体に沈着することから7)、扁桃摘出による病

巣感染の除去によりIgA産生が抑制され、ステロイドパルス療法によって糸球体毛細血管の炎症が消退されると考えられる2)。一方、扁摘パルス療法によって、早期寛解が得られたISKDC gradeIVの小児HSPN重症例も報告されている8)。今回の検討ではネフローゼ症候群をきたした症例や扁桃誘発試験が陽性の症例、またステロイド抵抗性かつHBV既往感染のため、免疫抑制剤の併用にリスクを伴う症例で扁摘パルス療法が施行された。ネフローゼ症候群をきたした1例では寛解に20ヶ月と長期間を要したものの、2例では5ヶ月以内と比較的早期に寛解が得られており、扁摘パルス療法の有効性が示唆された。

またISKDC gradeIIIと組織障害の強い症例やネフローゼ症候群をきたした症例に対し、ステロイド療法やCyA併用治療を行い、全例で観察期間内に寛解が得られた。寛解に1年以上を要した症例は、初期のステロイド量が少なかったことが一因と考えられた。ステロイド療法群は経過観察群に比べ、尿蛋白が多い傾向にあったが、ステロイド療法群の方が寛解が早く、ステロイドを用いた積極的な治療は寛解導入に有効であることが示唆された。

一方、経過観察群の3例でも腎機能の増悪はなく、長期間を要したが全例寛解に至った。経過観察群では3例全てにおいて半月体形成を認めず、尿蛋白量も少なかったことから、腎炎の活動性が低かったことによるものと考えられた。また経過観察群の1例はISKDC gradeIIIであったが、腎生検で得られた総糸球体数が4個と少なかったため、組織評価が不十分であったと考えられた。

Table3. Histopathological and laboratory data of all patients

	年齢	性別	ISKDC Grade	治療	血清 Cr(mg/dL)		尿蛋白 (g/gCr)		陰性化に要した期間(月)	
					治療前	1年後	治療前	1年後	潜血	蛋白
ステロイド療法群	35	F	III	扁桃摘出+	0.52	0.57	1.83	0.11	5	5
	55	M	II	ステロイド	0.83	1.05	6.70	0.48	20	15
	20	F	III	パルス	0.52	0.61	1.13	陰性	3	2
	31	F	II	ステロイド	0.65	0.71	9.43	0.14	17	11
	64	M	III	ステロイド	0.80	1.00	0.19	0.12	13	0
経過観察群	70	M	III	ステロイド	1.47	1.16	10.71	0.23	12	11
	36	M	II	ARB + ジラゼブ塩酸塩	1.00	0.90	0.42	0.06	22	2
	20	F	III	なし	0.50	0.50	0.31	0.21	87	74
	72	M	I	Ca拮抗薬	0.75	0.82	0.68	1.1	未寛解	未寛解

IgA腎症においては罹病期間が長いほど糸球体係蹄の非可逆的な障害が進行してしまい、糸球体硬化が進み蛋白尿が消えずに寛解率が低下し、また再発率も上昇する9)。また小児HSPNにおいても組織学的に軽症であっても早期に増悪する症例があること、平均尿蛋白1g/日以上では腎予後が不良であること(血清Cr値2倍への相対危険度1.77倍、透析導入への相対危険度1.73倍)、尿所見の寛解が得られなかった症例では腎機能低下率が高い傾向にあることが報告されている10)、11)、12)。一般的に尿蛋白が少ない症例では積極的に腎生検やステロイド導入は行われず、経過観察となることも多いが、成人HSPNにおいても、寛解率や腎予後、また長期間の通院に伴う社会的なデメリットを考慮すると、寛解を目指して早期にステロイド治療を行う意義はあると考えられる。

成人HSPNの15年後予後は末期腎不全11%とされている13)。成人例での腎機能予後因子として①年齢、②血清Cr、③尿蛋白量、④女性、⑤経過中の平均尿蛋白量が報告されている7)、10)。今回の検討では観察期間が最長でも8年1ヶ月と短期間であること、症例数が少ないことから各群における腎機能の差を認めなかった。また尿蛋白陰性化例では、全例が尿潜血も陰性化して寛解に至っており、尿蛋白の陰性化が成人HSPNの寛解の予測

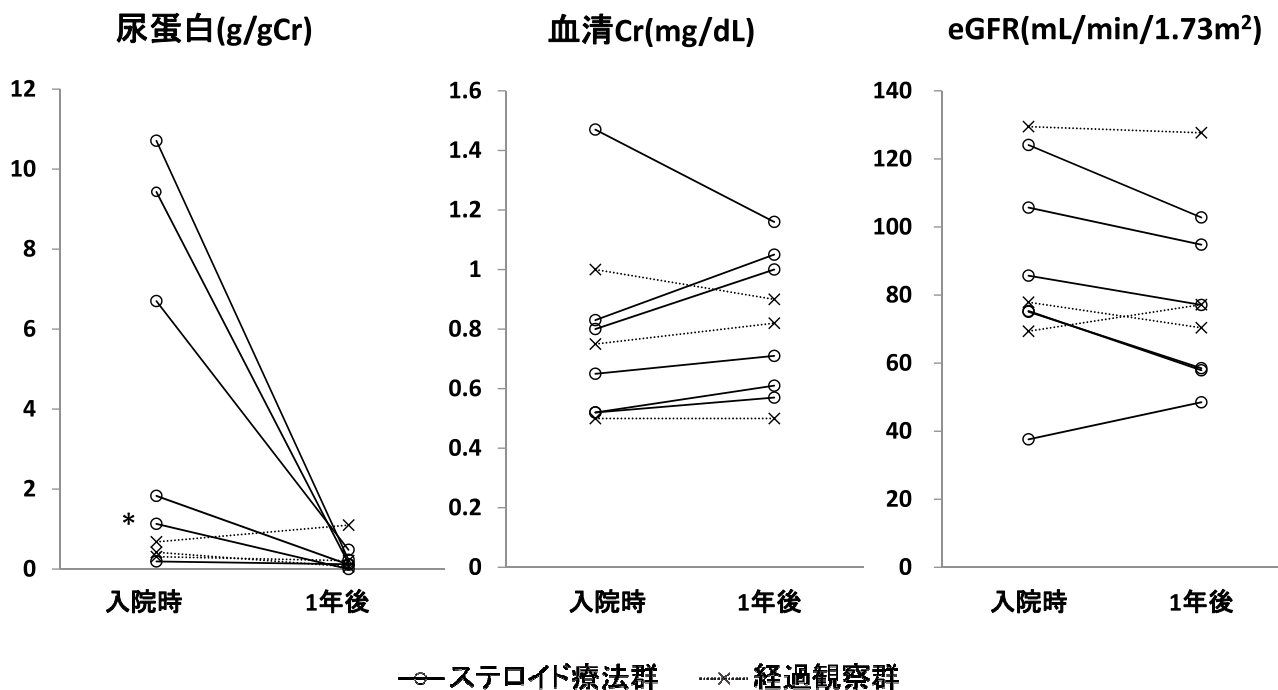
因子になる可能性が示唆された。

今回我々は成人HSPN9例における治療法とその臨床経過について検討し、成人HSPNにおいて、ステロイド療法あるいは扁桃摘出療法による、早期寛解を目的とした積極的治療の意義が考えられた。今回の検討では、症例数が少なく統計学的な解析による評価は困難であるため、今後症例を重ねて更なる検討を行う必要があると考えられた。

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Fig.1 Changes of Urine protein, serum Cr and eGFR from day before therapy to 12-month follow-up



* Because one case that was urine protein negative did not enforce an examination for fixed-quantity one year later, I transcribe it in urine protein 0 mg/dL.

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Reduced port surgery にて腹腔鏡下盲腸切除術を施行した 虫垂粘液嚢胞腺腫の一例

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A Case Report of Appendiceal Mucinous Adenoma Resected by Reduced Port Surgery

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Abstract

Mucinous cystadenoma of the appendix is a relatively rare disease that is a variant of appendiceal mucocele. Because of the risk for peritoneal pseudomyxoma by rupture of appendiceal mucocele, careful maneuvering is required during surgical resection. Although there are many case reports of laparoscopic surgery for appendix mucocele, there are only a few reports of reduced port surgery (RPS). We report a case of mucinous cystadenoma of the appendix that was safely resected by RPS. A 73-year-old man was diagnosed as having mucinous cystadenoma of the appendix and underwent laparoscopic-assisted partial cecectomy. RPS is satisfactorily feasible for the resection of an appendiceal mucocele that requires a precise surgical maneuver.

Key words: Appendiceal mucocele, Mucinous cystadenoma of the appendix, Reduced port surgery

緒言

虫垂粘液嚢胞腺腫は比較的稀な虫垂粘液嚢腫の一種であり、未破裂の虫垂粘液嚢腫に対しては早期の外科手術が必要とされる¹⁾。術式選択に関して、虫垂粘液嚢腫が破裂した際に生じうる腹膜偽粘液腫の発生を避けるためには開腹手術が安全とする報告がある^{2) 3)}。一方、腹腔鏡手術が普及した現在、腹腔鏡下で安全に虫垂粘液嚢腫切除が可能であるとの報告も多数見られる^{4) 5)}。Reduced port surgery (RPS) はポート数の減数や鉗子細径化を併用することでより低侵襲で高い整容性の得られる術式として近年適応症例が増加している^{6) 7)}。しかし、虫垂粘液嚢腫の切除手術に対するRPSの適応や有用性に関する報告は未だ少ないのが現状である^{5) 8)}。

今回、我々はRPSにて安全に腹腔鏡下盲腸部分切除術を施行した虫垂粘液嚢胞腺腫の症例を経験したので報告する。

症例

患者：73歳，男性。

主訴：便潜血陽性。

既往歴：特記事項なし。

家族歴：特記事項なし。

現病歴：自覚症状なし。検診にて便潜血を指摘され，下部消化管内視鏡検査を施行したところ盲腸に腫瘤を指摘されて当科紹介となった。

現症：特記事項なし。

血液検査所見：特記事項なし。CEAの上昇なし。

下部消化管内視鏡検査：盲腸に粘膜下腫瘍様の隆起物があり，その一部に虫垂開口部と思われる環状の構造を認めvolcano signと考えられた(図1)。超音波内視鏡検査では管腔内に突出する嚢胞性病変として描出され，嚢胞内に明らかな腫瘤は認めなかった(図2)。

注腸透視検査：盲腸に3cm大の表面平滑で球状の透亮像を認めたが，虫垂は描出されなかった(図3)。

腹部造影CT検査：虫垂の腫大と虫垂根部付近の液体貯留がみられたが，嚢胞内に充実成分は認めなかった(図4)。

腹部MRI検査：回盲部に3cm大の嚢胞構造あり。T2強調画像で内部信号は中等度高信号であった(図5)。

以上の所見より，虫垂粘液嚢胞腺腫と診断し，嚢腫が虫垂根部に近かったため，腹腔鏡下に盲腸切除あるいは回盲部切除を行う方針とした。

手術所見：臍に25mmの皮膚切開をおきEZアクセス®(Hakko)を装着し，5mmトロッカーを2本挿入した。さらに右下腹部より5mmトロッカーを挿入し，RPSを行った(図6)。虫垂根部は嚢状に腫大し，既知の腫瘍と判断した。周囲への癒着はなく，外側アプローチで盲腸周囲の腹膜を切開し，回盲部を剥離受動した。臍部創より回

盲部を体外に挙上し，直視下に病変とパウヒン弁を確認し，自動縫合器を用いて盲腸部分切除術を行った。

摘出標本肉眼所見(図7)：根部に球状腫瘤を伴い，虫垂は腫大していた。腫瘤内部には多数の粘液球を認めた。病理組織所見：粘膜は平坦あるいは乳頭状に發育する軽度異型を伴った腺管の増生を認め(図8)，虫垂粘液嚢胞腺腫と診断された。

術後経過：術後経過は良好で，術後8日目で軽快退院した。

考察

虫垂粘液嚢腫は虫垂切除例の0.2~0.4%に見られる比較的稀な疾患であり，組織学的に過形成，粘液嚢胞腺腫，粘液嚢胞腺癌の3つに分類される⁹⁾。虫垂粘液嚢腫は中高齢の女性に多く⁹⁾，症状は虫垂の嚢腫形成に起因する右下腹部の腫瘤触知，疼痛，発熱などがある。しかし20~30%は無症状であり，検診等で偶然に見つかることも少なくない^{11) 4)}。鑑別疾患としては盲腸粘膜下腫瘍，虫垂カルチノイド，虫垂膿瘍，卵巣嚢腫，子宮内膜症などがあるが，画像診断のみでは術前診断が困難な場合も多く，術中所見や術後の病理組織診断にて初めて虫垂粘液嚢腫と診断された報告もある¹⁰⁾。また，CT検査で虫垂壁が造影される場合や，内腔への乳頭状隆起や限局性の結節を認める場合には，虫垂粘液嚢胞腺癌が示唆される¹¹⁾が，術前に虫垂粘液嚢胞腺腫と虫垂粘液嚢胞腺癌を鑑別することは困難である。本症例では上述の悪性を疑う所見に乏しかったことから，術前に虫垂粘液嚢胞腺腫と診断した。

虫垂粘液嚢腫の治療には，破裂した際の腹膜偽粘液腫への進展も考慮して早期の外科手術が必要とされる¹⁾。腹膜偽粘液腫は大部分が虫垂腫瘍に起因するとされ¹²⁾，虫垂粘液嚢腫の破裂や粘液の漏出により腹膜偽粘液腫となりうることから，手術操作で病変自体を圧迫しないように，慎重な手術操作が必要である¹³⁾。そのため，虫垂粘液嚢腫からの粘液の漏出を避けるという点で，腹腔鏡手術よりも開腹手術が優れているとする報告もある^{2) 3)}が，腹腔鏡手術を施行した報告も多く，その利点と安全性が報告されている^{4) 8)}。山本らの報告では，これまでの報告例において腹腔鏡手術による術中操作で粘液漏出の報告は認めておらず，安全な手術が可能である⁴⁾。利点としては術後の整容性の向上，疼痛の軽減，早期の術後回復と入院期間の短縮などが挙げられる⁸⁾。

さらに近年では，より良い整容性を考慮した単孔式腹腔鏡手術による虫垂粘液嚢腫切除例の報告もあり⁸⁾，今後も虫垂粘液嚢腫に対する腹腔鏡手術は，安全性を担保して適応拡大していくと思われる。

術式選択に関しては，術前の良悪の鑑別が困難であることから確立されたものはなく，術中所見に応じた柔軟

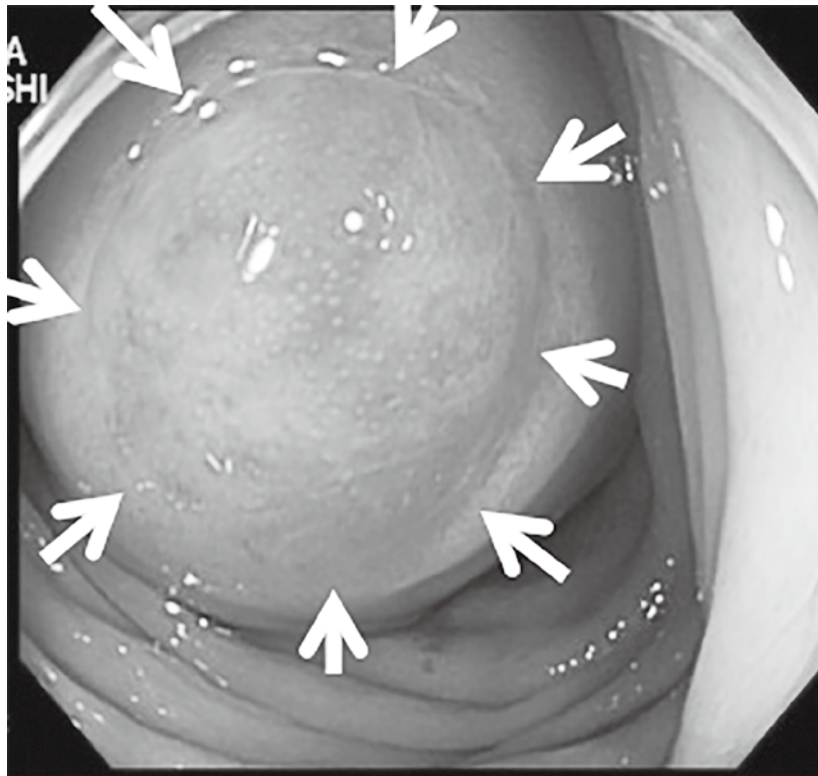


図1 : Colonoscopy

There is a lesion resembling a submucosal tumor in the cecum. The tumor exhibits the volcano sign in the appendiceal opening (white arrows).

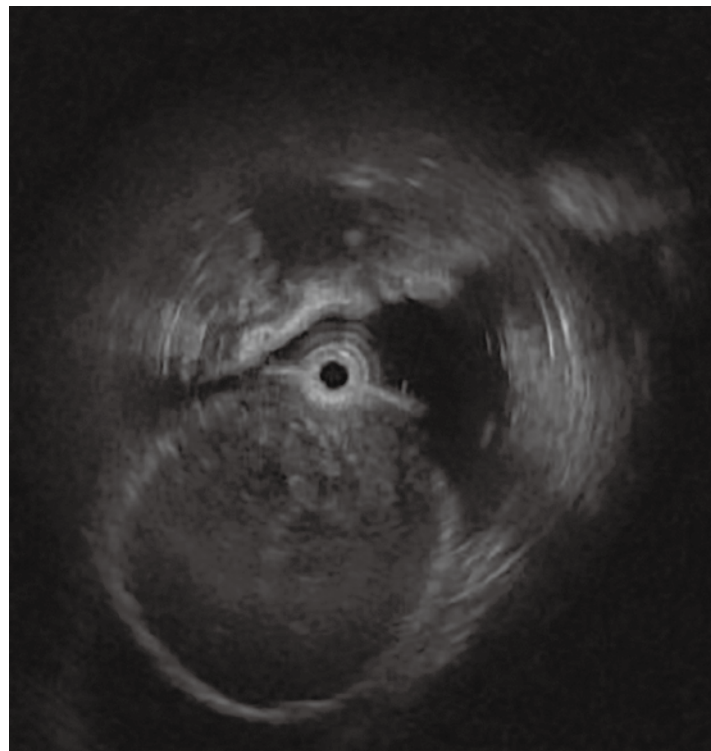


図2 : Endoscopic ultrasonography

A cystic lesion is noted in the lumen. No tumorous tissue is present in the cystic lesion.

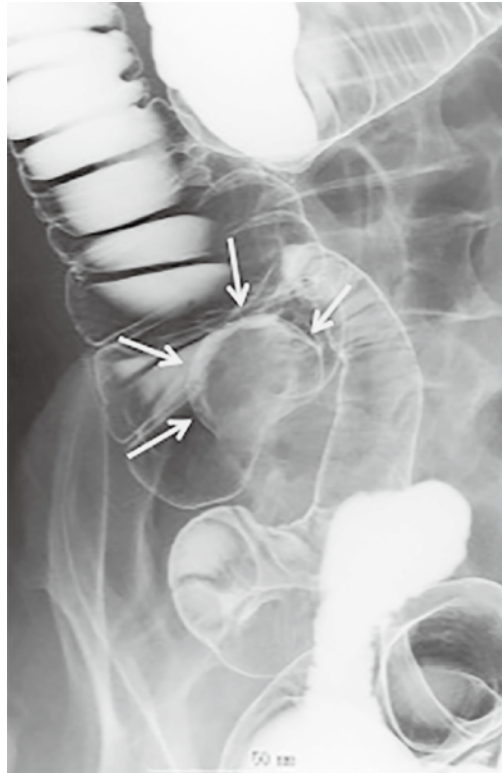


図3 : Barium enema examination
A 3-cm spherical lesion with smooth margins is noted in the cecum. The appendix is not visualized on radiologic examination.

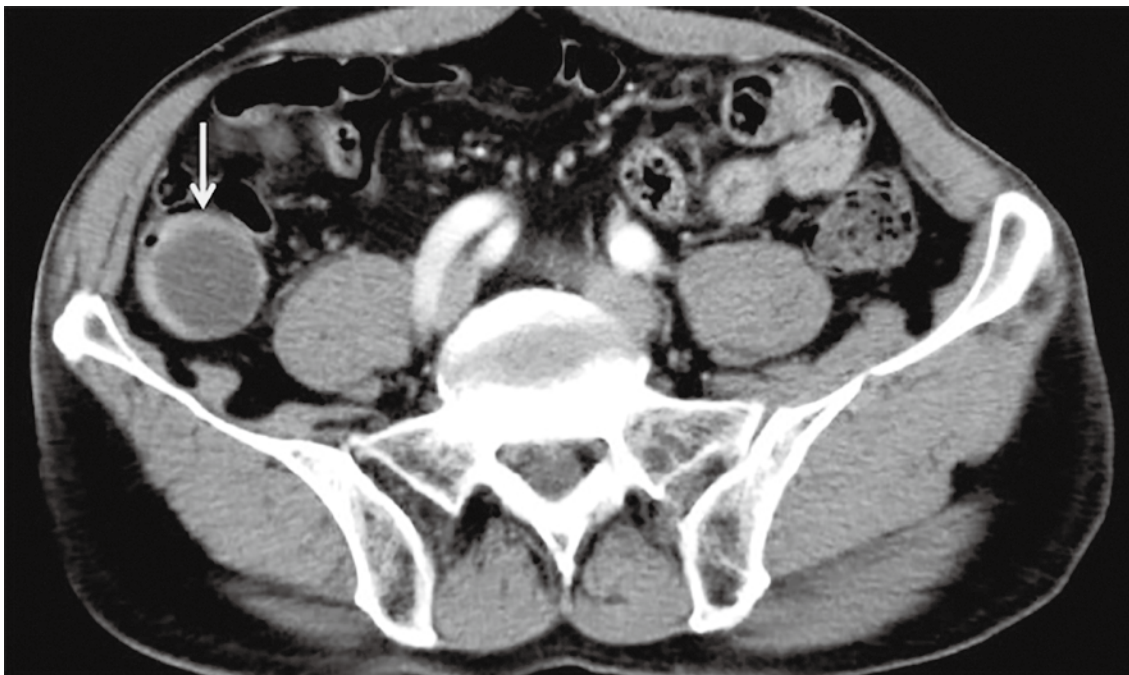


図4 : Computed tomography
Fluid accumulation and expanded appendix is noted. No enhanced cystic component is present.



図5 : Magnetic resonance imaging (T2-weighted image, coronal plane)
A 3-cm cystic structure is noted in the ileocecal region. No solid component is present within the cyst.

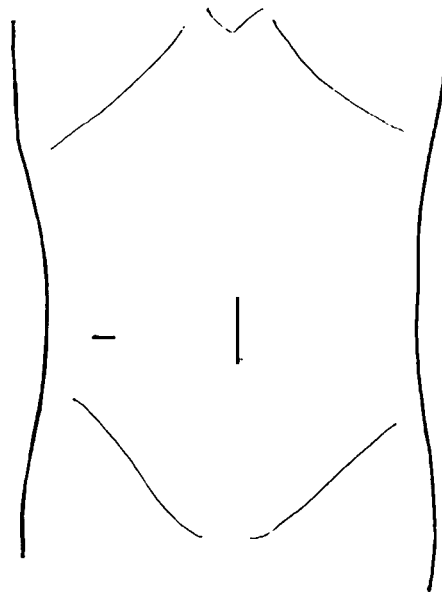


図6 : Surgical wounds
The EZ access® port was inserted through the umbilicus, and a 5-mm port was inserted into the right lower quadrant of the abdomen.



図7 : Macroscopic image of the resected specimen
A spherical tumor is present in the expanded root of the appendix.



図8 : HE-stained pathologic photomicrograph
Papillary proliferation of a hyperplastic glandular duct with slight atypia is noted.

な対応が必要である³⁾。すなわち、良性の場合には病変の大きさと虫垂内での局在に応じて虫垂切除あるいは盲腸部分切除を選択し、悪性を疑う場合にはリンパ節郭清を伴う回盲部切除あるいは右半結腸切除が必要となる¹³⁾。また、術中に腹腔内への粘液漏出を認めた際には腹腔内温熱化学療法⁴⁾の追加も検討する必要がある⁵⁾。綿密な術中観察が必要である⁵⁾。腹腔鏡下手術は、術中に腹腔内全体の詳細な観察が可能であり、虫垂粘液嚢腫でも、腫瘍の局在、粘液や腹膜播種の有無など詳細に確認できる⁴⁾。また、盲腸受動の際も回腸終末部の間膜を把持し頭側腹側に挙上することで、虫垂に一切触れることなく剥離操作が可能で、安全に病巣を体外へ挙上することが可能である¹³⁾。自験例でもRPSにて盲腸を受動した後、臍の小切開孔より回盲部を安全かつ迅速に体外挙上することが可能で、直視下に腫瘍とパウヒン弁を確認後、盲腸部分切除を行った。このように、特にRPSでも、病変自体を圧迫しない手術操作が十分に可能であり、整容性の観点からも有用であると考えられた。

RPSは、ポート数の減数や鉗子細径化を併用することにより低侵襲で高い整容性を目指し、手術難度と体壁損傷を最小化する術式として位置づけられるが、その用語は必ずしも定着しているものではなく、single port surgery (SPS) とneedle scopic surgeryのアイデアを混用して生まれたものである⁷⁾。通常の腹腔鏡手術とRPSを比較したRCTの報告は現在までにないが、虫垂切除術に関して従来のマルチポートの腹腔鏡手術とSPSとを前向きに比較した報告では、術後の経過は同等で、整容性や患者満足度についてはSPSが優れているが、手術時間の延長や高コストなどが報告されている¹⁵⁾。RPSの利点もSPSに準じたものになると予想されるが、操作性の向上や手術時間の短縮も期待され、今後の症例の蓄積や大規模な解析が待たれる。手術操作の安全性、患者満足度、手術難度と低侵襲性などの点を考慮すると、虫垂粘液嚢腫に対するRPSは十分に応用可能で、有用と考えられる。

結論

RPSにて腹腔鏡補助下盲腸部分切除術を施行した虫垂粘液嚢胞腺腫の一例を経験した。特に愛護的な手術操作が必要とされる虫垂粘液嚢腫ではRPSが有効であると考えられる。

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Mechanical Circulatory Support as a Potentially Useful Strategy in Patients with Severe Cyclophosphamide-induced Cardiotoxicity

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Abstract

Cyclophosphamide is one of the most widely used antineoplastic drugs. It is also a potent immunosuppressive agent administered to patients undergoing bone marrow transplantation (BMT). Here we report two cases of aplastic anemia in which severe cardiac dysfunction followed the serial administration of cyclophosphamide (50 mg/m² for 4 days). Both patients gradually developed dyspnea and showed oliguria 3–4 days after BMT. Cardiomegaly was seen on chest X-ray. Echocardiography showed reduced left ventricular contraction, pericardial effusion, and myocardial thickening. Cyclophosphamide-induced cardiotoxicity was suspected and the patients were treated accordingly but were refractory to pharmacotherapy. They were transferred to the intensive care unit where they received mechanical cardiopulmonary support, which improved left ventricular cardiac performance and led to a regression of myocardial thickening. Although both patients died because of severe pulmonary and renal complications, the rapid initiation of mechanical cardiopulmonary support may be a useful strategy in patients with a deteriorating condition, by allowing cardiac recuperation and therefore gaining time for further, potentially life-saving treatment.

Key words: cyclophosphamide, bone marrow transplantation (BMT), cardiotoxicity, percutaneous cardiopulmonary support (PCPS), intra-aortic balloon pump (IABP)

Introduction

Cyclophosphamide (CPA) is widely used as a chemotherapeutic agent and in conditioning regimens for patients undergoing bone marrow transplantation (BMT).¹⁾ However, CPA-induced cardiotoxicity is a dose-limiting toxic effect and a well-known complication. The cardiac manifestations that result from high-dose CPA are heterogeneous and range from innocuous to fatal, but there is little risk of cumulative toxicity.¹⁾ Here we report the cases of two patients with aplastic anemia who developed severe cardiac dysfunction following the serial administration of cyclophosphamide (50 mg/m² for 4 days) prior to BMT. Post-transplantation, both suffered profound cardiopulmonary failure and in both cases the clinical course was deemed inevitably fatal without definitive hemodynamic support. Mechanical circulatory support was provided in the form of percutaneous cardiopulmonary support (PCPS) and the use of an intra-aortic balloon pump (IABP). The enormous advances in mechanical circulatory support have provided additional options for achieving hemodynamic stability in patients suffering profound cardiopulmonary failure, cardiogenic shock, or cardiac arrest. The use of these procedures in a wide variety of clinical settings²⁾ can be expanded to include the acute life-threatening situations described herein.

Case Presentation

Case 1

A previously healthy 15-year-old girl developed purpura on her lower extremities and facial pallor. A peripheral blood examination indicated pancytopenia, with white blood cell counts (WBC) of 2,900/ μ l, a hemoglobin concentration (Hb) of 5.5 g/dl, and a platelet count (Plt) of 2.4×10^4 / μ l. She was therefore referred to our hospital, where she underwent bone marrow aspiration, which revealed a hypocellular marrow (nucleated cell count (NCC) 1.5×10^4 / μ l, no megakaryocytes) but no chromosomal abnormalities. Flow cytometry showed a CD55 deficiency, based on a detection rate of 5.2%, 9.3%, and 16.8% of her red blood cells (RBCs), neutrophils, and monocytes. A CD59 deficiency was also detected (5.1%, 10.8%, and 53.1%, respectively). She was diagnosed as having aplastic anemia with paroxysmal nocturnal hemoglobinuria (PNH). She was admitted to our hospital for BMT. Her body weight, height, and body surface area were 55.5 kg, 149.8 cm, and 1.52 /m², respectively. Laboratory findings were as follows: WBCs, 1,680/ μ l; neutrophils, 479/

μ l; Hb, 5.0 g/dl; Plt, 2.6×10^4 / μ l; and reticulocyte counts, 41,850/ μ l. She was administered 30 mg/m² of fludarabine, 2.5 mg /kg of rabbit anti-human thymocyte immunoglobulin (ATG), and 50 mg/m² of CPA for 4 days prior to BMT (days -5 to -2). She was transplanted with a graft from her HLA-matched brother. On day 4, she complained of chest pain and dyspnea, with concomitant systemic involvement as evidenced by a decrease in urine output (<1,000 ml/day) and an increase in her body weight. Echocardiography showed pericardial effusion with diastolic collapse of the right atrium (RA), a moderate free echo space of 17.0 mm behind the posterior wall of the left ventricle (LV) and of 10.0 mm ahead of the anterior right ventricular (RV) wall in diastole. Severe myocardial thickening based on an intraventricular septal thickness at diastole (IVSd) of 15.0 mm, a LV posterior wall thickness at dimensions (LVPWd) of 17.0 mm, and a reduced left ventricular ejection fraction (LVEF) of 50.0% (Fig. 1A). She was transferred to the intensive care unit (ICU) on the same day. Despite an intermittent infusion of diuretics and a continuous infusion of human atrial natriuretic peptide (hANP), olprinone, and dobutamine hydrochloride, her pulse and blood pressure gradually dropped. On day 5, she developed low-output syndrome (cardiac index below 2.0 ml/kg/m² or less) and oliguria (<500 ml/day) with reduced LV contraction (LVEF 30.0%) as determined on echocardiography. Shortly thereafter, she went into cardiac arrest. Return of spontaneous circulation after resuscitation, a 21-French sheath of PCPS drainage cannula (CX-EB21VLX: Terumo, Tokyo, Japan) was withdrawn from the right femoral vein and a 16.5-French sheath of blood supply cannula (CX-EB16ALX: Terumo, Tokyo, Japan) was inserted into the right femoral artery. Subsequently PCPS was initiated as an additional treatment with an initial blood flow was 1.8 L/min and a rotation rate of the biopump was 1,800 rpm using a Capiiox SP Pump Controller Sp-100 plus (Terumo, Tokyo, Japan) to support the state of low cardiac output. These measures resulted in an improvement of LV contraction and the regression of myocardial thickening. On day 11, the use of an IABP was added to obtain a synergistic effect. On day 19, echocardiography showed improved LV contraction (LVEF 55.0%) and reductions of myocardial thickening (IVSd 15.0 \rightarrow 12.0 mm, LVPWd 17.0 \rightarrow 11.0 mm) and pericardial effusion (posterior wall of the left ventricle 17.0 \rightarrow 5.0 mm) (Fig. 1B). PCPS flow was gradually decreased when PCPS flow was 1.0 L/min and hemodynamics were stable as systolic blood pressure was more than 80 mmHg, central venous pressure was less than 15 mmHg, and pulse pressure was more

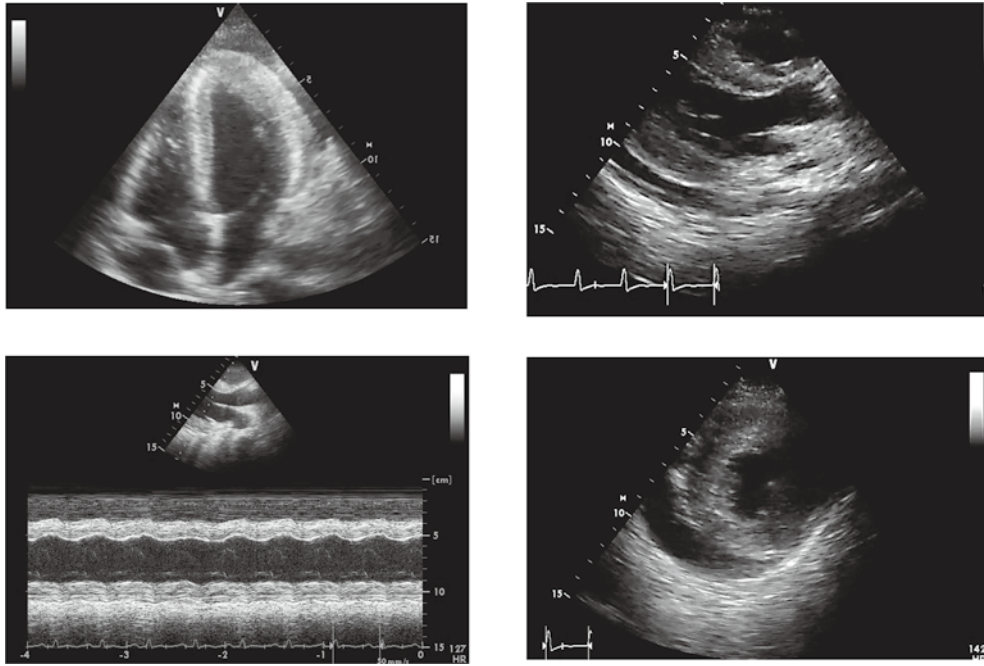


Fig 1A. Echocardiography showed pericardial effusion with diastolic collapse of the right atrium, reduced left ventricular contraction and severe myocardial thickening on day 4 after BMT.

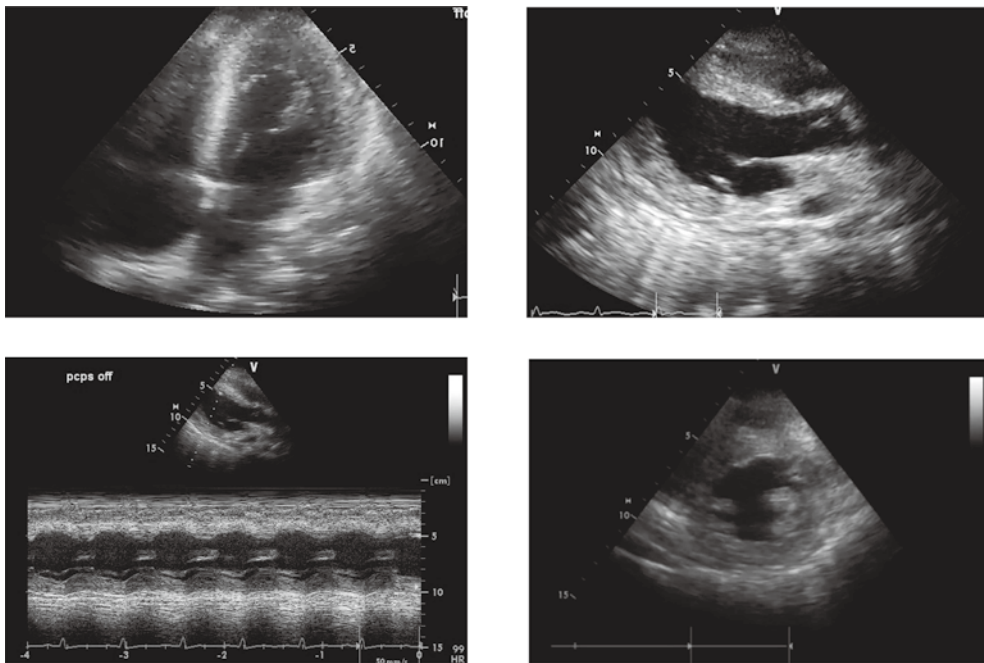


Fig 1B. Echocardiography showed improved left ventricular contraction and reductions of myocardial thickening and pericardial effusion on day 22 after BMT.

old, she was admitted to our hospital for a second BMT. Her body weight, height, and body surface area were 40.7 kg, 156.3 cm, and 1.33 /m², respectively. She was administered 20 mg/m² of fludarabine, 2.5 mg/kg of ATG, and 50 mg/m² of CPA for 4 days (days -5 to -2) and 2 Gy of total body irradiation (days -2 to -1). Following transplantation with bone marrow from her HLA-mismatched mother, her volume status was carefully monitored and included the administration of diuretics to increase urine output and relieve fluid tension. However, her renal function deteriorated and she gradually complained of dyspnea. On day 3, she developed low-output syndrome and oliguria (<500 ml/day). Cardiomegaly was seen on chest X-ray. Echocardiography showed mildly reduced LV contraction (LVEF 50.0%) with myocardial thickening (IVSd, 10.0 mm; LVPWd, 15.0 mm) and pericardial effusion both behind the posterior wall of the LV (6.0 mm) and ahead of the anterior RV wall (14.0 mm) in diastole (Fig. 3A). Despite the continuous infusion of dopamine hydrochloride and hANP, her condition deteriorated further. On day 5, she was transferred to the ICU, where she was managed with a continuous infusion of olprinone hydrochloride, nicorandil, and randiorol hydrochloride, but their effects were limited. Soon thereafter, she lost consciousness because of a dramatic fall in blood pressure and went into cardiac arrest. Return of spontaneous circulation after resuscitation, a 21-French sheath of PCPS drainage cannula (CX-EB21VLX: Terumo, Tokyo, Japan) was withdrawn from the right femoral vein and a 16.5-French sheath of blood supply cannula (CX-EB16ALX: Terumo, Tokyo, Japan) was inserted into the right femoral artery. Subsequently PCPS was initiated as an additional treatment with an initial blood flow was 2.2 L/min and a rotation rate of the biopump was 2,800 rpm using a Capiiox SP Pump Controller Sp-100 plus (Terumo, Tokyo, Japan) to support the state of low cardiac output. IABP and CHDF were also initiated for the treatment of severe cardiopulmonary failure. Under close supervision, those treatments resulted in improved myocardial thickening (IVSd 10.0→6.0 mm, LVPWd 15.0→8.0 mm) and LV contraction (LVEF 70%) as well as the disappearance of the pericardial effusion. PCPS flow was gradually decreased when PCPS flow was 1.0 L/min and hemodynamics were stable as systolic blood pressure was more than 90 mmHg, central venous pressure was less than 13 mmHg, and pulse pressure was more than 50 mmHg with sufficient preload and requisite dose of catecholamine. On day 18, she was successfully weaned from PCPS and IABP (Fig. 3B). However, she could not be weaned off mechanical support (CHDF and ECMO). On day 57, she

died from a moderate disturbance of oxygenation with lung injury, progressive renal impairment, and sepsis due to fungal infection (Fig. 4).

Discussion

In patients with severe aplastic anemia, ATG and high-dose CPA have been used as combination chemotherapy and to enhance engraftment after BMT.³⁾ However, CPA is associated with life-threatening toxic adverse effects such as heart failure, myocarditis, and pericarditis. Thus, cardiotoxicity is the dose-limiting toxic effect of CPA.^{1, 4-7)} It occurs abruptly within days of drug infusion and is fatal, but there is little risk of cumulative toxicity.¹⁾ A total dose >170–180 mg/kg per course or 1.55 g/m²/day are correlated well with the incidence of CPA-induced cardiotoxicity.^{6, 7)}

The pathophysiology of high-dose CPA-induced cardiotoxicity may involve endothelial damage followed by extravasation of toxic metabolites, resulting in damage to the myocardium, interstitial hemorrhage, and edema.⁸⁾ In addition, CPA may cause ischemia-related damage via the development of capillary microemboli or coronary angiospasm.⁹⁾ The histological findings of CPA-induced cardiotoxicity include multiple areas of myocardial hemorrhage, extravasation of blood, interstitial edema, and multifocal myocardial necrosis with fibrin microthrombi. A loss of myofilaments and damage to mitochondrial cristae has been observed in electron micrographs obtained from animal models of CPA-induced cardiotoxicity.¹⁰⁾ The early recognition of CPA-induced cardiotoxicity and the prompt initiation of treatment of these patients may have potent beneficial therapeutic effects, given that CPA-induced toxicity seems to be transient and the end-organ toxicity is reversible.^{1, 11)}

In mild or moderate cases of CPA-induced cardiotoxicity, elevated ventricular filling pressure should be treated with diuretics, vasodilators, and β -blockers unless contraindicated.¹²⁾ In patients suffering severe cardiopulmonary failure and with a worsening clinical course that seems to be inevitably fatal, mechanical circulatory support may be therapeutically promising. Early diagnosis and intervention are important in preventing hypoperfusion-related injury and death. Mechanical circulatory support may improve LV contraction via reducing in LV volume and restoring of a more elliptical cardiac chamber, which suggests that the remodeling process is reversible.¹³⁾ Moreover, these support was shown to reverse structural and molecular remodeling and to improve both baseline contractility and contractile

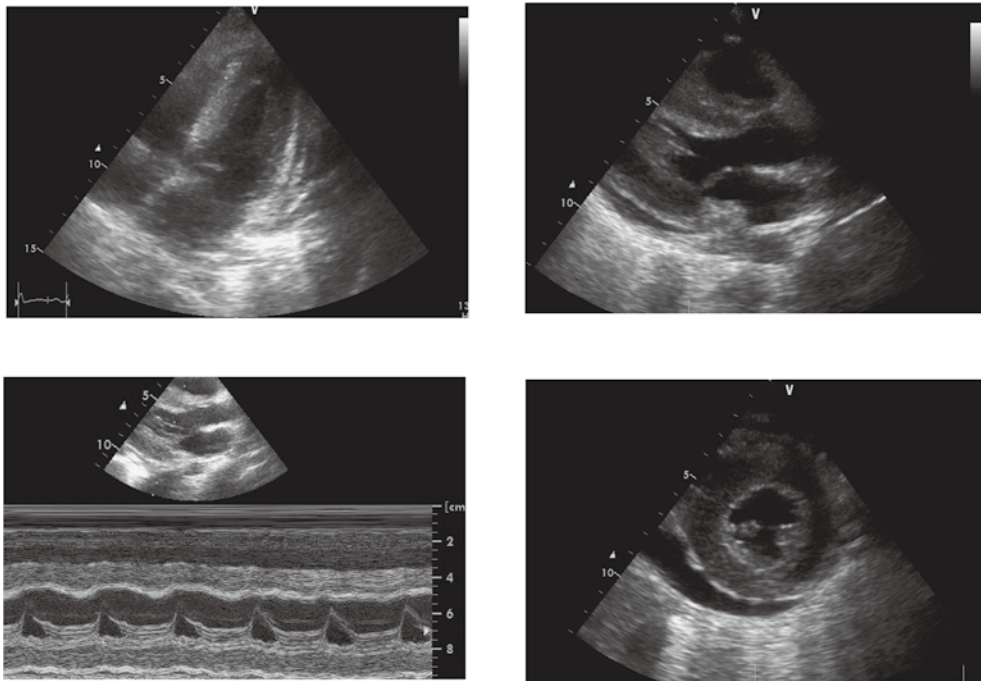


Fig 3A. Echocardiography showed pericardial effusion both behind the posterior wall of the left ventricle and ahead of the anterior right ventricle wall in diastole, reduced left ventricular ejection fraction with myocardial thickening on day 5 after BMT.

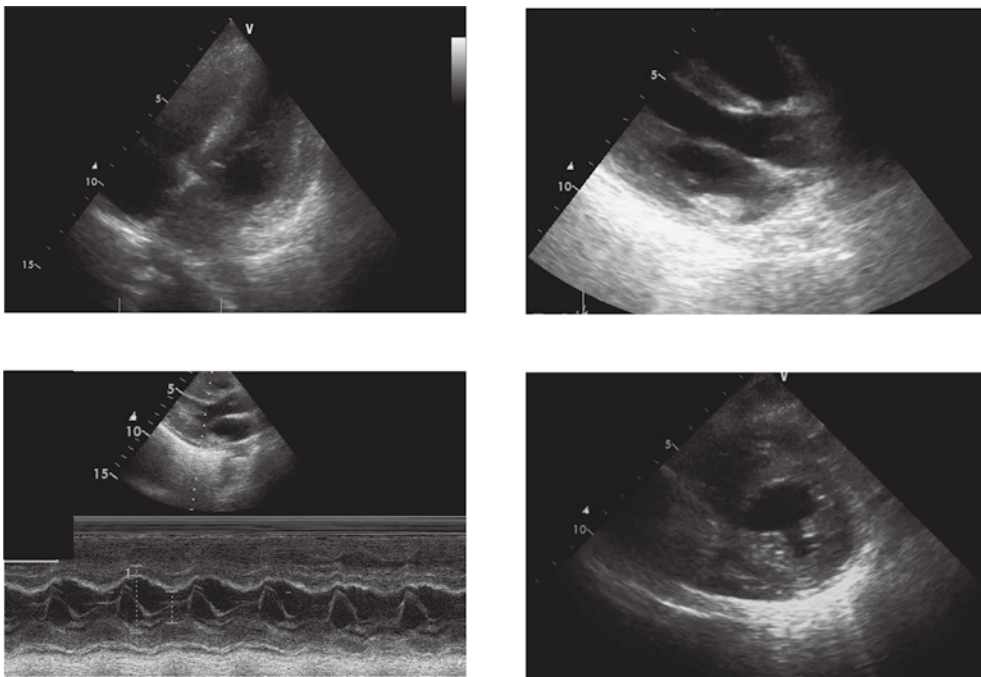


Fig 3B. Echocardiography showed improved left ventricular contraction and reductions of myocardial thickening and pericardial effusion on day 18.

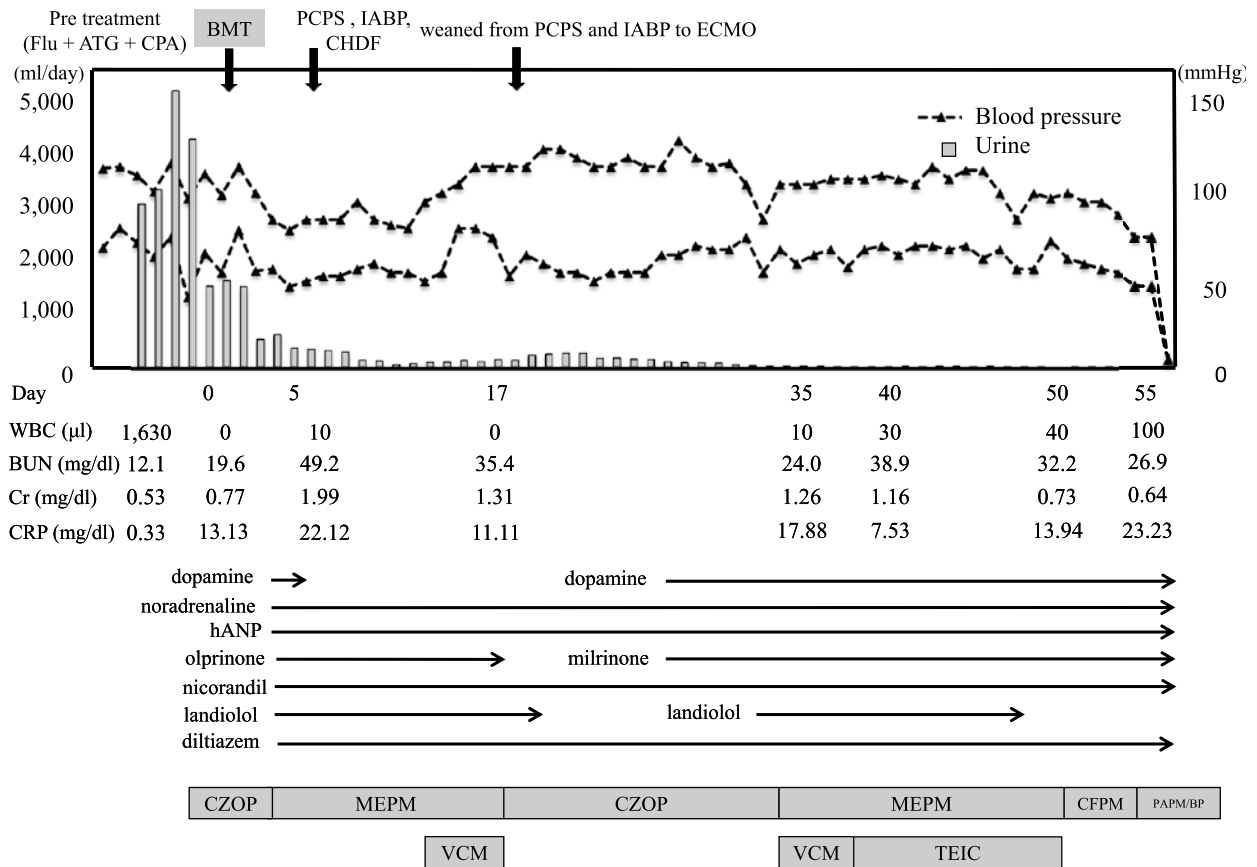


Fig 4. Case2; Patient’s clinical course and laboratory data

Patient developed dyspnea and showed oliguria after BMT, and was transferred to the intensive care unit where they received mechanical circulatory support, which improved left ventricular cardiac performance. However, she died from a moderate disturbance of oxygenation with lung injury, progressive renal impairment, and sepsis due to fungal infection.

Flu, fludarabine; ATG, rabbit anti-human thymocyte immunoglobulin; CPA, cyclophosphamide; BMT, bone marrow transplantation; PCPS, percutaneous cardiopulmonary support; IABP, intra-aortic balloon pump; CHDF, continuous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; WBC, white blood cell counts; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; hANP, human atrial natriuretic peptide; CZOP, cefozopran; MEPM, meropenem; CFPM, cefepime; TAZ/PIPC, tazobactam/piperacillin; TEIC, teicoplanin; ABK, arbekacin; VCM, vancomycin; MINO, minomycin; AMK, amikacin; PAPM/BP, panipenem/betmipron

response, thereby increasing the heart rate and the response to β -agonist stimulation.¹⁴⁾ Combined PCPS and IABP were introduced in our patients with severe CPA-induced cardiotoxicity, neither of whom responded to conventional medical treatment, and those were useful to maintain total circulation by quick application.¹⁵⁾ In our patients, there were no clear indications for the use of PCPS, but PCPS need to be initiated because deteriorating of systolic pressure

after using inotropic agents, hypoxia and acidosis. The experiences with the presented two patients, both of whom had oliguria, cardiomegaly, a decrease in cardiac contraction, and pericardial effusion in spite of appropriate medical treatment, suggest that the rapid administration of mechanical circulatory support is an effective and valuable approach to achieve clinical improvement. Although, our patients could be successfully weaned off PCPS over time, long-term

support with ventricular associated device (VAD) should be considered as a bridge to myocardial recovery to resuscitate impaired organ function.¹⁶⁾ Because, PCPS cannot augment coronary blood flow which could be one of the contributors to a lower rate of left ventricle recovery and may gradually increase left ventricular afterload.¹⁵⁾ There was few report and no established therapy for patients with CPA-induced cardiotoxicity suffering severe cardiopulmonary failure, these mechanical circulatory support could be an useful therapeutic effect and could extend a life prognosis.

Our patients could be successfully weaned off PCPS and their cardiac function improved, they eventually died because of severe pulmonary and renal complications in the presence of sepsis. Pulmonary complications may have arisen from the cardiogenic pulmonary edema resulting from the increased capillary hydrostatic pressure secondary to elevated pulmonary venous pressure or from the sepsis-related multiple organ failure, driven in part by graft failure. Oxidative stress or using CPA as conditioning agents prior to BMT also could be a risk factor for CPA-induced lung toxicity.^{17, 18)} Early-onset pneumonitis due to CPA is generally reversible process following discontinuation of CPA.¹⁹⁾ The role of glucocorticoids in the treatment in CPA-induced lung toxicity remains unclear, but most successfully treated patients have received glucocorticoids though magnitude of benefit due to glucocorticoid use remains unknown.²⁰⁾ Moreover, genetic susceptibility was reported to be associated with the development of lung toxicity in humans.²¹⁾ Further intensive-care management and more effective hematologic treatment may lead to a better prognosis for patients with pulmonary, renal, and cardiac complications of CPA-induced toxicity.

This report described two cases in which pediatric patients with aplastic anemia developed severe heart failure following the serial administration of high-dose CPA before BMT. Our experience showed that mechanical circulatory support for patients with CPA-induced cardiotoxicity could allow the recovery of cardiac function such that the other clinical manifestations can be adequately addressed. Therefore, the early recognition and initiation of mechanical circulatory support may be life-saving in patients with CPA-induced cardiotoxicity.

Disclosure of potential conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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シクロフォスファミドに伴う重症心筋障害を合併した患者に対する補助循環装置の有用性について

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シクロフォスファミドは抗腫瘍薬として、また骨髄移植の前処置時に免疫抑制薬としても広く使用されている。われわれは、シクロフォスファミド投与後(50mg/m² 4日間)に重症心筋障害をきたした再生不良性貧血の2症例を経験した。両患者ともに移植後3-4日で呼吸困難、乏尿がみられ、胸部エックス線で心拡大、心エコー検査で左室収縮能の低下、心嚢液貯留および心筋肥厚所見を認めた。シクロフォスファミドによる重症心筋障害から循環不全をきたしたと考え、循環作動薬で加療したが改善せず、集中治療室で経皮的心肺補助装置、大動脈内バルーンパンピングを用いた補助循環装置を導入した。補助循環装置での治療開始後、心収縮力は改善し、心筋肥厚も軽快した。両患者ともに補助循環装置から離脱することができたが、重篤な移植後合併症で死亡した。シクロフォスファミドによる重症心筋障害はまれに発生するが、早期の診断ならびに補助循環装置を用いた集中治療管理を行うことで心筋の回復が得られ、予後の改善に繋がる可能性がある。

HTLV-1 Carrier Mothers Need Continual Support to Accomplish Their Selected Nutrition Method for Mother-to-child Transmission Prevention in Kagoshima

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Abstract

INTRODUCTION: Since 2011, the nationwide mother-to-child transmission prevention program in Japan for HTLV-1 has recommended three nutritional methods: formula-feeding (FF), short-term breast-feeding (STBF) and frozen-thawed milk feeding. Here we clarify the support necessary for HTLV-1-positive mothers to accomplish their selected nutrition method in Kagoshima.

METHODS: We administered questionnaires to 93 HTLV-1-positive mothers to determine whether each baby was successfully fed by following the mother's selected nutrition method, and whether any problems were encountered. They were divided into 2 groups (FF and STBF) by chosen nutrition method and compared; the FF group comprised 23 women and the STBF group comprised 70 women.

RESULTS: We received responses from 70 of the 93 women enrolled. The success rate of accomplishing their selected nutrition method was lower in the STBF than the FF group, and the difficulty rate was higher in the STBF than the FF group. The major reasons for feeling a difficulty in accomplishing the STBF method were the lack of support for weaning, suffering from emotional stress, and inability to wean children from breast milk. In contrast, the major reason for feeling a difficulty in the FF group was not being understood by family members and/or neighbors.

CONCLUSIONS: HTLV-1-carrier mothers, especially mothers who selected the STBF method, needed continual support to accomplish their selected nutrition method for mother-to-child transmission prevention. It is necessary to improve the support environment for HTLV-1-carrier mothers in Japan without delay.

Key words: HTLV-1, mother-to-child transmission, breast-feeding

Introduction

The human T-lymphotropic virus type 1 (HTLV-1) is known to be the pathogenic agent of adult T-cell leukemia-lymphoma (ATL)^{1,2}. HTLV-1 is endemic in southern Japan, the Caribbean, Latin America and western Africa³. Three

main routes of HTLV-1 transmission are known. The first is mother-to-child transmission⁴, mainly due to ingestion of breast milk⁵. The second is sexual transmission, mainly from men to women⁶. The third is transfusion of blood that includes HTLV-1-positive cellular components⁷. Of the three, breast-feeding is the predominant route of transmission.

Lymphocytes in breast milk are responsible for transmitting HTLV-1⁵⁾. Refrain from breast-feeding is the best and easiest way to prevent mother-to-child transmission of HTLV-1. However, the advantages of breast-feeding over formula-feeding (FF) to prevent overall child morbidity and mortality have been well established⁸⁾, especially in developing countries⁹⁾. There are a couple of approaches to prevent mother-to-child transmission of HTLV-1 via breast milk other than refraining from breast-feeding. One is freeze-thawing of breast milk; the infectivity of HTLV-1 in breast milk was lost during the freezing and thawing processes¹⁰⁾. The next possible approach to reduce the milk-borne transmission is to limit the duration of breast-feeding¹¹⁻¹⁴⁾. This may be related to the protective effect of maternally derived anti-HTLV-1 IgG antibodies¹⁵⁾.

The prognosis for ATL is extremely poor, and no vaccine is yet available. Therefore, a public health system to prevent transmission from carrier mothers to infants is important. In 1990, the Japanese government decided not to introduce a nationwide system of HTLV-1 prevention based on the Health Labour Sciences Research Grant reports¹⁶⁾, which recommended implementation of appropriate prevention plans only in endemic areas. One of the reasons was that introduction of a prevention system in a non-endemic area might increase the risk of confusion. Another reason was that the number of HTLV-1 carriers was expected to decrease with or without intervention because there was a trend toward a reduced rate and duration of breast-feeding at that time.

However, the Health Labour Sciences Research Grant reports in 2010 suggested that the number of HTLV-1 carriers had not decreased, contrary to expectations, and that the distribution of HTLV-1 carriers had spread into non-endemic areas¹⁷⁾. The phenomenon may be explained by the flow of the population from endemic rural areas to non-endemic major urban cities during the period of high economic growth in Japan. A nationwide system of HTLV-1 prevention is needed under such circumstances, and the Ministry of Health, Labour and Welfare introduced a nationwide mother-to-child transmission prevention program. It recommended three nutritional methods: FF, short-term breast-feeding (STBF) of <3 months after birth, and frozen-thawed milk feeding. Nation-wide screening of pregnant women for HTLV-1 infection was implemented in Japan in 2011¹⁸⁾.

On the other hand, in 1985, Kagoshima University began a study on the prevention of HTLV-1 transmission in collaboration with the local government of Kagoshima Prefecture. Kagoshima prefecture is located in Kyushu, in

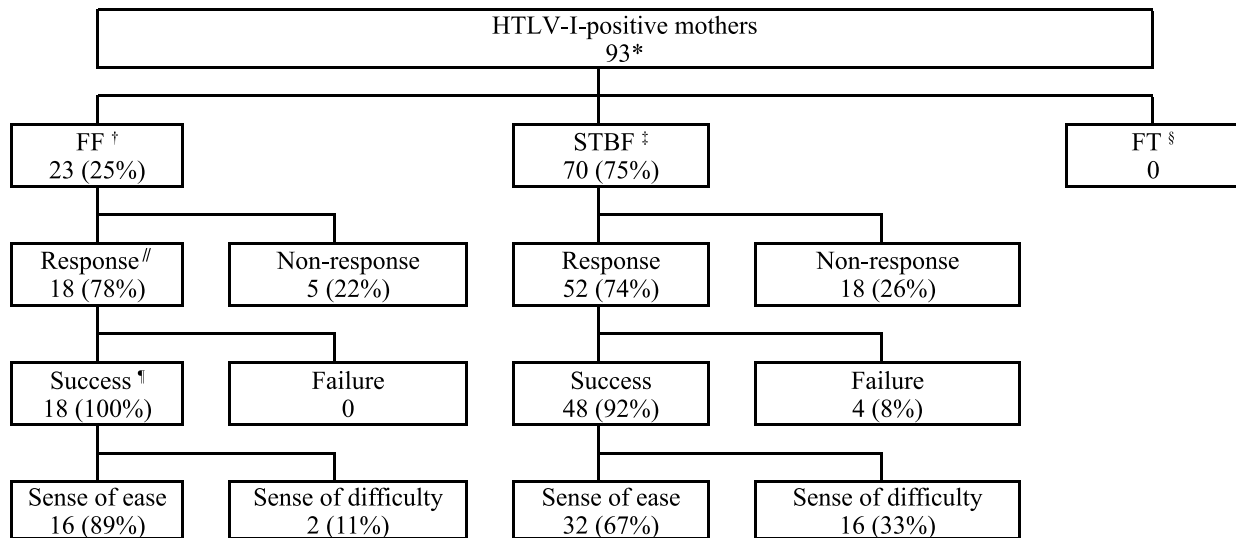
the south of Japan. Many HTLV-1-positive people live in Kyushu. In the 1985 study, Takahashi et al. determined that the seroconversion rate of STBF children was nearly equal to that of bottle-fed children¹¹⁾. Therefore, the prefecture-wide "ATL Prevention Decade Plan" to promote FF or STBF for HTLV-1 carrier mothers began in 1997. Approximately two-thirds of the HTLV-1 carrier pregnant women chose STBF, which was a higher rate than in other endemic prefectures¹⁹⁾. In the previous report, in Kagoshima Prefecture, there were not many obstetrics facilities that cared for HTLV-1 carrier mothers when weaning from the breast²⁰⁾. Therefore, only 75% of HTLV-1 carrier mothers accomplished their selected nutrition method. In this study, we introduced a support system performed by visiting public health nurses. But it remains unclear whether HTLV-1-positive pregnant mothers are successfully implementing their selected nutrition method, especially STBF; in addition, whether any support is necessary for success is unknown.

The aim of this study was to clarify the support necessary for HTLV-1-positive mothers to achieve success with their selected nutrition method in Kagoshima.

Methods

During the nation-wide screening of pregnant women for HTLV-1 infection, informed consents were obtained before screening for the antibody. Screening for HTLV-1 antibody was performed using the passive particle agglutination method (PA) or the chemiluminescent immunoassay (CLIA). Positive results were confirmed by Western blot analysis or an immunofluorescence assay¹⁸⁾. The obstetricians or midwives in the obstetrics facilities in Kagoshima Prefecture recommended HTLV-1 positive pregnant woman to use one of three nutritional methods: bottle-feeding, STBF (<3 months), or frozen-thawed milk, as outlined in the HTLV-1 mother-to-child transmission (MTCT) prevention health guidance manual compiled by the Ministry of Health, Labour and Welfare¹⁸⁾.

We obtained the cooperation of 48 of the 50 obstetrics facilities in Kagoshima Prefecture by the end of 2013. We visited these obstetrics facilities to obtain informed consent for this study from HTLV-1-positive pregnant woman between January 2013 and December 2013. We obtained informed consent from 93 HTLV-1-positive pregnant women. We investigated the choices made for nutrition methods before the delivery. No mother selected frozen-thawed milk (FT). Accordingly, the HTLV-1-positive pregnant women

Figure 1. Response rate, success rate, and rate of sense of difficulty in accomplishing the selected nutrition method"

* We visited obstetrics facilities in Kagoshima prefecture to obtain informed consent for this study from HTLV-1-positive pregnant woman between January 2013 and December 2013.

† FF: formula-feeding

‡ STBF: short-term breast-feeding (<3 months)

§ FT: frozen-thawed milk

// Response: We received replies from them.

¶ Success: They accomplished their selected nutrition method.

participants were divided into 2 groups: the FF group, consisting of 23 mothers; and the STBF group, consisting of 70 mothers.

In this study, support was introduced through visiting public health nurses after childbirth. They visited upon request from the mothers, with a frequency of approximately once per month. They provided consultation to help the mothers who were anxious about the nutritional status of their baby. We administered questionnaires to all 93 enrolled participants three months after delivery to determine whether each baby was successfully fed by following the selected nutrition method, and whether any problems were encountered. Frequency analysis was performed with the Fisher's exact test.

The study protocol was reviewed and approved by the Ethics Committee of Kagoshima University Graduate School of Medical and Dental Sciences (No.196).

Results

1. Response rate

We received replies from 52 of 70 (74%) STBF group subjects and 18 of 23 (78%) FF group subjects. Both groups had almost the same response rate (Fig.1). No significant differences were found between Kagoshima city and the urban area for the nutrition method choice.

2. Accomplishment rate

Successful use of the selected nutrition method was accomplished by 48 (92%) of the STBF group and the entire FF group. No significant difference was found between the two groups in accomplishment rate (Fig.1).

In addition, no significant differences were found in accomplishment rate between primiparas and multiparas.

3. Rate of feeling a difficulty in successful use of the selected nutrition method

In the STBF group, 16 (33%) found it difficult to achieve success with the selected nutrition method, as did 2 (11%) of the FF group. No significant difference in this rate was found

Table 1. The reasons for feeling a difficulty using the selected method

Group	Case number
Formula-feeding (FF) group	2
Feeling a difficulty	2
Lack of understanding from family members and/or neighbors *	2
Medical support was insufficient †	1
Short-term breast-feeding (STBF) group	20
Feeling a difficulty	16
Difficult to wean from the breast ‡	4
Trouble with breasts §	4
Sense of desolation after weaning from breast //	4
Medical support for how to wean was insufficient ¶	3
Lack of understanding from family members and/or neighbors	1
Failure to wean from the breast within 3 months	4
Difficult to wean from the breast	2
Medical support for how to wean was insufficient	1
Plan to go abroad **	1

(Multiple answers allowed)

- * “Lack of understanding from family members and/or neighbors” included “It was difficult to explain to friends and relatives, excluding parents, why breast feeding was impossible” and “suffered from questions about breast-feeding.”
- † “Medical support was insufficient” means that the mother did not receive support as expected from a medical institution (The details were unwritten).
- ‡ “Difficult to wean from the breast” means STBF mothers found it considerably difficult to wean from the breast.
- § “Trouble with breasts” included mastitis and pain or discomfort caused by engorged breasts with weaning.
- // “Sense of desolation after weaning from breast” included feelings of “I am not required by my baby” and “Why is it just me who cannot breast-feed?”
- ¶ “Medical support for how to wean was insufficient” means that the mother received insufficient support to wean from the breast.
- ** “Plan to go abroad” means that the mother expected to provide their baby passive immunity through the transfer of IgA antibodies found in breast milk in anticipation of traveling to a developing country.

between the two groups (Fig.1).

4. Reasons for feeling a difficulty in using the selected method

The reasons for feeling a difficulty for successful use of the selected nutrition method are listed in Table 1.

The major reason in the FF group was not being understood by family members and/or neighbors. In contrast, the major reasons for feeling a difficulty in accomplishing the STBF method were lack of support for weaning, suffering from emotional stress, and inability to wean children from breast milk. The major reasons for feeling a difficulty differed between groups.

Discussion

This study shows that HTLV-1-positive mothers found it considerably difficult to use their selected feeding method, regardless of the method chosen. Therefore, HTLV-1-positive mothers need much support to be successful with their selected method. Furthermore, the STBF group needed

more support than the FF group, as evidenced by their lower accomplishment rate and the higher rate of feeling a difficulty with using the method despite the major reasons for feeling a difficulty differing between groups (Fig.1).

Because the total success rate (92%) of this study was higher than the rate (75%) of the previous report²⁰⁾, the support by public health nurses might be effective. However, not all mothers could achieve their goals by using this support. Because the major reasons for feeling a difficulty with the STBF method were the lack of the support for weaning, suffering from emotional stress, and the inability to wean children from breast milk, further support is necessary (Table 1). Support by midwives may resolve these problems since they are specialists in childbirth, postpartum issues (including nursing), and women’s health care. They can also help resolve the cognitive, emotional and technical problems of weaning. However, the economics of introducing such support is problematic.

On the other hand, the major reasons for feeling a difficulty

while using the selected method in the FF group was different that the STBF group in that feeling a lack of being understood by their family members and/or neighbors would make some mothers feel afraid of revealing their HTLV-1 carrier status (Table 1), which could occur if they attempted to explain why they refrained from breast feeding¹⁹⁻²¹). To eliminate prejudice against the HTLV-1 carriers, educational activities are required.

All 18 mothers in the FF group accomplished their selected nutrition method. According to our results, FF seemed to be the most reliable and easiest way to prevent mother-to-child transmission of HTLV-1. Additionally, in developed countries, including Japan, infectious diseases and malnutrition are not main causes of infant mortality. In light of this, the question of why the Japanese government recommends STBF as a nutrition method for these mothers is raised. Although the benefit of STBF is unclear, breast-feeding per se is beneficial to not only the health of the infants but also the health of mothers⁸). HTLV-1 causes ATL or HAM in only a minority (approximately 5%) of carriers after a long incubation period. In addition, the FF method cannot protect against all mother-to-child transmission. Approximately 3% of infants will be infected by their mothers, even if formula fed. The infection route of HTLV-1 when the FF method is used remains unknown¹⁸). Therefore, the optimal nutrition method for HTLV-1 carrier mothers is still controversial; more studies are needed to clarify this issue.

The limitations of this study include its small sample size and a possible selection bias. However, in 2012, the rate of pregnant carrier women was only 1.3% even in Kagoshima, which is located in a pandemic area. Theoretically, there are approximately 200 pregnant carrier women per year in Kagoshima. This study enrolled approximately half of all suspected carrier pregnant women in Kagoshima, which lends credence to the results.

In conclusion, HTLV-1-carrier mothers, especially mothers who chose the STBF method, need continual support to accomplish mother-to-child transmission prevention. Despite the fact that the Japanese government introduced a HTLV-1 mother-to-child transmission prevention health program by recommending three post-delivery nutrition methods, there exists no post-delivery system of support to achieve success in preventing transmission via those methods. In our study, 8% of STBF mothers failed in their selected method, as such, approximately 20% of those mothers' babies could become HTLV-1 carriers, of which 5% could suffer from associated diseases including ATL and HAM in future. However, if a

support system were introduced, it would take time to see the effect. So even if there are unsolved problems, it is necessary to immediately improve the support environment for HTLV-1-carrier mothers in Japan. Any future trials in Japan will be important in informing optimal preventative strategies in other countries.

Disclosure of potential conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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鹿児島県の HTLV- I 母子感染予防の栄養法達成のための 母親への継続的な支援が必要

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【背景】2011年より栄養法として人工栄養、短期母乳、凍結母乳の3つが選択候補にあげられた HTLV-1 母子感染対策は全国的な取り組みが開始された。鹿児島県において HTLV-1 陽性妊婦が出生前に決定した栄養法が実施完了するのに必要な支援について明らかにする。

【方法】同意取得した出産3か月経過後の母親93名に質問票を送付し回収した。決定した栄養法で人工栄養、短期母乳の2群に分け、比較検討した。

【結果】93名のうち70名から回答を得た。選択した栄養法を完遂できた率は、人工栄養群にくらべ短期母乳群が低かった。また、栄養法を遂行するのに困難を感じた率は人工栄養群にくらべ短期母乳群が高かった。その困難を感じた主な原因は、短期母乳群では「断乳時の支援不足」、「感情的な苦しみ」、「子どもがお乳から離れない」であった。対照的に人工栄養群では「家族または周囲の人々の理解不足」であった。

【考案】HTLV-1 母子感染対策のために HTLV-1 陽性の母親が出生前に選択した栄養法を完遂するには継続的な支援が必要である。それは短期母乳を選択した母親で特に認められた。

全国的な取り組みが開始された現在、HTLV-1 陽性の母親を支援する環境を迅速に改善していく必要がある。

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