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Hospital plaza Building 1F
9-15 Sanbancho, Chiyoda-ku, Tokyo 102-0075, Japan
TEL: +81-3-3265-0079
FAX: +81-3-3265-0083
E-mail: info@ningen-dock.jp
URL : http://www.ningen-dock.jp/

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CONTENTS
Vol. 3 No. 1
March, 2016

Ningen Dock International
Official Journal of Japan Society of Ningen Dock

Original Article

Case Report

Report

Notifications

Original Article

Ningen Dock International 2016 ; 3 : 3–6

CT Emphysema Constitutes a High Risk for Future Airflow Obstruction

Takeshi Nawa[1], Suzushi Kusano[2], Tohru Nakagawa[2], Tetsuya Mizoue[3], Hiroaki Tachi[1], Kei Shimizu[1], Yusuke Yamamoto[1], Shinji Hirai[1]

Abstract

Background and Methods: To evaluate differences in the frequency of airflow obstruction between the presence and absence of emphysematous changes (CT emphysema) detected in low-dose CT screening, we performed a retrospective cohort study in males who annually underwent a health check-up (Ningen Dock) for employees over a long period. Among males with a smoking history (≥ 20 pack-years) who underwent low-dose CT screening in a health check-up between April 1998 and March 2006, those who also underwent check-ups between April 2009 and March 2012 were included as the subjects. The subjects consisted of 2,164 males (285 in the CT emphysema group and 1,879 in the non-emphysema group). Their mean age was 51.4 years, and the mean amount of smoking was 33.4 pack-years. Pulmonary function tests were performed 11.5 times during a mean period of 12.1 years.

Results: The cumulative frequency of moderate or severe airflow obstruction, which was defined as both forced expiratory volume % in one second (FEV_1%) < 70% and percent forced expiratory volume in one second (%FEV_1) < 80%, in the CT emphysema group was 37.2%, markedly higher than that (14.8%) in the non-emphysema group. Multivariate analysis revealed that the odds ratio of moderate or severe airflow obstruction due to CT emphysema was 3.21 (2.24–4.58), and that due to smoking continuation was 8.16 (3.54–18.81).

Conclusion: CT emphysema may be a radiological sign of future airflow obstruction risk.

Keywords low dose CT screening, emphysema, airflow obstruction, risk factor

Chronic obstructive pulmonary disease (COPD) is considered to be the 4th leading cause of death in the world[1]. In Japan, the estimated number of people with this disease was more than 5,300,000 in 2004[2]. In COPD patients, emphysema and airway involvement are present to varying degrees due to long-term exposure to risk factors, especially smoking. Therefore, if emphysema and airway-related changes can be clarified before the development of COPD, early appropriate interventions may be possible.

We previously reported that emphysematous changes (CT emphysema) were observed in low-dose CT screening for lung cancer in 11.2% of males aged 50–69 years, and the majority (95.3%) of those with CT emphysema had smoking history[3]. We have also reported an increase in the frequency of airflow obstruction during follow-up of pulmonary function in those with CT emphysema[4], and inhibition of CT emphysema progression by long-term smoking cessation[5].

In middle-aged smokers with CT emphysema, airflow obstruction is often absent, and the degree of the increased risk of developing clinical COPD in the future is not clear. In this study, we evaluated the cumulative frequency of airflow obstruction according to the presence or absence of CT emphysema and smoking continuation in males who annually underwent a health check-up (Ningen Dock) over a long period.

Purpose

The purpose of this study was to evaluate differences in the frequency of airflow obstruction according to the presence or absence of CT emphysema and smoking continuation in males who annually underwent Ningen Dock over a long period.

Subjects and Methods

We conducted a retrospective cohort study using health check-up data obtained at Hitachi Health Care

[1] Department of Internal Medicine, Hitachi General Hospital ; [2] Hitachi Health Care Center ; [3] Department of Epidemiology and Prevention, Center for Clinical Sciences, National Center for Global Health and Medicine

Contact : Takeshi Nawa, Department of Internal Medicine, Hitachi General Hospital, 2–1–1, Jonan, Hitachi City, Ibaraki 317–0077, Japan.
Tel : +81–294–23–1111 ; Fax : +81–294–23–8767 ; E-mail : takeshi.nawa.nw@hitachi.com

Center. Subjects were selected from a total of 7,431 men with a history of smoking (≥ 20 pack-years) who underwent low-dose CT screening between April 1998 and March 2006, excluding those who received medication for bronchial asthma or COPD, who also underwent subsequent screening between April 2009 and March 2012. There were 2,164 men who met these criteria. If subjects underwent screening more than once in the first period, the date of the earliest screening was defined as baseline and if they were screened more than once in the second period the data from the latest screening was used to assess changes from baseline. This study was performed with the approval of the Ethics Committee of the Hitachi Health Care Center (No. 1998–2001).

Participants were aged 50–69 years. The study was performed after obtaining informed consent from them[6]. A single slice CT scanner had been used. The scanning parameters were 120 kV peak, 50 mA, 10-mm collimation, and 2:1 pitch. The whole lung field was scanned and completed at deep inspiration during a single breath-hold. Emphysematous changes were visually evaluated by two radiologists and one pulmologist, and a consensus reached. The severity of emphysema was classified as mild, moderate, and severe according to Goddard's classification[7].

Pulmonary function tests were performed as a part of the health check-up. Forced vital capacity (FVC) and forced expiratory volume during the first second (FEV_1) were measured using the forced expiration technique. The ratio of these two measurements (FEV_1/FVC, described as FEV_1%) was calculated. In addition, we used the ratio of the actually measured FEV_1 to the predicted FEV_1 (%FEV_1) for analysis. The predicted FEV_1 were calculated from formula provided by Japanese Respiratory Society[8]. According to the diagnostic criteria of the Japan Society of Ningen Dock[9], airflow obstruction was classified as mild (FEV_1% < 70%) and moderate or severe obstruction (FEV_1% < 70%, and %FEV_1< 80%), and the cumulative frequency of airflow obstruction during the whole follow-up period was calculated.

Logistic regression was used to estimate the odds ratio and its 95% confidence interval for an association between CT emphysema at baseline and risk of airflow obstruction, with adjustment for age and smoking intensity. Statistical analyses were performed using SPSS Version 19 (IBM).

Results

The characteristics of the subjects are shown in **Table 1**. Their mean age was 51.4 years, and the amount of smoking was 33.4 pack-years. During a mean period of 12.1 years, pulmonary function tests were performed 11.5 times. Age was slightly higher, and the amount of smoking was greater in CT emphysema subjects (N=285) than in those without CT emphysema (N=1,879). The severity of emphysema was mild in 89.1%, as determined by visual evaluation[9].

The results for frequency of airflow obstruction are shown in **Fig. 1**. In the CT emphysema group, the proportion of participants with airflow obstruction at the initial examination was 26.3%, and the cumulative frequency for all examinations was 57.2%. In the non-emphysema group, the proportion of participants with airflow obstruction at the initial examination was 9.3%, and the cumulative frequency was 26.0% (**Fig. 1a**). The frequency of moderate or severe airflow obstruction at the initial examination and the cumulative frequency in the CT emphysema group were 16.8% and 37.2%, respectively, which were markedly higher than the frequencies (5.9% and 14.8%) in the non-emphysema group (**Fig. 1b**).

As factors associated with the development of airflow obstruction, subject age, smoking status (current or past), amount of smoking (pack-years), and presence or absence of CT emphysema were evaluated. Univariate and multivariate analyses were performed with respect to smoking continuation and presence of CT emphysema at the initial health check-up (**Table 2**). In multivariate analysis with adjustment for age and amount of smoking, the odds ratio of developing airflow obstruction due

Table 1. Characteristics of Participants

	CT emphysema (+)	CT emphysema (–)	*p*
n	285	1879	
Age (mean ± S.D.)	52.1±5.2	51.3±5.1	0.026
Pack-years	35.8±16.3	33.1±11.7	0.011
Smoking status at baseline			
Current	244	1581	0.524*
Past	41	298	
Follow-up (years)	12.1±1.4	12.2±1.4	0.553
Times of Pulmonary Function Test	11.8±2.0	11.5±2.5	0.057
Severity of CT emphysema (Mild/Moderate/Severe) [7]	254/22/9 (89.1/7.7/3.2%)	0/0/0	–

t-test, * χ^2 test

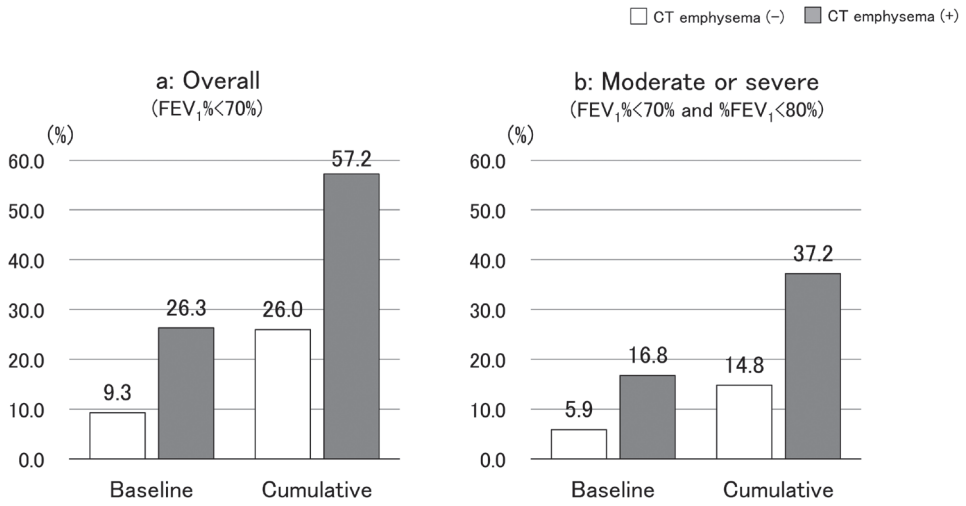

Fig. 1. Cumulative Frequency of Airflow Obstruction According to Presence or Absence of CT Emphysema
a: overall (mild to severe) airflow obstruction, b: moderate or severe airflow obstruction

Table 2. Logistic Regression Analysis for Association of CT Emphysema and Smoking Intensity at Baseline with Incidence of Airflow Obstruction

	Univariate analysis	Multivariate analysis
Odds ratio* of overall airflow obstruction		
CT emphysema	3.31 (2.45–4.49)	3.21 (2.37–4.36)
Smoking at baseline	2.43 (1.67–3.54)	2.56 (1.75–3.76)
Odds ratio* of moderate or severe airflow obstruction		
CT emphysema	3.33 (2.34– 4.74)	3.21 (2.24– 4.58)
Smoking at baseline	8.40 (3.66–19.30)	8.16 (3.54–18.81)

*Adjusted by age and pack-years (logistic regression model)

to CT emphysema was 3.21 (95% confidence interval, 2.37–4.36), and that of developing moderate or severe airflow obstruction was 3.21 (2.24–4.58) within the observation period. On the other hand, the odds ratio of developing airflow obstruction due to smoking continuation was 2.56 (1.75–3.76), and that of developing moderate or severe airflow obstruction was 8.16 (3.54–18.81) within the observation period. According to self-reporting on smoking habit, the proportion of current smokers had decreased to 35.8% in the CT emphysema group and 40.5% in the non-emphysema group by March 2012.

Discussion

The Japanese Respiratory Society Guidelines for the Diagnosis and Treatment of COPD state that "CT examination is useful for the early detection of emphysematous lesions, and allows early interventions such as smoking cessation guidance[10]". Sato *et al.* reported a high incidence of CT emphysema even in smokers aged < 50 years and an increase in its incidence with age[11]. A cohort study involving COPD patients showed that the severity of COPD is not always correlated with that of emphysema, suggesting that people with various pathological conditions were included in the COPD subjects, emphysema was severe in a group with a rapid decrease in pulmonary function, and the severity of emphysema is an important factor associated with the survival of COPD patients[12].

Though there have been many studies on emphysema and airway involvement on CT images in clinical COPD patients, a clear correlation of incidentally detected CT emphysema and future risk of COPD has not been demonstrated. With the widespread use of low-dose CT for lung cancer screening, smoking-related findings have been actively evaluated in screening participants. In this regard, a cross-sectional study by Ohmori *et al.* observed age-related increases in the incidences of CT emphysema and airflow obstruction[13]. A more recent study found that CT emphysema detected in low-dose screening CT scans is a factor predicting death from cardiovascular or respiratory diseases[14] and is associated with a future decrease in respiratory function[15].

In this study, in screening participants with CT emphy-

sema in their 50s, the risk of developing airflow obstruction after the age of 60 was approximately 3 times higher, and 1 in 3 of them developed moderate or severe airflow obstruction. These results suggest that the presence of CT emphysema is a strong risk factor that is independent of smoking history. Although interventions for smoking cessation are essential in all lung cancer screening participants, even stronger interventions are required in participants presenting CT emphysema. For example, health advice using participants' own CT images could play an important role in getting them to change their smoking behavior. Furthermore, close observation of patients with CT emphysema and smoking history is desirable in view of the high risk of future airflow obstruction in such patients.

The strengths of our study compared with other studies are as follows. First, our study found a high frequency of airflow obstruction during long-term follow-up of participants with CT emphysema. Second, the risk of airflow obstruction involved in CT emphysema was determined independently from smoking habits by comparing the CT emphysema and non-emphysema groups with adjustments for background factors.

This study has some limitations. Since it was a retrospective study involving males who annually underwent screening, there may have been a bias in their health status. In addition, since airway involvements and symptoms were not evaluated, COPD without CT emphysema might have been overlooked. However, since emphysema is considered to be the dominant phenotype in most clinical COPD patients[16], this approach using CT images may be useful to a certain degree.

The original purpose of low-dose CT screening is the early detection of lung cancer. However, CT emphysema is an important radiological risk factor for future airflow obstruction and a recent meta-analysis showed that participants with CT emphysema constitute a high-risk group for lung cancer[17]. CT emphysema could possibly be a strong risk factor for not only COPD but also smoking-related diseases, so more data needs to be accumulated.

Conclusion

CT emphysema is a strong risk factor in predicting future airflow obstruction. To enhance the utility of CT screening, appropriate evaluation of smoking-related findings is strongly recommended.

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Conflict of Interest

There was no conflict of interest concerning this study.

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Original Article

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Relationship between Bone Mineral Density and Metabolic Biomarkers in Postmenopausal Women who Underwent a Comprehensive Health Check-up

Michiyo Takayama, Hiroshi Hirose, Ryoko Shimizu, Kanako Makino, Juntaro Matsuzaki, Naomi Takata, Eisuke Shiomi, Toshifumi Yoshida, Nagamu Inoue, Yasushi Iwao, Yoshinori Sugino

Abstract

Objective: Several studies have indicated that there is a link between atherosclerosis and bone metabolism. We investigated a cross-sectional relationship between bone mineral density (BMD) and metabolic biomarkers among postmenopausal women who underwent a comprehensive health check-up.

Methods: Three hundred and eighty-six postmenopausal women, mean age 63.3 ± 8.3 years, were enrolled in this study. BMD at the lumbar spine and unilateral proximal total hip was measured by dual-energy X-ray absorptiometry, and the percentage of young adult mean (%YAM) was calculated. The lower %YAM of the two sites was used for analysis. We performed logistic regression analyses to evaluate factors related to the risk of low BMD, defined as %YAM < 80. Plausible variables, i.e. age, body mass index (BMI), blood pressure, fasting plasma glucose, triglycerides (TG), low-density lipoprotein cholesterol, alkaline phosphatase, C-reactive protein, smoking habit, drinking habit, and exercise habit were included in the model.

Results: One hundred and twenty-six participants were considered to have low BMD. Univariate logistic analyses adjusted for age and BMI revealed that TG was related to the risk of low BMD (odds ratio and 95% confidence interval; log TG by 1SD increase: 1.335 (1.038–1.707), $p< 0.05$). In the multivariate models adjusted for all other confounders, this significant relationship remained (odds ratio and 95% confidence interval; log TG by 1SD increase: 1.385 (1.056–1.818), $p< 0.05$).

Conclusions: These results suggest that, in addition to age and BMI, TG is a risk factor contributing to low BMD.

Keywords bone mineral density, postmenopausal women, triglycerides

As Japan has become a "super-aging society", the extension of healthy life expectancy has emerged as an important policy issue[1]. According to a report concerning long-term care insurance, bone/orthopedic disorders account for 20–30% of disability in activities of daily living in the elderly[2]. Although fracture is recognized as an important risk factor for a reduced healthy life expectancy, particularly in elderly women, the presence of underlying osteoporosis is often overlooked. Osteoporosis affects an estimated 12.8 million Japanese, with the prevalence in women approximately three times greater than that in men[3], of whom only an estimated 4.5 million receive treatment for this condition[4], indicating the importance of early identification and interventions for the prevention of osteoporosis and consequential fractures. Associations between atherosclerotic diseases, such as dyslipidemia and type 2 diabetes, and bone metabolism have been a focus of interest, and numerous studies have reported associations between such lifestyle-related diseases and bone metabolism[5–9], as well as their underlying mechanisms. *In vitro* studies have demonstrated that oxidative stress induces apoptosis of osteoblasts, and that glycation stress due to advanced glycation end-products inhibits bone marrow stromal cells from differentiating into osteoblasts[10,11]. However, clinical studies on associations between lifestyle-related diseases and bone metabolism have been inconclusive.

As described in the Japanese 2011 Guidelines for the

Center for Preventive Medicine, Keio University Hospital

Contact : Michiyo Takayama, Center for Preventive Medicine, Keio University Hospital, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–8582, Japan. Tel : +81–3–3353–1211 ; Fax : +81–3–5269–2468 ; E-mail : michiyo@z6.keio.jp

Prevention and Treatment of Osteoporosis, the purpose of osteoporosis screening is to identify individuals with or at risk of osteoporosis during asymptomatic stages in order to provide early interventions. By incorporating bone densitometry into a comprehensive health check-up, data on numerous clinical variables and bone mineral density (BMD) may be obtained at the same time-point, from which clinical surrogate markers of a low BMD can be explored at the early stage. In this study, we investigated a relationship between BMD and metabolic biomarkers in postmenopausal women who received a comprehensive health check-up.

Subjects

The present study included 386 postmenopausal women (age range, 46–85 years; mean age, 63.3± 8.3 years) who underwent bone densitometry during their comprehensive health check-ups at the Center for Preventive Medicine, Keio University Hospital, from August 2012 to February 2014. Potential candidates were excluded from the study if they were receiving medications for osteoporosis, had a history of thyroid dysfunction, rheumatoid arthritis or gastrectomy, were taking steroids, were receiving hormone replacement therapy or treatment for malignant diseases, or reported that menopause occurred after gynecologic surgery. Those suffering from severe hepatic dysfunction, chronic renal failure, or malnutrition were not included.

Ethical consideration

General informed consent was obtained from the participants. This study was carried out with approval from the Ethics Committee of Keio University School of Medicine (approval number: 20130445).

Methods

Clinical parameters were extracted from the results of the comprehensive health check-ups. The following plausible variables were selected: age, body mass index (BMI), blood pressure, fasting plasma glucose (FPG), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), alkaline phosphatase (ALP), and C-reactive protein (CRP). Biochemical tests were performed using an automatic biochemical analyzer (LABOSPECT008; Hitachi High-Technologies Corporation, Tokyo, Japan). The BMD was measured by dual-energy X-ray absorptiometry (DXA) using a LUNAR PRODIGY series X-ray bone densitometer (GE Healthcare Japan Corporation, Tokyo, Japan) at two sites, the lumbar spine (L1-L4) and unilateral proximal total hip. The BMD was measured in g/cm^2, and the percentage of young adult mean (%YAM) was calculated. The lower %YAM of the two sites was used for analysis. Participants were classified into three categories according to %YAM: normal BMD (%YAM ≥ 80), osteopenia (70 ≤ %YAM < 80), and osteoporosis (%YAM < 70). Those who had a %YAM less than 80 were defined as low BMD. Additionally, data on current smoking habits, current drinking habits, and exercise habits were collected through a questionnaire. A drinking habit was defined as "consumption of more than 40g of alcohol at least three times a week", and an exercise habit as "daily walking activity for at least 1 hour" or "performing more than 30 minutes of daily exercise of an intensity that produces mild sweating at least 2 days a week".

Statistics

Continuous variables were presented as means ± SDs, and categorical variables were presented as counts and percentages. Values of continuous variables with a non-normal distribution were analyzed after applying a logarithmic transformation. Univariate and multivariate logistic regression analyses were performed to identify risk factors for low BMD, defined as %YAM of less than 80. The following explanatory variables were included in the models: age, BMI, systolic blood pressure (SBP), FPG, TG, LDL-C, ALP, CRP, smoking habit (0, 1), drinking habit (0, 1), and exercise habit (0, 1). A value of $p < 0.05$ (two-sided) was considered significant. Data were analyzed with IBM SPSS Statistics version 22 for Windows (IBM Japan, Tokyo).

Results

Characteristics of participants

The baseline characteristics of the participants are shown in **Table 1** and **Table 2**. Participants were 46 to 85 years of age, with a mean age of 63.3 ± 8.3 years. The mean BMI, visceral fat area, blood pressure, and biochemical measurements were within the normal ranges, suggesting a relatively healthy study population. The mean %YAM was 85.0 ± 12.8 % (**Table 1**).

Regarding lifestyle habits, 11 (2.8 %) were current smokers, 92 (23.8 %) were current drinkers, and 189 (49.0 %) performed habitual exercise. The numbers of participants under medical treatment for hypertension, dyslipidemia, and type 2 diabetes were 84 (21.8 %), 82 (21.2 %), and 16 (4.1 %), respectively. As for %YAM categories, 260 women (67.4 %) were classified as normal BMD (%YAM ≥ 80), 85 (22.0 %) as osteopenia (70 ≤ %YAM < 80), and 41 (10.6 %) as suspected osteoporosis (%YAM < 70) (**Table 2**).

Risk factors for low BMD (logistic regression analyses)

Factors associated with a risk for low BMD were investigated using logistic regression analyses, in which presence of low BMD was entered as the dependent variable (1 for %YAM < 80 and 0 for %YAM ≥ 80), and age, BMI, SBP, FPG, TG, LDL-C, ALP, CRP, and smoking, drinking, and exercise habits as the independent variables.

In univariate logistic regression analyses, age, BMI, and CRP were identified as factors significantly related to low BMD (crude odds ratio (OR) and 95% confidence interval (CI); age by one year increase: 1.061 (1.033–1.090), BMI by 1 SD increase: 0.437 (0.319–0.599), log CRP by 1 SD increase: 0.782 (0.622–0.984), respectively, $p<0.05$). When adjusted for age and BMI, TG appeared to be a significant risk factor related to low BMD (OR and 95% CI; log TG by 1 SD increase: 1.335 (1.038–1.717), $p < 0.05$), while the significant association with log CRP disappeared (**Table 3**).

Next, we performed multivariate logistic regression analyses for three models. In model 1, age, BMI, SBP, FPG, log TG, and LDL-C were included as independent variables, and in model 2, all variables included in model 1 as well as ALP and log CRP were included. In model 3, all variables included in model 2 and life style habits were included. As shown in **Table 4**, in addition to age and BMI, TG remained a significant risk factor contributing to low BMD in all three models (in model 1, OR and 95% CI; age by one year increase: 1.089 (1.054–1.125); BMI by 1 SD increase: 0.339 (0.231–0.499); log TG by 1 SD increase: 1.388 (1.070–1.800), respectively, $p<0.05$).

Table 1. Baseline Characteristics of Participants: Clinical Parameters

		n = 386
		mean ± SD
Age	(years)	63.3 ± 8.3
BMI	(kg/m^2)	21.9 ± 3.7
VFA	(cm^2)	73.3 ± 39.4
SBP	(mmHg)	121.1 ± 22.5
DBP	(mmHg)	76.3 ± 11.0
Total protein	(g/dL)	6.9 ± 0.4
Albumin	(g/dL)	4.2 ± 0.3
AST	(IU/L)	23.9 ± 11.0
ALT	(IU/L)	20.5 ± 13.9
LDH	(IU/L)	185.2 ± 34.5
ALP	(IU/L)	214.5 ± 63.7
γ-GTP	(IU/L)	28.7 ± 30.5
UN	(mg/dL)	13.8 ± 3.4
Creatinine	(mg/dL)	0.65 ± 0.12
Uric acid	(mg/dL)	4.9 ± 1.0
FPG	(mg/dL)	103.3 ± 14.0
HbA1c	(%)	5.7 ± 0.5
TC	(mg/dL)	219.7 ± 33.3
TG	(mg/dL)	91.3 ± 52.3
HDL-C	(mg/dL)	64.8 ± 13.8
LDL-C	(mg/dL)	122.0 ± 29.3
CRP	(mg/dL)	0.07 ± 0.22
WBC	(×10^3/μL)	4.6 ± 1.1
RBC	(×10^4/μL)	435.7 ± 33.9
Hemoglobin	(g/dL)	13.3 ± 0.9
Hematocrit	(%)	39.9 ± 2.5
Platelets	(×10^4/μL)	22.7 ± 4.8
BMD	(g/cm^2)	0.821 ± 0.120
%YAM	(%)	85.0 ± 12.8

VFA: visceral fat area, BMD: bone mineral density, YAM: young adult mean.

Table 2. Baseline Characteristics of Participants: Habits, Metabolic Diseases on Medication, and %YAM Categories

	n (%)
Current smoking habit	11 (2.8)
Current drinking habit	92 (23.8)
Exercise habit	189 (49.0)
Hypertension on medication	84 (21.8)
Dyslipidemia on medication	82 (21.2)
Diabetes mellitus on medication	16 (4.1)
Normal BMD (%YAM >=80%)	260 (67.4)
Osteopenia (%YAM 70–80%)	85 (22.0)
Osteoporosis (%YAM <70%)	41 (10.6)

BMD: bone mineral density, YAM: young adult mean.

Table 3. Univariate Logistic Regression Analyses to Identify Factors Associated with Low Bone Mineral Density

	Crude OR			OR adjusted for age and BMI		
	Exp (B)	95% CI	*p*	Exp (B)	95% CI	*p*
Age (per 1 year increase)	1.061	1.033–1.090	<0.001*	NA	NA	NA
BMI (per 1 SD increase)	0.437	0.319–0.599	<0.001*	NA	NA	NA
SBP (per 1 SD increase)	0.975	0.789–1.204	0.811	0.875	0.675–1.135	0.316
FPG (per 1 SD increase)	0.794	0.611–1.031	0.084	0.894	0.664–1.203	0.459
log TG (per 1 SD increase)	0.975	0.787–1.207	0.814	1.335	1.038–1.717	0.024*
LDL-C (per 1 SD increase)	0.845	0.681–1.048	0.125	0.956	0.755–1.209	0.706
ALP (per 1 SD increase)	1.101	0.893–1.359	0.367	1.144	0.903–1.448	0.265
log CRP (per 1 SD increase)	0.782	0.622–0.984	0.036*	1.047	0.795–1.379	0.745
Current smoking habit (0,1)	1.185	0.340–4.125	0.790	1.166	0.315–4.311	0.818
Current drinking habit (0,1)	0.737	0.466–1.168	0.194	0.821	0.501–1.347	0.436
Exercise habit (0,1)	1.257	0.820–1.926	0.295	1.068	0.671–1.702	0.781

* $p<0.05$, OR: odds ratio, Exp: exponentiation, NA: not available

Table 4. Multivariate Logistic Regression Analyses to Identify Factors Associated with Low Bone Mineral Density

	Model 1			Model 2			Model 3		
	Exp (B)	95% CI	*p*	Exp (B)	95% CI	*p*	Exp (B)	95% CI	*p*
Age (per 1 year increase)	1.089	1.054–1.125	<0.001*	1.088	1.053–1.125	<0.001*	1.087	1.050–1.125	<0.001*
BMI (per 1 SD increase)	0.339	0.231–0.499	<0.001*	0.336	0.224–0.503	<0.001*	0.323	0.214–0.487	<0.001*
SBP (per 1 SD increase)	0.864	0.662–1.129	0.285	0.847	0.646–1.110	0.228	0.868	0.661–1.140	0.309
FPG (per 1 SD increase)	0.875	0.643–1.189	0.393	0.881	0.649–1.197	0.419	0.904	0.669–1.223	0.514
Log TG (per 1 SD increase)	1.388	1.070–1.800	0.014*	1.376	1.055–1.794	0.019*	1.385	1.056–1.818	0.019*
LDL-C (per 1 SD increase)	0.919	0.724–1.167	0.491	0.934	0.733–1.190	0.581	0.917	0.716–1.174	0.492
ALP (per 1 SD increase)	NA	NA	NA	1.135	0.888–1.452	0.312	1.104	0.863–1.411	0.432
Log CRP (per 1 SD increase)	NA	NA	NA	0.992	0.744–1.323	0.957	0.992	0.740–1.329	0.958
Current smoking habit (0,1)	NA	NA	NA	NA	NA	NA	0.893	0.212–3.763	0.877
Current drinking habit (0,1)	NA	NA	NA	NA	NA	NA	0.855	0.508–1.441	0.557
Exercise habit (0,1)	NA	NA	NA	NA	NA	NA	1.120	0.694–1.809	0.643

* $p < 0.05$, Exp: exponentiation, NA: not available
Model 1 adjusted for age, BMI, SBP, FPG, TG, and LDL-C.
Model 2 adjusted for all variables included in Model 1, and ALP and CRP.
Model 3 adjusted for all variables included in Model 2, and smoking, drinking and exercise habits.

Discussion

We analyzed an association of BMD with metabolic biomarkers in 386 relatively healthy, postmenopausal women who received a comprehensive health check-up, and found that high TG levels were associated with the risk of low BMD.

Recent attention has been focused on inter-organ crosstalk involved in atherosclerosis and bone metabolism. A 25-year longitudinal investigation in the Framingham Heart Study revealed a strong positive correlation between bone loss and abdominal aortic calcification in women[12]. Other previous studies have indicated that estrogen, vitamin D, and oxidized lipids play roles both in arterial calcification and bone formation[13–15]. While numerous clinical studies have found associations between lipid metabolism and BMD, consistent conclusions have not been reached. Regarding an association between LDL-C and BMD, Poli *et al.*[6], in an investigation of 1,303 postmenopausal women, found that those with high LDL-C levels (≥ 160 mg/dL) were at a higher risk of low BMD. Also, a study involving Japanese postmenopausal women demonstrated that BMD was negatively correlated with LDL-C and positively correlated with HDL-C[5]. It has been suggested that the mechanisms underlying these associations may involve oxidative stress-induced oxidized LDL, which prevents bone marrow stromal cells from differentiating into osteoblasts. However, a conflicting finding has been reported for men: a positive correlation between BMD and LDL-C was observed[16].

The present study enrolled only postmenopausal women, and neither univariate nor multivariate logistic regression analyses revealed a significant association between LDL-C and low BMD. On the other hand, each standard deviation increase in log TG was associated with a 1.38-fold greater risk of low BMD in the multivariate logistic regression analyses. Similar results were obtained when we performed multivariate logistic regression analyses with the presence of osteoporosis, i.e., %YAM < 70, as the dependent variable, instead of low BMD (data not shown).

A limited number of previous studies have observed an association between TG and BMD. Cui *et al.*[17] assessed BMD and serum lipid profiles in 375 premenopausal and 355 postmenopausal Korean women, and found a significantly lower lumbar-spine BMD among premenopausal women in the higher quartiles of TG levels, a trend which was not observed in postmenopausal women. They also noted that there was a weak positive correlation ($r = 0.11$, $p < 0.05$) between the trochanteric BMD and TG levels in postmenopausal women, and that, even in the premenopausal women, there were no marked differences in BMD at the proximal femur across the quartiles of TG levels, suggesting complex relationships between lipid profiles and BMD.

It is likely that increased oxidative stress associated with dyslipidemia, such as hyper-LDL-cholesterolemia and hypertriglyceridemia, acts to inhibit osteogenesis and/or promote osteocyte apoptosis. The inconsistent results among the above studies may be attributed to gender, race, method and site of BMD measurement, and effects of oral medicines taken, such as the osteogenesis-promoting effect of hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors[18,19], or negative effect on BMD of thiazolidinedione[20] and selective serotonin reuptake inhibitors (SSRI)[21]. In the present study, 69 participants were taking HMG-CoA reductase inhibitors, 2 were taking thiazolidinedione, and 4 were taking SSRI. To eliminate any possible effects of these agents on the results, we conducted the multivariate logistic regression analysis after excluding those who were taking statins, thiazolidinedione, and/or SSRI. The results were similar to those of the primary analyses, with age and BMI remaining as

significant contributing factors, and TG marginally related to low BMD in model 1 (data not shown).

One possible explanation for the association between high TG levels and a low BMD is the involvement of osteocalcin. Synthesized in osteoblasts, osteocalcin is known to be a marker of bone formation, and also to play a role in energy metabolism in the body. It has been reported that osteocalcin enhances insulin secretion from pancreatic β cells and adiponectin release from adipocytes, stimulates tissue glucose utilization, and, thereby, increases energy metabolism[22]. A longitudinal study by Kanazawa *et al.*[23], in which they examined relationships between glucose/lipid metabolism and markers of bone metabolism in type 2 diabetic patients, demonstrated that increased TG levels were associated with reduced osteocalcin levels, suggesting that reduced osteocalcin levels resulting from high TG levels may lead to decreased bone formation and cause a low BMD as a consequence. Although data on osteocalcin levels were not available in this study, our results suggest that risk of low BMD could be identified at an early stage by incorporating assessment of bone metabolism markers into routine BMD measurements performed in osteoporosis screening. This merits further investigation.

Several limitations of the present study should be noted. It involved examinees of comprehensive health checkups, who have a relatively high level of health consciousness, making it unreasonable to assume that its results are representative of the general population. Additionally, because of its cross-sectional, observational nature, this study does not allow us to make any inferences about the causal relationships between BMD and TG levels. Future studies are needed to follow-up serial BMD changes in participants who return for repeat examinations in order to perform a longitudinal evaluation of an association between them and metabolic markers.

Conclusion

Associations between BMD and metabolic biomarkers were examined cross-sectionally in postmenopausal women who underwent a comprehensive health checkup. The present results suggested that, in addition to older age and lower BMI, high TG is a risk factor contributing to low BMD.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Original Article

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Serum Albumin is Positively Correlated with Serum Potassium and Inversely Associated with Incident Hypertension in a Health Screening Population

Eiji Oda

Abstract

Background: Albumin is reported to be a potent inhibitor of angiotensin converting enzyme (ACE) and its inhibiting potency is tissue-dependent, while a decrease in serum albumin is reported to be a predictor of incident hypertension.

Methods: This was a retrospective 5-year follow-up study in a health screening population including 2,045 subjects. The mean (SD) serum potassium and incidence of hypertension in the first (lowest), second, third and fourth (highest) quartiles of serum albumin (Q1, Q2, Q3 and Q4) were calculated. The hazard ratios (HRs) of hypertension for each 1 SD increase in serum albumin and for Q1, Q2 and Q3 compared with Q4 were calculated and adjusted for baseline blood pressure and other confounders.

Results: During 5 years of follow-up (mean: 3.8 years), 400 subjects developed hypertension (3.9%/year). The incidence of hypertension was 4.7%/year, 3.8%/year, 3.8%/year and 3.4%/year, respectively (p for trend<0.001), in Q1, Q2, Q3 and Q4. The mean (SD) serum potassium levels for Q1, Q2, Q3 and Q4 were 4.26 (0.28) mEq/L, 4.33 (0.32) mEq/L (p=0.004), 4.34 (0.32) mEq/L (p=0.003) and 4.39 (0.36) mEq/L (p<0.001), respectively (p: compared with Q1). The adjusted HRs of hypertension for each 1 SD increase in serum albumin and for Q1, Q2 and Q3 compared with Q4 were 0.79 (p<0.001), 1.73 (p=0.003), 1.45 (p=0.017) and 1.18 (p=0.350), respectively.

Conclusions: Serum albumin is positively correlated with serum potassium and inversely associated with incident hypertension.

Keywords albumin, aldosterone, hypertension, potassium

Hypertension has been established to be an independent risk factor for cardiovascular disease. It is important to delineate predictors of hypertension so that appropriate strategies for the prevention of cardiovascular disease can be developed.

Albumin is the most abundant plasma protein, normally constituting about 50% of plasma protein, and serves as a carrier for molecules of low water solubility, including lipid soluble hormones, bile salts, unconjugated bilirubin, free fatty acids, calcium, and drugs like warfarin, fibrates and phenytoin. One of its most important roles is to regulate the colloid osmotic pressure of blood.

Previous cross-sectional studies reported that serum albumin was positively associated with blood pressure (BP) [1–3], while a cross-sectional and longitudinal study found that serum albumin levels were associated with BP only in cross-sectional models, not in longitudinal models [4]. The author observed that a decrease in serum albumin levels predicted incident hypertension among a health screening population in a retrospective 4-year follow-up study [5]. Albumin is reported to be a potent physiological inhibitor of angiotensin converting enzyme (ACE) and the enzymatic activity of intravascular ACE appears to be almost completely suppressed by serum albumin when it is present at physiological concentrations [6]. Therefore, in contrast to the cross-sectional positive association observed between serum albumin and BP, it can be speculated that serum albumin would be inversely associated with incident hypertension via its suppression of the renin-angiotensin-aldosterone system.

Medical Check-up Center, Tachikawa Medical Center

Contact : Eiji Oda, Medical Check-up Center, Tachikawa Medical Center, Nagachou 2–2–16, Nagaoka, Niigata, 940–0053, Japan,
E-mail: ijie@venus.sannet.ne.jp ; Tel: +81–258–36–6221 ; Fax: +81–258–34–1113

The aims of the present 5-year follow-up study were to confirm the results of the previous 4-year follow-up study[5] and to investigate an association between serum albumin levels and serum potassium levels as a possible surrogate marker of plasma aldosterone levels.

Methods

This study was approved by the ethics committee of Tachikawa Medical Center and the procedures were in accordance with the Declaration of Helsinki, 1964 and Declaration of Tokyo, 1975, as revised in 2008.

Subjects

Between April 2008 and March 2009, 3,866 individuals visited our medical check-up center for annual general health screenings and provided their written informed consent. They were required to complete a questionnaire including questions about their history of coronary heart disease and stroke, smoking, alcohol consumption, physical activity and use of antihypertensive, antidiabetic and antihyperlipidemic drugs. Physical activity was defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week. For the follow-up study, the exclusion criteria were a history of coronary heart disease or stroke and use of antihypertensive, antidiabetic or antihyperlipidemic drugs and the inclusion criterion was normotension at baseline. There were 2,623 candidate subjects for the follow-up study. There were 578 dropouts so 2,045 individuals (1,227 men aged 24–81 years and 818 women aged 30–82 years) who revisited our medical check-up center for annual health screenings between April 2009 and March 2014 were enrolled in the follow-up study. Among 2,946 individuals who passed the exclusion criteria, 1,251 who revisited our medical check-up center between April 2013 and March 2014 and were not using antihypertensive drugs at the time of revisiting were included in the correlation study. Additionally, a relationship between serum albumin levels and urinary albumin levels was investigated in 354 subjects whose urinary albumin levels were optionally measured between April 2009 and March 2014. Hypertension was defined as systolic BP of ≥ 140 mmHg, diastolic BP of ≥ 90 mmHg and/or use of antihypertensive drugs.

Measurements

After an overnight fast, blood samples were obtained to measure blood levels of routine medical check-up parameters, including fasting glucose, triglycerides, HDL cholesterol, LDL cholesterol, uric acid, high-sensitivity C-reactive protein (hsCRP), total bilirubin, albumin, potassium and creatinine. Proteinuria was qualitatively measured with a dipstick. Urinary albumin levels were optionally measured in spot morning urine samples obtained from the above-mentioned 354 subjects with latex immune-nephelometry using N-assay TIA Micro Alb E-Type (Nittobo Medical Co., LTD., Tokyo, Japan) and expressed in mg/g of creatinine. LDL cholesterol was measured using a direct surfactant method with Choletest-LDL (Sekisui Medical Inc., Tokyo, Japan). The chemical assessments were all performed at BML Nagaoka (Nagaoka, Japan) except for the assessment of hsCRP, which was performed at BML General Laboratory (Tokyo, Japan) with nephelometry using N-latex CRP-2 (Siemens Healthcare Japan, Tokyo, Japan). The measurement limit of hsCRP was 0.02 mg/L, and a value of hsCRP less than the measurement limit was considered as 0.01 mg/L. Estimated glomerular filtration rate (eGFR) was calculated using the following equation according to the recommendation from the Japanese Society of Nephrology: eGFR (mL/min/1.73m^2) = 194 × creatinine$^{-1.094}$ × age$^{-0.287}$ in men, and 194 × creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 in women[7]. BP was automatically measured with MPV-3301 (NIHON KOHDEN Inc., Tokyo, Japan) in a sitting position after 5 min of rest for each measurement. Average systolic and diastolic BP values were calculated from two measurements. Body weight and height were measured using TBF-210 (TANITA, Tokyo, Japan) with the subjects wearing light clothes provided by our medical check-up center and the weight of the clothes was subtracted from the measured body weight. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters.

Statistical analysis

Baseline data were compared between the candidates and actually followed-up subjects as well as between the subjects who developed hypertension and those who did not. The means were compared with two-sided *t*-tests and percentages were compared with χ-squared tests. Triglycerides and hsCRP were compared after log transformation because their distributions were highly skewed.

Pearson's correlation coefficients were calculated between serum albumin levels at baseline and serum potassium levels, systolic and diastolic BPs at baseline and changes in systolic and diastolic BPs over 5 years in the above-mentioned 1,251 subjects.

Incidence of hypertension and mean serum potassium level were calculated for each quartile of serum albumin. The mean serum potassium levels for the higher quartiles (Q2, Q3 and Q4) were compared with the lowest quartile (Q1) using Scheffe's method after ANOVA.

Using Cox regressions in which years were used as the unit of survival, the first diagnosis with hypertension in the annual health screenings was ascertained as the outcome and subjects without the outcome were assessed at their last visits. Hazard ratios (HRs) of incident hypertension for each 1 SD increase in serum albumin and for Q1, Q2 and Q3 compared with Q4 were calculated with adjustment for systolic BP, sex, age, current smoking,

daily alcohol drinking and, physical activity (Model 1), further adjusted for BMI, proteinuria, eGFR, uric acid, fasting glucose (Model 2), and further adjusted for log triglycerides, HDL cholesterol, LDL cholesterol, log hsCRP, total bilirubin and potassium (Model 3). The levels of triglycerides and hsCRP were log transformed before the calculations because their distributions were highly skewed. Diastolic BP was not included in the adjusting covariates to avoid multicollinearity because the Pearson's correlation coefficient between systolic BP and diastolic BP was 0.897. The above statistical analyses were repeated, stratified by gender.

Then, HRs of incident hypertension for each 1 SD increase in potassium, log hsCRP, total bilirubin and uric acid were calculated, adjusted for Model 1.

Age and sex adjusted partial correlation coefficients were calculated between serum albumin and log urinary albumin in the above-mentioned 354 subjects.

All statistical analyses were performed using Dr-SPSS-2 (IBM Japan, Tokyo, Japan). *p* values of less than 0.05 were considered to be statistically significant.

Results

Baseline data of the candidate subjects and actually followed-up subjects are presented in **Table 1**. There were no significant differences in the baseline data between the candidate and followed-up subjects.

The baseline data of subjects who developed hypertension and those who did not are presented in **Table 2**. Age, BMI, systolic and diastolic BPs, potassium, fasting glucose, triglycerides, uric acid and hsCRP were significantly higher and male sex, current smokers and daily drinkers were significantly more frequent, while albumin and eGFR were significantly lower, among subjects who developed hyperten-

Table 1. Baseline Data for Candidate and Actually Followed-up Subjects

	candidates	followed-ups	*p*
n	2623	2045	
male (%)	58.6	60	0.333
age (years)	49.4 (9.0)	49.5 (8.7)	0.671
body mass index (kg/m^2)	22.2 (2.8)	22.2 (2.8)	0.930
systolic blood pressure (mmHg)	112.0 (12.4)	112.1 (12.3)	0.755
diastolic blood pressure (mmHg)	70.9 (8.2)	71.0 (8.2)	0.699
albumin (g/dL)	4.31 (0.22)	4.31 (0.22)	0.986
potassium (mEq/L)	4.31 (0.32)	4.33 (0.32)	0.174
fasting glucose (mg/dL)	91.3 (11.7)	91.2 (10.8)	0.791
triglycerides (mg/dL)	85 (61–121)	85 (61–121)	0.828[3]
HDL cholesterol (mg/dL)	61.9 (15.2)	62.1 (15.2)	0.655
LDL cholesterol (mg/dL)	121.5 (30.0)	121.7 (29.5)	0.866
uric acid (mg/dL)	5.37 (1.38)	5.40 (1.35)	0.541
high-sensitivity CRP (mg/L)	0.25 (0.13–0.52)	0.25 (0.13–0.51)	0.844[3]
total bilirubin (mg/dL)	0.81 (0.33)	0.81 (0.34)	0.856
eGFR[1] (mL/min/1.73m^2)	80.1 (12.5)	79.9 (12.4)	0.520
proteinuria (%)	2.9	2.6	0.479
current smoker (%)	25.5	25.8	0.814
daily drinker (%)	36.6	36.9	0.801
physical activity[2] (%)	34.4	34.2	0.861

mean (SD), median (interquartile range) or %, [1] estimated glomerular filtration rate, [2] defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week, [3] compared after log transformation

Table 2. Baseline Data Stratified by Development of Hypertension

	developers	non-developers	*p*
n	400	1645	
male (%)	72.5	57.0	<0.001
age (years)	51.6 (8.7)	49.0 (8.7)	<0.001
body mass index (kg/m^2)	23.0 (2.7)	22.0 (2.8)	<0.001
systolic blood pressure (mmHg)	121.9 (11.3)	109.7 (11.3)	<0.001
diastolic blood pressure (mmHg)	78.2 (7.3)	69.2 (7.5)	<0.001
albumin (g/dL)	4.28 (0.22)	4.31 (0.22)	0.004
potassium (mEq/L)	4.36 (0.32)	4.32 (0.32)	0.024
fasting glucose (mg/dL)	92.6 (9.7)	90.9 (11.0)	0.004
triglycerides (mg/dL)	95 (67–136)	83 (60–118)	0.012[3]
HDL cholesterol (mg/dL)	61.3 (14.9)	62.3 (15.3)	0.280
LDL cholesterol (mg/dL)	122.5 (30.4)	121.5 (29.3)	0.524
uric acid (mg/dL)	5.78 (1.35)	5.31 (1.33)	<0.001
high-sensitivity CRP (mg/L)	0.30 (0.16–0.62)	0.24 (0.12–0.47)	<0.001[3]
total bilirubin (mg/dL)	0.81 (0.34)	0.81 (0.34)	0.993
eGFR[1] (mL/min/1.73m^2)	78.0 (12.6)	80.3 (12.3)	0.001
proteinuria (%)	3.5	2.4	0.202
current smoker (%)	30.8	24.6	0.011
daily drinker (%)	50.8	33.6	<0.001
physical activity[2] (%)	35.3	33.9	0.615

mean (SD), median (interquartile range) or %, [1] estimated glomerular filtration rate, [2] defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week, [3] compared after log transformation

sion than those who did not.

Pearson's correlation coefficients between serum albumin at baseline and serum potassium and systolic and diastolic BPs at baseline and changes in systolic and diastolic BPs are presented in **Table 3**. The Pearson's correlation coefficients between serum albumin at baseline and serum potassium and systolic and diastolic BPs at baseline, and changes in systolic and diastolic BPs were 0.166 ($p<0.001$), 0.139 ($p<0.001$), 0.154 ($p<0.001$), −0.150 ($p<0.001$) and −0.092 ($p=0.001$), respectively, for the subjects overall.

During the 5 years of follow-up (mean of 3.8 years), 290 men and 110 women developed hypertension (4.7%/year in men and 2.7%/year in women). The mean serum potassium level and incidence of hypertension for each quartile of serum albumin are presented in **Table 4**. A significant difference in serum potassium was found between Q1 and the higher quartiles of serum albumin in all subjects and in men. A significant linear trend in the incidence of hypertension was seen through the quartiles of serum albumin in all subjects and in men. No such differences were observed in women.

The HRs of hypertension for each 1 SD increase in serum albumin and for Q1, Q2 and Q3 compared with Q4 are shown in **Table 5**. The HRs of hypertension were significant for each 1 SD increase in serum albumin and for Q1 and Q2 in all three models in all subjects, for each 1 SD increase in serum albumin in all three models and for Q1 in Model 1 and Model 2 in men, and for each 1 SD increase in serum albumin in Model 1 and for Q1 in Model 2 and Model 3 in women.

HRs (95% CIs) of incident hypertension for each 1 SD increase in potassium, log hsCRP, total bilirubin and uric acid were 1.02 (0.93–1.13) ($p=0.661$), 1.05 (0.95–1.16) ($p=0.323$), 0.99 (0.89–1.09) ($p=0.797$) and 1.08 (0.95–1.22) ($p=0.245$), respectively, adjusted for Model 1.

Among the 354 subjects (235 men and 119 women aged 33–84 years) whose urinary albumin levels were optionally measured, the mean (SD) and median (interquartile range) of urinary albumin were 10.4 (17.4) mg/g creatinine and 4.9 (3.1–10.1) mg/g creatinine, respectively, and the age and sex adjusted correlation coefficient between serum albumin and urinary albumin was 0.151 ($p=0.005$).

Table 3. Pearson's Correlation Coefficients between Baseline Serum Albumin and Other Parameters

	baseline potassium	baseline SBP[1]	baseline DBP[2]	changes in SBP[3]	changes in DBP[4]
all subjects	0.166	0.139	0.154	−0.150	−0.092
n=1251	*p*<0.001	*p*<0.001	*p*<0.001	*p*<0.001	*p*=0.001
men	0.140	0.070	0.036	−0.163	−0.104
n=770	*p*<0.001	*p*=0.052	*p*=0.319	*p*<0.001	*p*=0.004
women	0.099	0.098	0.166	−0.092	−0.122
n=481	*p*=0.030	*p*=0.031	*p*<0.001	*p*=0.044	*p*=0.007

[1] systolic blood pressure, [2] diastolic blood pressure, [3] changes in SBP over 5 years, [4] changes in DBP over 5 years

Table 4. Mean Serum Potassium Level and Incidence of Hypertension for each Quartile of Serum Albumin

	Q1	Q2	Q3	Q4	*p* for trend
all subjects					
n	477	727	341	500	
albumin (g/dL)	3.0–4.1	4.2–4.3	4.4	4.5–5.0	
mean (SD) K (mEq/L)	4.26 (0.28)	4.33 (0.32)	4.34 (0.32)	4.39 (0.36)	
p[1]		0.004	0.003	<0.001	
incident hypertension[2]	4.7	3.8	3.8	3.4	<0.001
men					
n	236	412	220	359	
albumin (g/dL)	3.6–4.1	4.2–4.3	4.4	4.5–4.9	
mean (SD) K (mEq/L)	4.29 (0.29)	4.37 (0.33)	4.38 (0.33)	4.43 (0.35)	
p[1]		0.024	0.036	<0.001	
incident hypertension[2]	6.3	4.8	4.5	3.7	<0.001
women					
n	241	155	160	262	
albumin (g/dL)	3.0–4.1	4.2	4.3	4.4–5.0	
mean (SD) K (mEq/L)	4.22 (0.26)	4.25 (0.29)	4.28 (0.32)	4.27 (0.32)	
p[1]		0.892	0.279	0.322	
incident hypertension[2]	3.2	2.3	2.8	2.4	0.330

[1] compared with Q1, [2] %/year

Table 5. Hazard Ratios of Hypertension for 1 SD Increase in Serum Albumin and for Lower Quartiles of Serum Albumin Compared with Highest Quartile

	Model 1[1] hazard ratio (95% CI[4])	*p*	Model 2[2] hazard ratio (95% CI[4])	*p*	Model 3[3] hazard ratio (95% CI[4])	*p*
all subjects						
1 SD increase	0.80 (0.72–0.89)	<0.001	0.79 (0.72–0.88)	<0.001	0.79 (0.70–0.88)	<0.001
1st quartile[5]	1.73 (1.25–2.38)	<0.001	1.71 (1.23–2.38)	0.001	1.73 (1.21–2.49)	0.003
2nd quartile[5]	1.40 (1.05–1.87)	0.021	1.41 (1.04–1.89)	0.025	1.45 (1.07–1.97)	0.017
3rd quartile[5]	1.16 (0.83–1.62)	0.386	1.13 (0.81–1.58)	0.481	1.18 (0.84–1.66)	0.350
men						
1 SD increase	0.80 (0.71–0.91)	<0.001	0.79 (0.70–0.91)	<0.001	0.80 (0.69–0.92)	0.002
1st quartile[5]	1.70 (1.15–2.52)	0.008	1.63 (1.09–2.45)	0.018	1.55 (0.99–2.42)	0.056
2nd quartile[5]	1.36 (0.97–1.89)	0.074	1.41 (0.99–2.00)	0.054	1.41 (0.98–2.02)	0.067
3rd quartile[5]	1.07 (0.73–1.56)	0.729	1.01 (0.69–1.49)	0.954	1.06 (0.71–1.57)	0.780
women						
1 SD increase	0.83 (0.70–0.99)	0.040	0.86 (0.72–1.03)	0.105	0.85 (0.71–1.02)	0.075
1st quartile[5]	1.77 (0.99–3.19)	0.056	1.99 (1.06–3.74)	0.033	2.15 (1.08–4.27)	0.029
2nd quartile[5]	1.47 (0.82–2.63)	0.196	1.44 (0.80–2.60)	0.229	1.53 (0.83–2.81)	0.175
3rd quartile[5]	1.93 (0.93–4.04)	0.079	1.99 (0.93–4.25)	0.074	1.89 (0.86–4.17)	0.116

[1] adjusted for systolic blood pressure, sex, age, current smoking, daily alcohol drinking and physical activity, [2] further adjusted for body mass index, proteinuria, estimated glomerular filtration rate, uric acid, fasting glucose, [3] further adjusted for log triglycerides, HDL cholesterol, LDL cholesterol, log high-sensitivity C-reactive protein, total bilirubin and potassium, [4] confidence interval, [5] compared with the highest quartile

Discussion

The present 5-year follow-up study demonstrated that serum albumin was positively correlated with serum potassium and inversely correlated with changes in BPs, and that a decreased serum albumin level was a significant predictor of incident hypertension, in a health screening population. When analyzed separately by gender, the relationships between serum albumin and serum potassium as well as incident hypertension were weak in women, which may have resulted from the weaker activity of the renin angiotensin aldosterone system in women than in men.

Serum albumin levels were reported to be positively correlated with cross-sectional BP[1–4] and consistent with this, there were significant positive cross-sectional correlations between serum albumin levels and BP in the present study. The cross-sectional positive association between serum albumin levels and BP may be due to an increase in vascular volume caused by an increased osmotic pressure accompanying an increased level of serum albumin.

In contrast to the positive cross-sectional correlations observed between serum albumin levels and BP mentioned above, the previous[5] and present studies found inverse longitudinal correlations between serum albumin levels and changes in BP.

A dietary intervention study demonstrated that potassium depletion decreases serum potassium levels and increases BP but suppresses plasma aldosterone levels and has no effect on plasma renin activity or on arginine vasopressin or catecholamine levels[8]. Another dietary intervention study observed that after potassium supplementation, plasma potassium, renin, angiotensin Ⅱ and aldosterone levels were increased significantly, while plasma catecholamine levels were unchanged and that the exaggerated presser responsiveness to catecholamine was normalized and BP was decreased in normotensive members of hypertensive families and patients with hypertension[9]. However, serum potassium levels were not significantly associated with incident hypertension in the present study. Furthermore, in contrast to serum albumin, the mean serum potassium level was paradoxically higher in subjects who developed hypertension than those who did not (**Table 2**). Therefore, the antihypertensive effect of albumin cannot be explained by the positive correlation between serum albumin and serum potassium.

Hypertension is associated with inflammation, oxidative stress and endothelial dysfunction[10,11], while albumin possesses anti-inflammatory and antioxidant properties[12,13]. However, the three markers of inflammation and oxidative stress, hsCRP, total bilirubin and uric acid, were not associated with incident hypertension in the present study. Therefore, it is unlikely that the antihypertensive effect of albumin is mainly due to its anti-inflammatory and antioxidant properties.

Klauser *et al.* identified serum albumin as an endogenous inhibitor of ACE in 1979[14], and it has been reported that the postoperative infusion of serum albumin frequently evokes hypotension in patients receiving ACE inhibitor therapy[15]. Fagyas *et al.* reported that serum albumin is a potent physiological inhibitor of ACE, and the enzymatic activity of intravascular ACE appears to be almost completely suppressed by serum albumin when it is present at physiological concentrations[6]. They also tested ACE inhibition by albumin in human sera and human blood vessels and suggested that ACE activity is significantly suppressed as long as the albumin concentration is

at least 3.0 g/dL[16]. The physiological levels of serum albumin are several times higher (3.5–5.2 g/dL) than the half maximal ACE inhibitory concentrations for albumin (0.57–0.98 g/dL), suggesting complete suppression of intravascular ACE activity by serum albumin *in vivo*[6]. Fagyas *et al.* hypothesized that serum albumin does not inhibit all forms of ACE equally. So in contrast to intravascular ACE, tissue ACEs may be partially inhibited by tissue albumin in proportion to its concentration. Moreover, albumin may not significantly inhibit pulmonary ACE, which is thought to be a major player in controlling BP, because albumin is not negatively but positively correlated with cross-sectional BP.

Among tissue ACEs, adrenal ACE may play an important role in the pathogenesis of hypertension through the secretion of aldosterone. It is possible that decreased inhibition of adrenal ACE due to a decreased concentration of albumin results in increased secretion of aldosterone. The positive correlation between serum albumin levels and serum potassium levels found in the present study suggests a possible inverse correlation between serum albumin levels and plasma aldosterone levels. However, plasma aldosterone levels are regulated by complex mechanisms. Therefore, direct measurements of plasma aldosterone levels are mandatory for clarifying the relationship between serum albumin levels and plasma aldosterone levels.

The determinants of serum albumin levels within the normal range in apparently healthy individuals in the present study are unknown. However, a previous study observed a positive association between serum albumin levels and animal, but not vegetable, protein intake[17]. Significant independent inverse relationships between BP and both 24-hour urinary total nitrogen and urea nitrogen have been reported[18], which suggests an inverse association between protein intake and BP. Thus, the decreased levels of serum albumin within the normal range observed in the present study may possibly result from an inadequate protein intake or alternatively, they may be due to urinary excretion of albumin. Although albuminuria is reported to be a predictor of incident hypertension[19,20], there was a significant positive correlation between serum albumin levels and log urinary albumin levels in the 354 subjects whose urinary albumin levels were optionally measured. Therefore, the decreased levels of serum albumin were not associated with increased levels of urinary albumin.

Limitations

The present study is a retrospective study and the subjects were not from a general population, but from a health screening population. Among the 2,623 candidate subjects, 578 (22.0%) dropped out. However, there was no significant difference in baseline data between the candidate and actually followed-up subjects. Also, hypertension was diagnosed at only one time point and may have included white coat hypertension, and no dietary-related information other than that on smoking habit and alcohol drinking was available. In addition, residual confounders might have influenced the results. Furthermore, urinary amounts of albumin were only optionally measured in 354 subjects and plasma aldosterone levels were not measured at all. Therefore, the conclusion of the present study is hypothetical. Future studies must include directly measured aldosterone data.

Conclusions

The present study found that serum albumin was positively correlated with serum potassium and inversely correlated with the changes in BP and that a decreased serum albumin level was a significant predictor of incident hypertension, in a health screening population.

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Conflict of Interest

The author has no conflict of interest to disclose.

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Original Article

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Asymptomatic Pneumonia-like Opacity Detected by CT

Shigeaki Moriura[1], Satoko Ono[1], Kumiko Sugiyama[1],
Satoshi Ito[2], Yuji Ito[3]

Abstract

Background: The management of asymptomatic pneumonia-like opacity detected by CT has not been clarified.

Methods: We reviewed 12 cases of asymptomatic pneumonia-like opacity from 2,762 chest CTs performed at our check-up center between 2012 and 2014. Cases under treatment for respiratory disorders and those suspicious of specific infections were excluded.

Results: In all 12 cases, CT findings of pneumonia-like opacity disappeared without chemotherapy.

Conclusion: Patients with asymptomatic pneumonia-like opacity can be managed by observation if chronic respiratory disorders and specific infections have been ruled out.

Keywords pneumonia, spontaneous cure

Radiological diagnosis of pneumonia is occasionally made by chest CT for examinees in health check-ups who have no symptoms, such as cough, sputum or fever. As the management of examinees with asymptomatic pneumonia-like opacity in CTs has not been well described in the literature or guidelines[1–4], we reviewed chest CTs at our check-up center to clarify the clinical course of asymptomatic pneumonia-like opacity.

Subjects and Methods

The number of chest CTs performed at the center between January 2012 and December 2014 was 2,762. Diagnosis was made by 2 radiologists, with double-checking. There were 27 pneumonias categorized as D1: treatment or medical control required. Four cases of patients under treatment for chronic respiratory disorders were excluded. Another 4 cases in which findings suggested tuberculosis or non-tuberculous mycobacterial infection (NTM) were also excluded. Out of the remaining 19 cases, we reviewed 12 that could be followed up. For follow-up examination, 64-row helical CT was used and 5 mm-axial images were evaluated.

Results

The mean age of the 12 subjects was 62 years (SD: 14). None of them were associated with respiratory symptoms or fever. The mean volume of attenuation estimated on CT images was 26.2 cm^3, ranging widely from 4.9 to 136.9 cm^3. The attenuation was most frequently located in segment 9 (in 5 subjects), followed by segment 2 (in 3 subjects), but varied. Regarding distribution, the attenuation was airway dominant or peribronchial spread in 10 subjects and periphery of the lung in 2. The extent of attenuation was ground-glass opacification in 10 subjects and suggested infiltration in 2. In 7 subjects, check-ups using PET with Fluorodeoxy-glucose (FDG) were performed, and in 3 subjects, accumulation of FDG was observed in the corresponding part of the lung. An increase in CRP was observed in 3 subjects and leukocytosis in 1. One subject was a smoker (case 3) and he had a history of childhood asthma. Other subjects did not have a history of allergic disorders or respiratory disease.

In all 12 cases, the pneumonia-like opacity on the chest CT disappeared without the use of antibiotics or bactericidal drugs. No subjects manifested respiratory symptoms following the first CT examination. In the 5 cases where the Department of Respiratory Medicine was consulted, the pneumonia-like opacity on CT disappeared in 5 to 50 days. In the other 7 cases, disappearance of the opacity was noted on chest CTs taken because of other disorders or during annual health check-ups.

Case Reports

Case 1

A 62-year-old man visited our center for a health

[1] Check-up Center, Daiyukai Daiichi Hospital ; [2]Department of Radiology, Daiyukai Daiichi Hospital ; [3]Department of Respiratory Medicine, Daiyukai General Hospital

Contact : Shigeaki Moriura, Check-up Center, Daiyukai Daiichi Hospital, 1–6–12 Hagoromo, Ichinomiya, Aichi, 491–0025, Japan
Tel : +81–586–26–2008 ; Fax : +81–586–23–3388 ; E-mail : moriura@daiyukai.or.jp

check-up including chest CT. His hypertension had been controlled by a single drug. CT revealed an acute inflammatory change in the right upper pulmonary lobe (**Fig. 1**). FDG-PET examination was positive for the corresponding area. The CRP level was slightly elevated at 3.54 mg/dL and WBC normal. That evening, we were able to contact him just as he was about to start a journey. He had no respiratory symptoms or fever but we asked him to consult a doctor nearby as soon as possible. Five days later, he visited the respiratory medicine department of another hospital and a chest CT showed no abnormal attenuation in the lung fields. He visited our center the following year for an annual check-up and spontaneous cure of pneumonia-like opacity was confirmed by chest CT.

Case 2

A 38-year-old man had a check-up at our center. Chest CT revealed ground-glass opacification, suggesting pneumonia in the right lower lobe (**Fig. 2**). WBC was slightly elevated at 10,200/mm^3 and CRP was normal. He consulted the Department of Respiratory Medicine at our general hospital. T-SPOT® for tuberculosis was negative and PCR for mycobacterium avium complex was also negative. His pulmonary opacity disappeared in 50 days.

Case 3

A 44-year-old man who had a health check-up at our center was a smoker and had a history of childhood asthma. His chest CT revealed slightly increased attenuation, suggesting pneumonia, in the right lower lobe (**Fig. 3**).

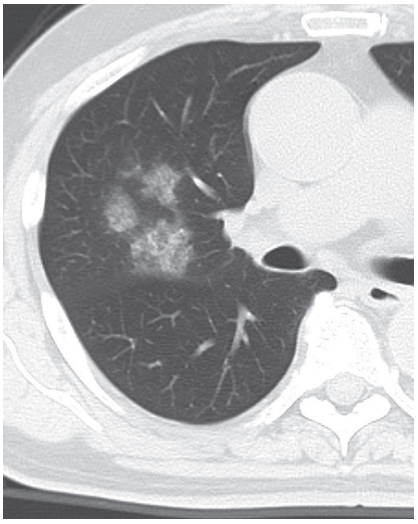

Fig. 1. CT Shows Airway-dominant Infiltration in Segment 3a, which Disappeared in 5 days

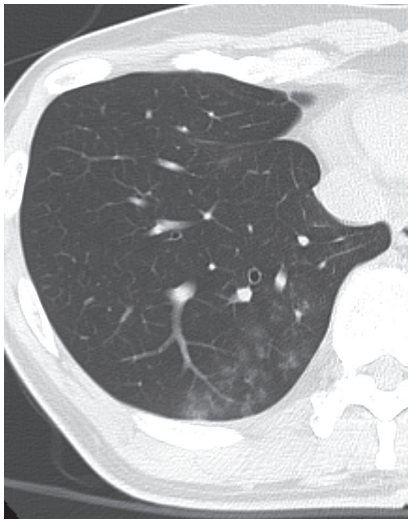

Fig. 2. CT Demonstrates Peribronchial Ground-glass Opacification in Segment 9, which Disappeared in 50 days

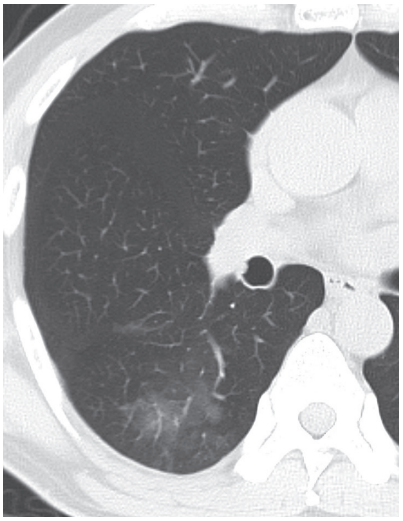

Fig. 3. CT Shows Slightly Increased Attenuation in Right Segment 6, which was not Observed in CT for an Annual Check-up Performed 11 Months Later

FDG-PET was positive for the corresponding area of the right lung. He did not agree to consult a specialist and visited us 11 months later for an annual check-up. CT at the time revealed no abnormal opacity in the lower lobe.

Discussion

Pneumonia is a major infectious disease and is responsible for significant morbidity and mortality throughout the world. In Japan, pneumonia supplanted cerebrovascular disease as the third leading cause of death in 2011, according to a report by Japan's Ministry of Health, Labor, and Welfare. The estimated overall incidence rates of adult community-acquired pneumonia, hospitalization, and in-hospital death have been recently reported as 16.9 (95% CI, 13.6 to 20.9), 5.3 (4.5 to 6.2), and 0.7 (0.6 to 0.8) per 1,000 person-years, respectively, by a multicenter prospective study[4]. While its etiology was studied in detail, asymptomatic pneumonia was not targeted by the study[5]. Furthermore, guidelines for treating pneumonia do not mention the management of asymptomatic pneumonia-like opacity in CT[2,3].

Our study was essentially based on healthy subjects, and those who had chronic respiratory disorders, whether with or without medication, were excluded. Cases that suggested tuberculosis or NTM were also excluded. Such specific infections, which present management difficulties for general practitioners, should be handled by specialists. One of the 4 patients with suspected tuberculosis or NTM was diagnosed with *M. avium* infection and received medication for 6 months. We did not encounter any pneumonia associated with immune suppression, but such pneumonia should also be treated by specialists.

In the 12 cases, the pneumonia-like opacity disappeared spontaneously without medication. In some of them, there was a slight increase in CRP or WBC at the time of the CT examination, but no symptoms were observed during the clinical course. Such cases can be managed by general practitioners.

We regret that we could not adequately follow up all the subjects. In 7 out of the 27 subjects with pneumonia-like opacity, follow-up was unsuccessful. Nevertheless, we encouraged each subject to consult a doctor. It was difficult to obtain consent to conduct follow-ups because the lesions were small and there were no symptoms. However, pneumonia is essentially a pathology that should be properly managed and considerable care is required.

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Solitary Necrotic Nodule of the Liver Mimicking a Malignant Tumor : a Case Report

Yoshinori Torii, Yoshiaki Katano, Junji Yoshino, Kazuo Inui

Abstract

A 76-year-old woman was hospitalized with an asymptomatic liver tumor detected by ultrasonography during a health check-up. A physical examination produced no pertinent findings. Blood test results were negative for hepatitis virus markers and tumor markers. Ultrasonography showed a hypoechoic tumor in segment 6 of the liver with a distinct margin and smooth contour, measuring 10 × 10 mm in diameter. Computed tomography demonstrated contrast enhancement in the periphery of the tumor. From pathologic examination of a needle biopsy specimen a necrotic hepatocellular carcinoma could not be ruled out, so resection was performed. The final diagnosis was solitary necrotic liver nodule, a rare mimic of hepatocellular carcinoma. Although this is a rare disease, it is necessary to consider it as one of the differential diagnoses if an atypical neoplastic lesion differing from typical hepatocellular carcinoma is detected intrahepatically on imaging.

Keywords solitary necrotic nodule of the liver, hepatocellular carcinoma, ultrasonography, histopathology

Solitary necrotic nodule (SNN) of the liver is a rare benign lesion first reported by Shepherd and Lee in 1983[1]. Histopathologically, this benign lesion of unknown cause shows complete central necrosis within a dense fibrous capsule, with an intervening zone containing collagen fibers. As it is clinically difficult to discriminate it from cancer, a definitive diagnosis can only be reached after resection, as described in the present case.

Case Report

A 76-year-old woman was referred to our hospital for management of an asymptomatic liver tumor that was found on ultrasonographic screening. The ultrasound performed by her family doctor showed a hypoechoic tumor in segment 6 of the liver that had not been present 1 year earlier. Her past medical history raised no special concerns; she was on drug treatment for hypertension and hyperlipidemia. Physical examination was noncontributory. Blood test results were normal; hepatitis virus markers were absent and tumor markers were not elevated (**Table 1**).

Ultrasonography showed a hypoechoic tumor (10 × 10 mm in diameter) with a distinct margin and a smooth contour in segment 6 of the liver (**Fig. 1**). No clear halo or reinforcement of echoes was apparent. The surround-

Table 1. Blood Examination

Peripheral blood	
WBC	8000 /uL
RBC	435x10^4 /uL
Hb	13.2 g/dL
Ht	40.1%
Plt	56.1x10^4 /uL
Biochemistry	
T.Bil/D.Bil	0.5/0.2 mg/dL
AST / ALT	28/20 IU/L
LDH	201 IU/L
ALP/γ-GTP	241/50 IU/L
Amy	104 IU/L
BUN/Cr	13/0.7 mg/dL
Na/K/Cl	138/4.2/97 mEq/L
Ca/P	10.3/4.4 mEq/L
HCV antibody	(–)
HBs antigen	(–)
HBe antigen	(–)
HBe antibody	(–)
Serology	
CRP	0.03 mg/dL
Tumor markers	
PIVKA-II	27 mAU/mL
AFP	3.0 ng/mL
CEA	1.4 ng/mL

Department of Internal Medicine, Second Teaching Hospital, Fujita Health University, School of Medicine
Contact : Yoshinori Torii, Department of Internal Medicine, Second Teaching Hospital, Fujita Health University, School of Medicine, 3–6–10, Otobashi, Nakagawa-ku, Nagoya 454–8509, Japan.
Tel : +81–52–323–5646 ; Fax : +81–52–323–9886 ; E-mail : yoshinoritorii_free_ml@yahoo.co.jp

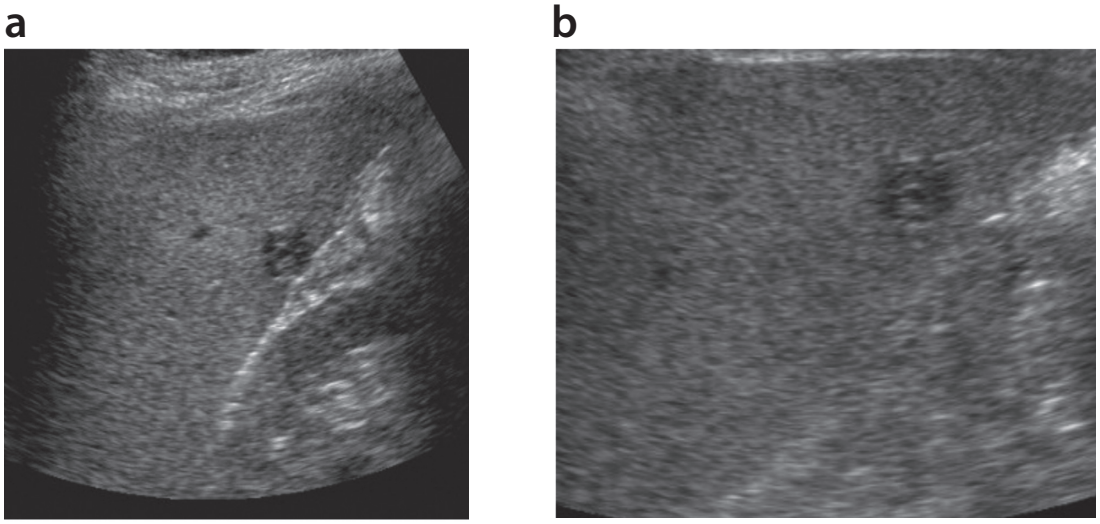

Fig. 1. Appearance of Lesion on Abdominal Ultrasonography
Panel b is an enlarged view of the hypoechoic area within the liver shown in panel a.

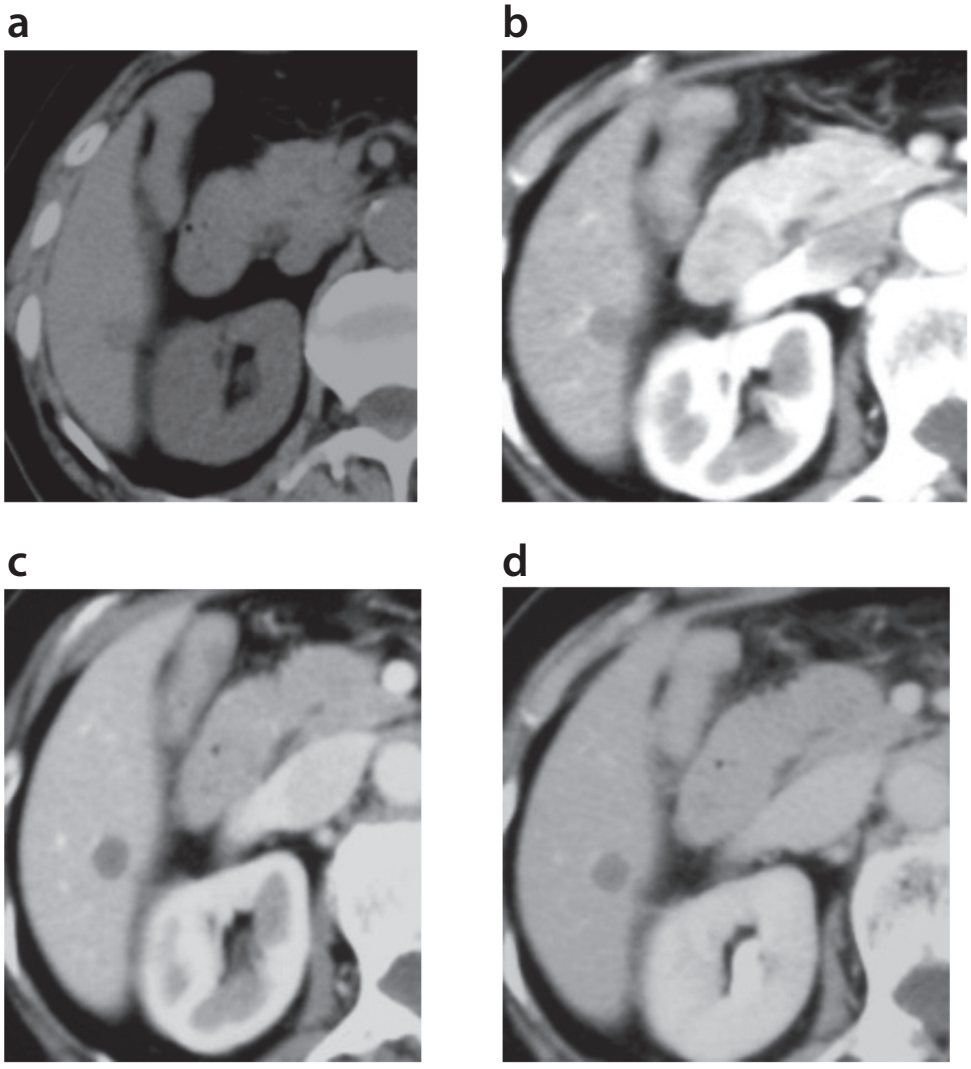

Fig. 2. Abdominal Computed Tomographic Findings
Panels b to d are images taken after contrast administration.

ing liver was slightly hyperechoic, indicative of steatosis. Parenchymal echo patterns were otherwise normal, with no suggestion of chronic hepatitis. Color Doppler imaging detected no blood flow signal in the tumor. Non-contrast computed tomography (CT) showed a hypodense mass in segment 6 of the liver. The tumor was enhanced after administration of contrast agent (**Fig. 2**) and the enhancement persisted in both the venous and equilibrium phases. Magnetic resonance imaging (MRI) did not detect the tumor.

Despite the lack of findings of chronic hepatitis, primary hepatocellular carcinoma was suspected. However, the findings on ultrasonography and dynamic CT differed from those that are typical of hepatocellular carcinoma. Endoscopy of the upper and lower digestive tract was performed to rule out metastatic liver tumor and no cancer was seen. Pathologic examination of a needle biopsy specimen from the tumor showed necrotic tissue with a fibrous capsule. Despite tumor necrosis, the outlines of liver cells in the lesion were maintained (**Fig. 3**).

Necrotic hepatocellular carcinoma could not be ruled out. Although we had initially suggested to the patient that she underwent careful follow-up every 3–6 months to monitor the tumor, we performed surgical resection as she had strongly requested this.

The lesion was surgically resected together with adjoining healthy liver tissue. Pathologic examination of the resected specimen showed a tumor, 10 mm in diameter, with coagulative necrosis and cavity formation (**Fig. 4**). The interior of the lesion was almost all homogeneously blue on Azan-Mallory staining, indicating that it consisted primarily of fibroblasts. The nodule had a fibrous capsule (**Fig. 5**). Silver staining showed a regular fasciculate array with a delicate fiber pattern just within the capsule (**Fig. 6**). The pathologic diagnosis was SNN.

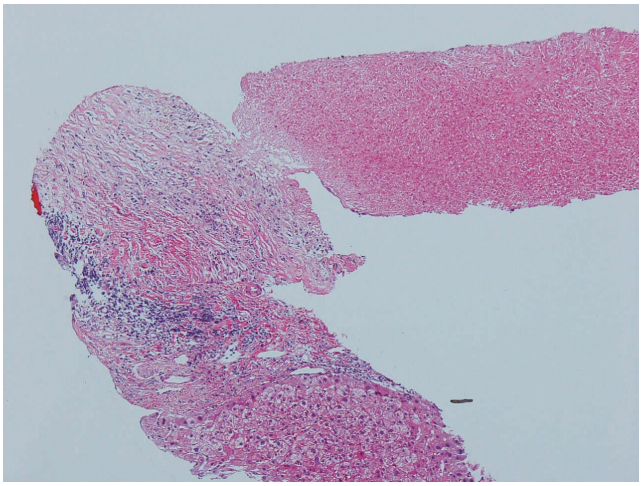

Fig. 3. Needle Biopsy Specimen of Liver Tumor Showing Necrotic and Fibrous tissue
Hepatocytic outlines persist in the necrotic portion. Hematoxylin and eosin; original magnification, × 40.

Discussion

The cause of SNN remains unknown. This benign lesion is characterized pathologically by the presence of complete central necrosis, a dense fibrous capsule, and an intervening zone rich in collagen fibers[2]. SNN is usually found in middle-aged women with no history of liver disease[3]. Hepatitis virus and tumor markers are usually negative, as was seen in our patient, and the tumor is difficult to discriminate clinically from cancer[2,4–5]. SNN is uncommon—it was detected in only 7 cases in over 3,000 autopsies and 1,000 laparotomies[4]. A search of the medical literature from 1983 to 2011 using the key term "solitary necrotic nodule of the liver" revealed only 8 previous cases from Japan, and only around 40 cases

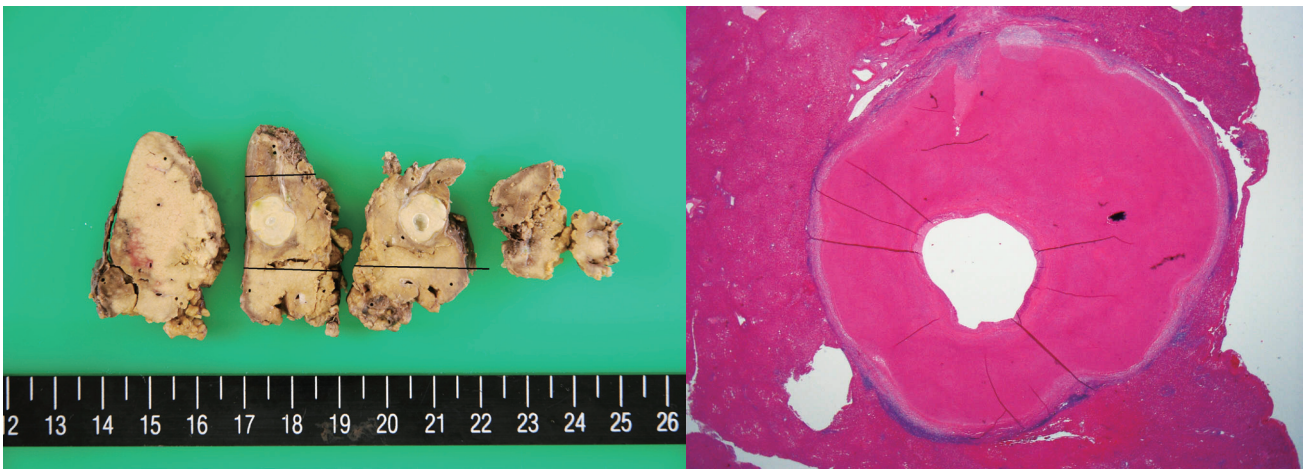

Fig. 4. Resected Specimen Findings
Left, macroscopic; arrow indicates the nodule surrounded by parenchyma. Right, low-power micrograph with central red area representing necrosis. Hematoxylin and eosin; original magnification, × 12,5.

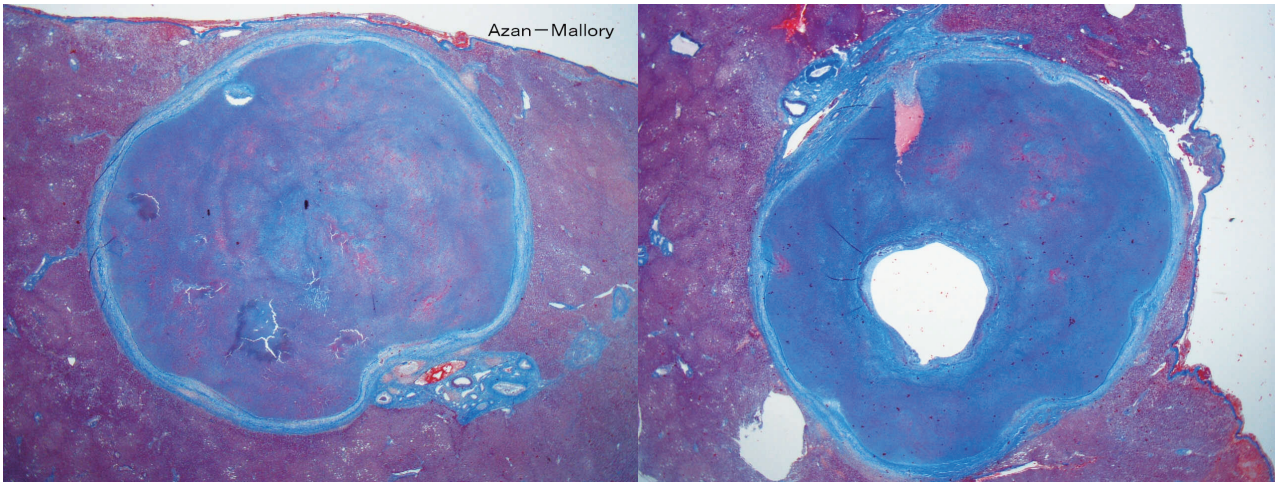

Fig. 5. On Azan-Mallory Staining, the Blue Area Represents Collagen Associated with Fibroblasts
Original magnification: left, × 12,5; right, × 12,5.

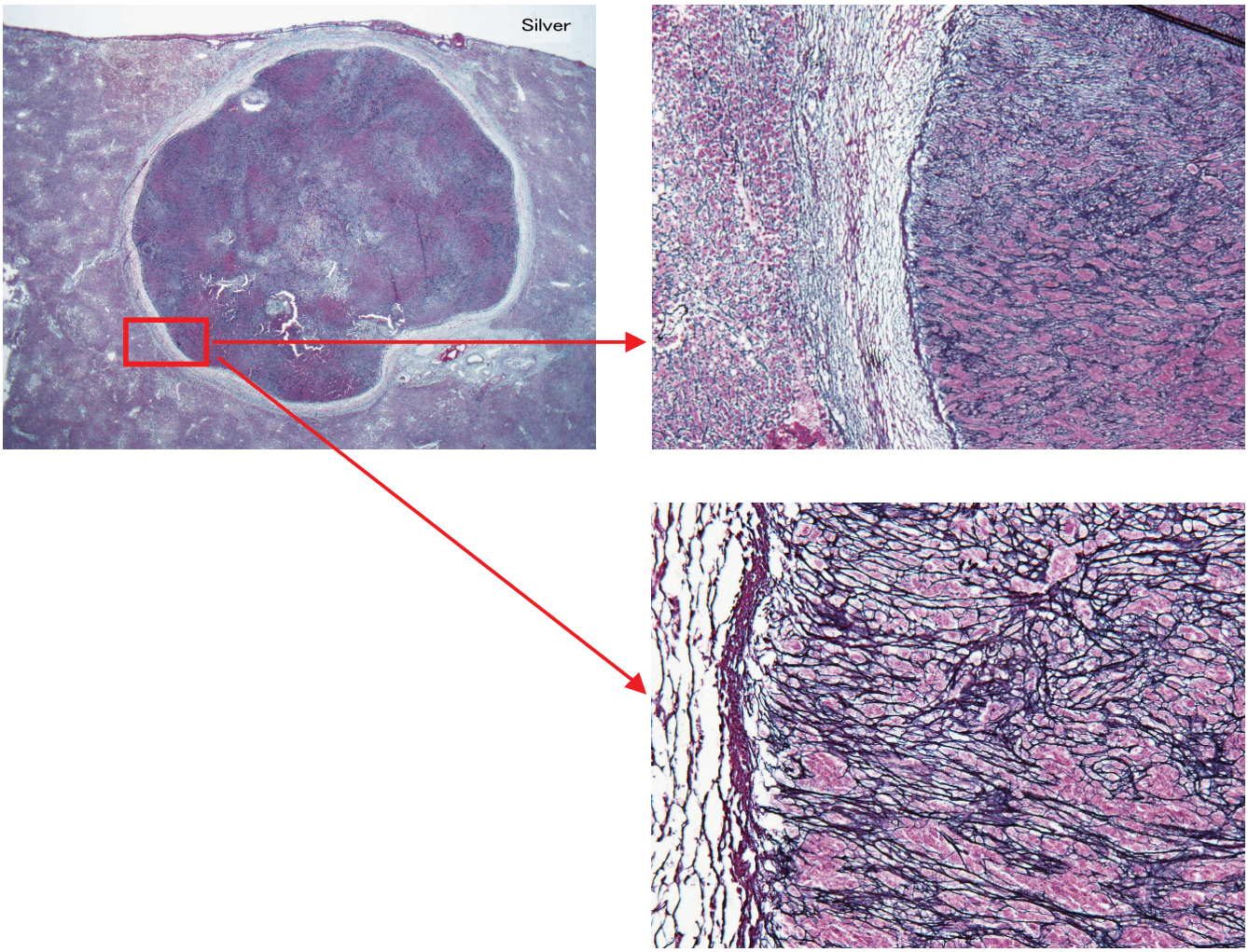

Fig. 6. Silver Staining for Reticular Fibers Shows a Fibrous Capsule and Delicate Collagen Fibers Deep into the Capsule
Original magnification: left, × 12,5; upper right, × 40; lower right, × 40.

had been reported worldwide[6].

SNN often occurs in the right hepatic lobe. Injury, infection, hemangioma with liver necrosis, and fibrosis may accompany cirrhosis, but none of these conditions were found to be associated with SNN[7]. As needle biopsy specimens consist of necrotic tissue, a definitive diagnosis is usually obtained through surgical liver resection[8]. SNN is often mistaken for a hemangioma, a simple cyst, or a regenerative nodule. No consistent size or form is evident in diagnostic images[9]. On ultrasonography, SNN is seen as a single hypoechoic nodule, 5–10 mm in diameter, with a distinct margin. CT with contrast administration may show a central hypodensity representing necrosis, surrounded by a zone of contrast enhancement beneath the capsule. No characteristic MRI findings have been identified to date, and reaching a diagnosis based on imaging remains difficult[10–12].

In this case, MRI could not detect the lesion before surgery. This could be attributed to the small size of the tumor and the necrotic components having the same signal intensity as the surrounding normal liver parenchyma. In recent years, it has been reported that ^{18}F FDG PET/CT was useful for assessing the histopathological constitution of tumor components[13], and Sonazoid US and EOB-MRI might also be useful for making a diagnosis. However, there have been few cases in which these examinations were used and the usefulness of disease-specific imaging findings is unclear.

SNN is a rare tumor with an unknown cause and natural history. Reports of cases usually involve surgical intervention with few documenting long-term follow-up. Differentiation from malignant tumors is the most important diagnostic problem. In this case, the tumor was found by ultrasound during a comprehensive health check-up. The blood biochemical findings and the tumor markers were normal. In addition, there were few imaging findings that suggested chronic hepatic disease. With regard to the patient's medical history, there was no history of abdominal injury and involvement of parasitic disease seemed unlikely. Typical hepatic cancer also seemed unlikely, but a malignant lesion could not be completely ruled out at the time since a hepatic mass had not been found on ultrasound during the comprehensive health check-up a year ago.

The following diseases characterized by an ischemic mass within the liver were considered in the differential diagnosis: atypical hepatocellular carcinoma mainly composed of necrotic components, necrosis in hemangioma, inflammatory pseudotumor, cholangiocellular carcinoma, and hepatic granuloma caused by infection. Initially, we recommended that the patient undergo strict follow-up with imaging, such as abdominal echography and contrast-enhanced CT, as well as blood tests, every 3 to 6 months. We also recommended her to undergo surgical resection or repeat liver biopsy if the tumor grew rapidly or its number increased. However, we performed surgical resection as the patient had strongly requested this. No specific abnormality that indicated the cause of disease was found in the resected specimen, and no finding suggestive of infection or a vascular disorder was noted. Furthermore, the mechanism of tumorigenesis remained unclear because no finding suggestive of chronic hepatitis was observed in the background liver tissue.

Although this is a fairly rare disease, SNN should be considered in the differential diagnosis of an atypical hepatic tumor after a comprehensive health check-up including assessment of medical history and imaging findings.

Informed consent was obtained from patient for being included in the study.

The authors have no conflict of interest to declare.

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Case Report

Ningen Dock International 2016 ; 3 : 28–32

A Case of Simultaneous Occurrence and Separate Localization of Gastric MALT and Gastric Cancer with *H. pylori* Infection

Yuji Nakamura[1], Eiji Ninomiya[1], Masanori Hirano[1], Misako Katsuki[2], Osamu Otsubo[3], Mituru Kaise[4], Naoko Inosita[5]

Abstract

Simultaneous occurrence of malignant lymphoma and malignant gastric cancer in a single patient is rare. Such cases may be positive or negative for *H. pylori* infection. A 60-year-old-man was examined at our clinic for evaluation of abnormal shadows in upper gastrointestinal radiography. Endoscopy of the upper gastrointestinal tract revealed early cancer in the fornix and mucosa-associated lymphoid-tissue (MALT) in the antrum of the stomach. At Toranomon Hospital, endoscopic submucosal dissection (ESD) was performed under a diagnosis of early gastric carcinoma. Histological findings for the upper gastric lesion were compatible with early moderately differentiated tubular adenocarcinoma of type 0-IIc, while those for the lesion in the antrum corresponded to MALT lymphoma. *H. pylori* was detected. The patient declined surgery and is currently under close observation. *H. pylori* infection may have had a major role in the development of adenocarcinoma of the stomach and MALT in this case.

Keywords gastric cancer, MALT, coexistence (separate type), *H. pylori*

The coexistence of gastric carcinoma and gastric lymphoma is rare. *Helicobacter pylori* (*H. pylori*) is believed to have a causative role in various gastric and duodenal diseases, and recent studies have suggested that both gastric cancer[1] and cancer of mucosa-associated lymphoid tissue (MALT)[2–3] are associated with *H. pylori* infection. Here, we report a case of simultaneous gastric cancer and MALT lymphoma with *H. pylori* infection. Informed consent was obtained from the patient.

Case Report

In March 2014, a 60-year-old man with *H. pylori* infection was examined at our clinic using upper gastrointestinal endoscopy. His family history was unremarkable. His own history included treatment of hypertension and hyperuricemia for 15 years. PSA had become elevated 8 years ago, but a biopsy of the prostate found no malignant tissue. He had been diagnosed with chronic gastritis 7 years ago.

At a health check-up in February 2014, the patient was in good general condition and was well nourished (BH 175 cm, BW 74 kg). His blood pressure was 148/94 mmHg. There were no abnormal findings in the chest and abdomen, and no edema in the extremities. Results for laboratory data, blood cell counts, liver function tests, renal function tests, and urinalysis were within normal ranges. In serological measurements (**Table 1**), RA was slightly elevated, PSA was 5.34 ng/mL, and the *H. pylori* titer was positive. Upper gastrointestinal radiography showed an abnormal shadow.

In March 2014, endoscopy of the upper gastrointestinal tract performed at our clinic revealed a shallow depressed lesion (0-IIc) in the fornix of the stomach (**Fig. 1**). Biopsy proved the lesion in the anterior and posterior wall of the gastric antrum to be a carcinoma and tumorous (**Fig. 2**). Microscopically, the specimen was diagnosed as signet cell-like carcinoma. The patient had no symptoms, and thus declined total gastrectomy.

In May 2014, when he was referred to Toranomon Hospital, pre-operative work-up demonstrated that 1) the antral lesion was MALT lymphoma with lymphoepithelial lesion (LEL) mimicking signet ring cell carcinoma (**Fig. 4**) and 2) there was 0-IIc cancer in the fornix. Pathology of an endoscopic submucosal dissection (ESD) specimen of the fornix lesion revealed 0-IIc cancer (**Fig. 3**) (18 × 13 mm in diameter, pSM2(530 μm), tub2 > tub1+muc.). He declined additional surgery and close observation was continued because the vertical margin

[1] Kasumigaseki Bldg. Clinic ; [2] Tohto Clinic ; [3] Kenkouigaku Foundation ; [4] Head of Gastroenterology Department, Toranomon Hospital ; [5] Division of Pathology, Toranomon Hospital

Contact : Yuji Nakamura, Kasumigaseki Bldg. Clinic, Kasumigaseki Bldg. 3rd Floor, 3–2–5 Kasumigaseki, Chiyoda-ku, Tokyo, 100–6003, Japan. Tel : +81–3–3581–6031 ; Fax : +81–3–3581–6130

Table 1. Laboratory Data (4th Feb 2014 at health check-up)

1. Hematology		3. Biochemistry		4. Serology	
Hemoglobin	16.6 g/dL	Total protein	7.4 g/dL	RF	50 U/mL
Hematocrit	47.8 %	Albumin	4.8 g/dL	CRP	0.17 mg/dL
RBC	534 $\times 10^4$/μL	T-Bil	1.0 mg/dL	H. pylori	positive
WBC	6400 /μL	GOT	18 IU/L	5. Tumor marker	
plt	21.8 $\times 10^4$/μL	GPT	22 IU/L	CEA	1.6 μg/L
2. Urinalysis		γ-GTP	34 IU/L	CA19-9	6.6 U/mL
Protein	(–)	LDH	181 IU/L	PSA	5.34 ng/mL
Sugar	(–)	ALP	200 IU/L	6. Chest X-P	no abnormality
Occult blood	(–)	CK	98 IU/L	7. ECG	Left ventricular hypertrophy (susp)
PH	6.5	Amylase	56 IU/L		
SG	1.018	FBS	100 mg/dL	8. Abdominal ECHO	Fatty liver
		HbA1c	6.0 %		
		TC	242 mg/dL		
		LDL	162 mg/dL		
		HDL	52 mg/dL		
		TG	77 mg/dL		
		BUN	14.1 mg/dL		
		Creatinine	0.82 mg/dL		
		Uric acid	6.4 mg/dL		

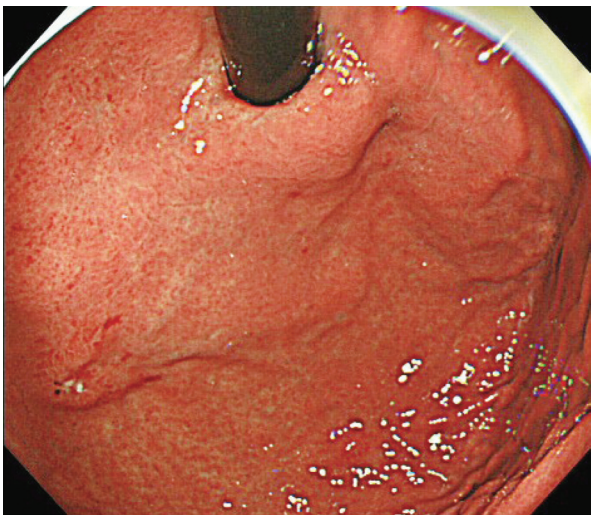

Fig. 1. Endoscopic Image Showing a Shallow Depressed Lesion

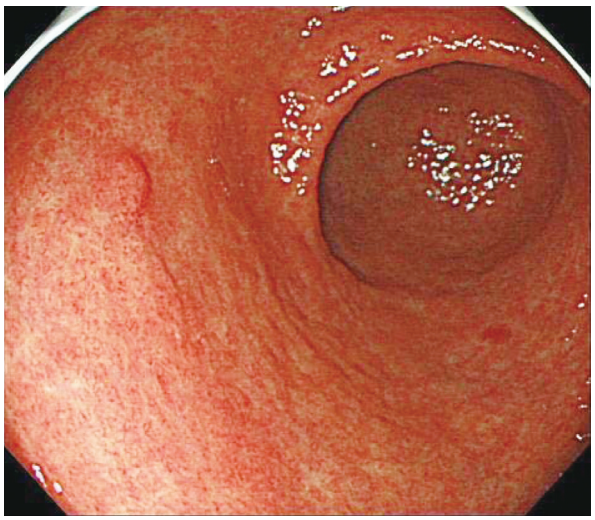

Fig. 2. Endoscopic Image Showing a Small Tumorous Lesion

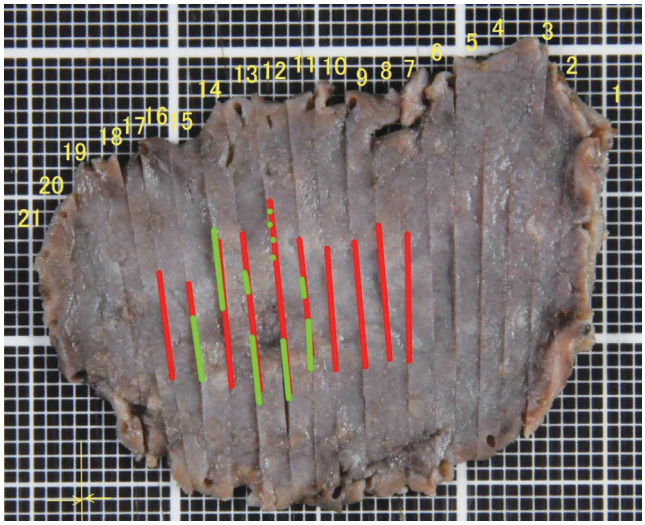

Fig. 3. Resected ESD Specimen Showing Mucosal Cancer (Red Line) and Submucosal Invasion (Green Line)

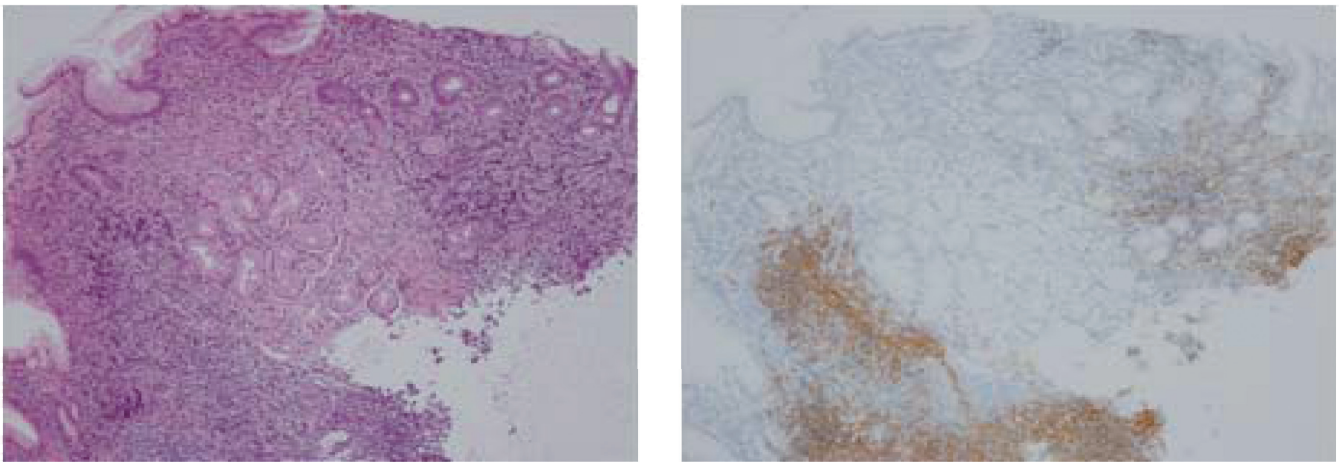

Fig.4. Histological Findings From HE Staining (Left Panel) and CD20 Staining (Right Panel) Showing the Presence of MALT

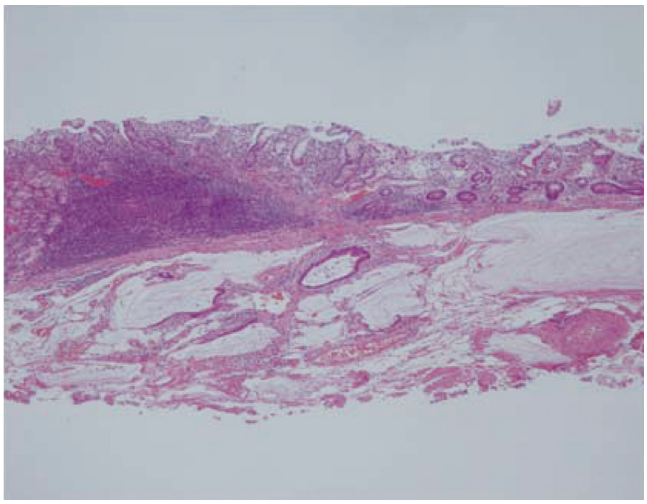

Fig.5. Histological Findings from HE Staining Revealed a mucous lake due to gastric cancer

was suspected to be positive due to the existence of a mucinous lake (**Fig.5**).

Discussion

MALT is characterized by prominent and often multifocal lymphoepithelial lesions with dense, diffuse infiltrates of centrocyte-like cells within lamina propria[4–5]. A total of 66 patients with coexisting gastric adenocarcinoma and MALT were reported from 1962 to 1994[6]. In a review of the clinicopathological features of 53 MALT cases in Japan, Isosaka[7] found that the patients ranged in age from 25 to 91 years (mean 65.2 years), and that the male: female ratio was 36:17. 1 patient had cancer in the fornix and maltoma in the upper body – antrum of the stomach (Case 26). This case was a collision type, but still a separate type. *H. pylori* infection status was positive in 38 cases, negative in 6, and unknown in 8.

Our patient was positive for *H. pylori*, whereas Yanai reported a similar case that was negative for *H. pylori* infection (**Table 2**). Therefore, the current case may be the first one of *H. pylori*-positive cancer and lymphoma reported. ESD was used to diagnose early cancer of the stomach, but thereafter the vertical margin appeared as a mucous lake and this raised doubts about early stage cancer. Therefore, endoscopic follow-up is required in the post ESD stomach.

The concept of MALT lymphoma was established by Isaacson and Wright in 1983[8]. It is generally accepted that the majority of lesions previously diagnosed as pseudolymphomas are actually low grade B-cell lymphomas of the MALT type, and thus it is probable that these represent further cases of combined gastric lymphoma and

Table 2. Cases (n=53) of Gastric Carcinoma and Gastric MALT Lymphoma Reported in the Japanese Population[7]

No	Author	Year	Age	Sex	Site	Gastric cancer			MALT				
						Tissue	Cancer Type	Depth	Site	Co/Sep	HP	ESD	Surgery
1	Hujimoto	1996	69	F	upper body	tub2	0-IIc	SM	lower body-angle	Sep			+
2	Iimura	1997	54	M	angle	sig	0-IIc	early	middle body	Sep			+
3	Nakamura	1997	27	M	antrum		0-IIa	M	middle body	Sep	+		+
4	Nakamura	1997	38	M	middle body		0-IIc	SM1	middle body	Sep	+		+
5	Nakamura	1997	70	M	antrum		0-IIc	M	middle body	Sep	+		+
6	Nakamura	1997	72	M	antrum		2	SE	upper body	Sep	+		+
7	Nakamura	1997	75	F	antrum		0-IIa	M	upper body	Sep	+		+
8	Nakamura	1997	53	M	middle body		0-IIc	SM	upper body	Co	+		+
9	Nakamura	1997	67	F	middle body		0-IIa	SM	upper body	Co	+		+
10	Hisai	1998	43	F	middle body	sig	0-IIc	M	lower/body / upper body	Sep	+		+
11	Kodera	1998	62	F	lower body / fornix	sig/sig	0-IIc	M/SM	antrum	Sep	+		+
12	Mori	1998	64	M	angle		0-IIc/0-IIb +I	SM1	body	Sep			+
13	Kanamoto	1998	47	M	antrum		0-IIc	M	antrum	Co	+		+
14	Momiyama	1999	73	M	antrum / middle body	por2/tub1 3	0IIa+IIb	MP/SM	upper body	Sep	+		+
15	Nishiyama	1999	70	F	antrum	tub1	0-IIa+IIc		lower body	Sep	+		+
16	Mochizuki	2000	62	M	upper body	por2	3	SE	antrum	Sep	+		+
17	Takahashi	2001	37	M	body	tub1	0-IIb	M	body-antrum	Co	+		+
18	Yoshida	2001	72	M	total stomach	sig-por	4	SE	middle body	Mix			+
19	Tyoushi	2001	71	M	body	tub2	3	SE	fundus	Sep	+		+
20	Sakatoku	2001	79	F	upper body	tub2	0-I	SM	upper body	Sep	+		+
21	Mieno	2002	69	F	upper body	tub2-por/tub	2/1		total stomach	Sep	+		+
22	Terada	2002	70	M	cardia	pap	0-I	M	upper body	Sep	+		+
23	Terada	2002	86	M	lower body	tub2	3	SE	upper body	Sep	–		+
24	Yajima	2002	76	M	angle	tub1	0-I	M	middle body	Sep	+		+
25	Hisano	2002	70	F	lower body	sig	0-II c	M	fundus	Sep	+		+
26	Yanai	2003	57	F	fornix	tub2	0-IIa+IIc	MP	upper body-antrum	Sep	–		+
27	Sakai	2003	51	F	middle body	tub2	0-II c	M	fornix	Sep	+		+
28	Suenaga	2003	73	M	middle body	tub1	0-I＋IIa	MP	total stomach	Co	–		+
29	Hayase	2004	73	M	upper body	tub1	0-IIc	SS	upper body	Sep	+		+
30	Masuda	2004	64	M	lower body	sig	0-IIc	M	antrum	Sep	+	+	
31	Okamoto	2004	68	M	middle body	por	2	MP	angle	Sep	+		+
32	Syugo	2004	91	M	antrum	tub1	0-IIa		upper body	Sep	+	+	
33	Ehara	2004	72	F	cardia antrum	por2	2	SE	cardia antrum	Co			+
34	Ishikawa	2005	71	M		tub2	0-IIc	M			+		+
35	Yamaki	2005	25	M	upper body		0-IIc	MP	total stomach	Sep			+
36	Hori	2005	48	M	cardia	tub1		M		Mix	+		+
37	Yoshizawa	2006	80	M	lower body / lower body		0-IIa/0-IIa	M/SM1		Sep	+	+	
38	Nakayama	2007	76	M	upper body	tub2			upper body	Co	+		+
39	Kudo	2007	78	M	antrum-pylorus	tub2	Borr3	SE	duodenum-body	Co			+
40	Suzuki	2007	70's	M		tub1-2	0-IIa	M			+	+	
41	Irahara	2007	58	M	fornix	por1	3	SE	fornix	Sep			+
42	Koga	2008	80's	M	body-antum / fornix	tub1/tub1	2 / 1	SE/SE	fornix	Co	+		+
43	Tanaka	2009	64	M	lower body	por2	0-IIc	M	antrum	Sep	+	+	
44	Shindou	2009	64	F	angle	tub2			body-antrum	Co	+		+
45	Akiba	2009	69	M	upper body	tub2	0-IIc	SM	upper body	Mix	–		+
46	Imada	2010	69	F	antrum	sig	0-IIc+ Ⅲ	M	antrum	Co	–		+
47	Kurobe	2010	71	M	upper body	muc	1	SS	middle body	Sep	+		+
48	Oonita	2011	79	M	lower body	tub1	0-IIa	M	lower body	Co	+	+	
49	Hamabe	2011	71	M	cardia/antrum	tub1/tub1	0-IIa/0-IIa	M/SM	body/cardia	Sep	+		+
50	Takahashi	2012	68	F	lower body -antrum	sig	0-IIc	SM2					+
51	Ueno	2012	73	F	antrum	tub1	0-IIc	M	body	Sep	+	+	
52	Arai	2013	74	M	upper body	tub2	0-IIc	M	upper body	Co	–		+
53	Isosaka	2013	60	F	lower body	tub1	0-IIa+IIc	SM	lower body	Co	+	+	

Sep: separate type, Co: collision type, Mix: mixed type, a blank column: not record

carcinoma[9-10]. A gastroenterologist and a pathologist reached the conclusion that MALT lymphoma was the definite diagnosis in our case because lymphoepitelioid lymphoma (LEL) is rare at Toranomon Hospital.

The role of *H. pylori* in lymphoma has been suggested, but little is known about the clinicopathological characteristics of such cases.

Our findings suggest that gastroenterologists should pay attention to the existence of double malignancies in endoscopic examination of the upper gastrointestinal tract.

Ethics

The case report was consistent with the Declaration of Helsinki and informed consent was obtained from the patient.

Conflict of Interest

The authors state that they have no conflict of Interest.

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Report

Ningen Dock International 2016 ; 3 : 33–36

Public and Private Missions to the Philippines by the International Committee

International Committee, Japan Society of Ningen Dock
Junichi Kaburaki, Yukito Shinohara

This report addresses an international role of Japan Society of Ningen Dock. Our society cooperates with Medical Excellence JAPAN (MEJ) to promote the establishment of overseas medical centers to expand Japanese advanced medical services like Ningen Dock, Health Evaluation and Promotion. In this case, the International Committee of Japan Society of Ningen Dock had the opportunity to give a presentation on the prevention of lifestyle related diseases in the Philippines along with MEJ in October, 2015.

Medical Excellence JAPAN (MEJ)

MEJ promotes the globalization of Japanese superior medical services, which integrate medical devices, education and expertise through government (public) and private efforts as an international medical cooperation[1]. In these situations, the medical world can provide advanced medical services and advanced medical technologies to foreign countries. The industrial world can introduce new medical devices and invest in medical business. MEJ is a hub for all Japanese initiatives in the private sector, as MEJ provides a medical business platform through public and private cooperation to support medical institutions and various companies which have strategic plans to set up a wide variety of overseas operations.

Until now, MEJ has promoted representatively the establishment of the Russia-Japan Cardiac Imaging Training Center in Moscow, Breast Cancer Screening Center in Myanmar, Advanced Diagnostic Imaging Center in Vladivostok, Advanced Endoscopy Training Center in Vietnam and Advanced Endoscopy Training Center in Indonesia.

Medical Care in the Philippines

The Philippine Health Insurance Corporation, which is called PhilHealth, was established in 1995 to provide universal health insurance coverage for the Philippine people[2]. PhilHealth belongs to the Department of Health (DoH), and is thus a government-owned and government-controlled corporation. Philhealth claimed to have achieved universal coverage for 86% of the population in 2010. Funding varies based on the population covered, although the majority of funds have come from general taxation, especially the "sin taxes" on alcohol and tobacco, since 2013. Therefore, the budget of the DoH in the Philippines is increasing (**Fig. 1**).

The private sector plays a crucial role in the Philippine hospital system[3]. In 2014, while 542 national hospitals had 46,054 beds, 912 private hospitals had 50,742 beds. However, private hospitals care more for people in the upper socioeconomic classes, which are estimated to account for approximately 30% of the people in the Philippines. The public health care system is divided into three parts. The first is the primary health care system, which is operated by district clinics and is directed at primary care and vaccinations. The second is operated by provincial hospitals, and the third part of the health care system is operated by 72 national hospitals, which are established for specific fields, such as infectious diseases, etc.

In this situation, the target diseases have changed in the Philippines. The problem of reproductive diseases and infectious diseases has been partly solved and now more significance is being given to non-commutable diseases.

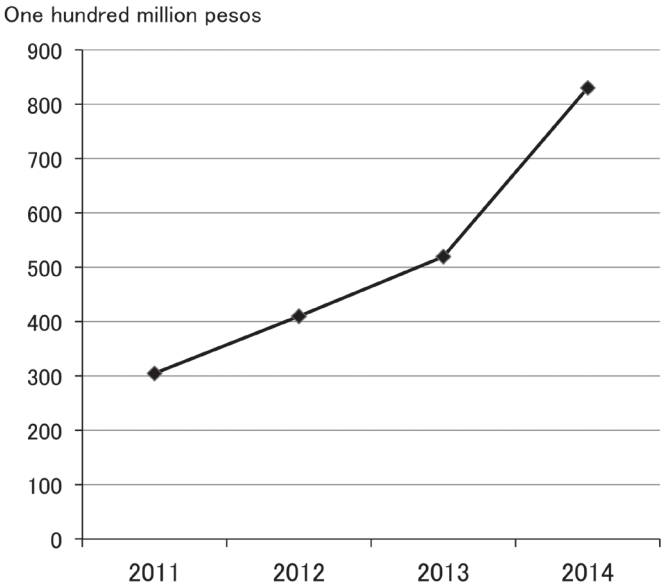

Fig. 1. Budget of the Department of Health in the Philippines
The budget of the Department of Health (DoH) in the Philippines has been increasing, especially since 2013 when the "sin tax" was imposed on alcohol and tobacco.
Taken from data presented by the Japan International Cooperation Agency (JICA) at a meeting with Medical Excellence JAPAN (MEJ) on October 12, 2015.

Fig. 2 shows chronological change in causes of death in the Philippines[2]. In the middle of the 20th century, communicable diseases were the leading cause of death, but this situation has gradually changed. Heart diseases, cancers, obesity, diabetes mellitus and chronic obstructive pulmonary diseases (COPD) have recently become more important causes of death. Heart diseases took the first place as a cause of death in the latest report, and other vascular diseases and cancers followed them (**Table 1**). The DoH reported that 90% of adult Filipinos have at least one or more risk factors for cardiovascular diseases, chronic respiratory diseases, diabetes mellitus and cancers. Against this background, the Philippine Star News, a representative newspaper in Manila, published a survey which indicated that 59% of 700 Filipinos did not exercise regularly, 46% slept less than 6 hours a day, 41 % had a habit of eating unhealthy food, 18% were aware of a family history of chronic health issues and 17% were overweight or obese[4]. Therefore, it is essential to prevent lifestyle related diseases and manage these diseases in the early phases in the Philippines.

The Philippine-Japan Medical Seminar

One of authors (JK) gave a presentation entitled "Preventive Health Care System in Japan" at the Philippine-Japan Medical Seminar and talked about part 2 as below at a meeting with officials from DoH. This presentation consisted of 2 parts. Part 1 discussed reasons for the necessity of a preventive health care system. Then, part 2 described the practices of a preventive health care system, especially the high-level Ningen Dock, Health Evaluation and Promotion, in Japan.

In part 1, the author mentioned that very old people, centenarians, have rapidly increased since the late 1990's[5], and that universal health insurance has contributed to achieving a longer life expectancy at birth in Japan[6]. However, the significance of healthy survival without any assistance has been recently pointed out[7]. It is important to prevent the process of atherosclerosis causing cardiovascular diseases and cancers in order to extend healthy survival without assistance, leading to increased longevity. In this sense, it was clarified that risk factors for diabetes mellitus and cancer are common[8]. Possible mechanisms for a direct link between diabetes mellitus and cancers include hyperinsulinemia, hyperglycemia and inflammation. Therefore, healthful diets, physical activity, and weight management would reduce such risk factors improve

Table 1. Causes of Death in the Philippines

Causes of Death	2006 (per 100 thousand population)
Heart diseases	95.5
Vascular diseases	63.8
Cancers	49.5
Accidents	41.6
Pneumonia	40.2
Tuberculosis	29.7
Unknown	(24.6 in 2005)
chronic obstructive pulmonary diseases (COPD)	24.4
Diabetes mellitus	23.3
Diseases in perinatal period	13.8

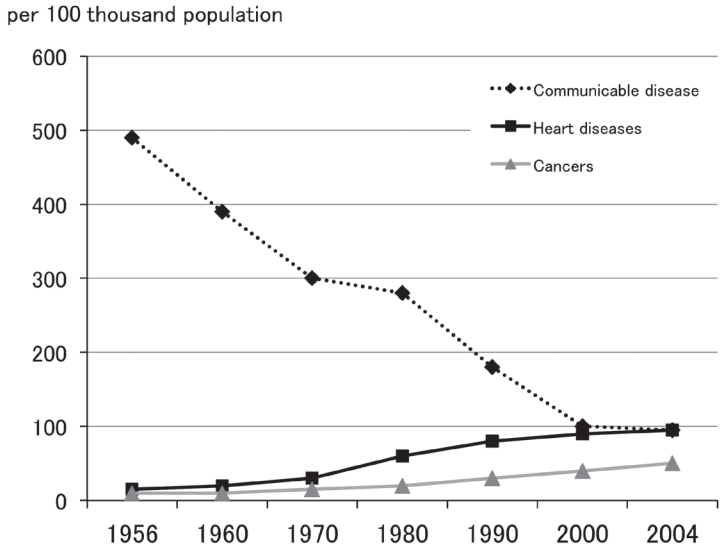

Fig. 2. Chronological Changes in Causes of Death in the Philippines

The proportions of heart diseases and cancers have increased, whereas the number of communicable diseases overall has dropped.
Taken from data presented by the Japan International Cooperation Agency (JICA) at a meeting with Medical Excellence JAPAN (MEJ) on October 12, 2015.

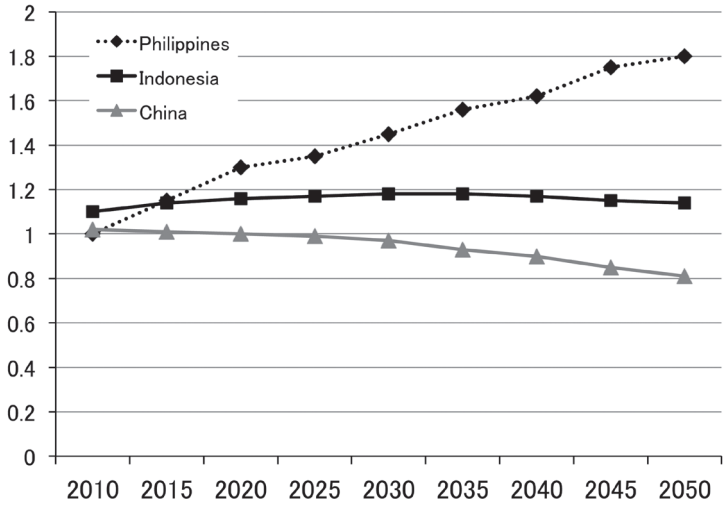

Fig. 3 . Chronological Changes in Working Age Populations

Working age population in 2010 were determined to be 1.0 in each country. The working age population is estimated to increase in the Philippines, compared to Indonesia and China.
Taken from data presented by the Japan International Cooperation Agency (JICA) at a meeting with Medical Excellence JAPAN (MEJ) on October 12, 2015.

outcomes of type 2 diabetes and prevent some forms of cancer, and should be promoted to all people.

In part 2, the author explained the preventive health care system in Japan, which includes the general preventive health care system and the optional preventive health care system.

Firstly, a representative system of the former is "Tokutei-kenshin". The author explained the usefulness of this system, which decreased the frequency of metabolic syndrome by up to 1.34% from 2008 to 2012, and reduced the total number of diabetes mellitus and suspected diabetes mellitus patients from approximately 2,210,000 in 2007 to 2,050,000 in 2012[9].

Secondly, the author mentioned the characteristics of the optional preventive health care system, Ningen Dock, which is supported by the Japan Society of Ningen Dock. It was emphasized that high technology is used in examinations and that results are explained and then health education is given to each examinee on the same day. For example, clinical laboratory systems, which include clinical analyzers and web systems, have been established at Ningen Dock facilities. Also mentioned were the effectiveness of colorectal cancer screening and significance of Ningen Dock in achieving reductions in annual medical costs, according to the literature[10, 11].

Future Tasks

It is estimated that the Philippines will grow more than other Asian countries[3]. Annual Gross Domestic Product (GDP) growth was 7.2% in 2013 and 6.1% in 2014, and its population is expanding at the approximate rate of 2.0% per year. **Fig. 3** shows estimates of working age populations. The working age population will increase in the future in the Philippines, compared to Indonesia and China. Therefore, it is important to prevent lifestyle related diseases in this country. Ningen Dock, Health Evaluation and Promotion, can play a significant role in this point.

To achieve a preventive health care system, we must solve at least 2 problems. Firstly, we should recognize the difference between private and public hospitals in the Philippines, and help with the establishment of facilities in public hospitals. Philippine General Hospital is one of the public hospitals, and the outpatient clinic building of this hospital was built 26 years ago with financial support from the Japanese government. A centrifuge which was bought 26 years ago is still working in a laboratory. San Lazaro Hospital belongs to DoH, and specializes in infectious diseases. However, it does not have a CT apparatus, only 2 plain X-ray apparatuses. Although the temperature goes up to 32 ℃ in Manila in October, there is no air-conditioning system. There are several electric fans in the outpatient clinics of these hospitals. On the other hand, De Los Santos Medical Center is a private hospital and belongs to a private medical service group. As a group, hospitals have not only CT apparatuses, but also MRI apparatuses. Another private hospital which we visited was St Luke's Medical Center. St Luke's Medical Center provides preventive medical services in the Health and Wellness Center. Fees are high, as the basic health screening package including tests for serum creatinine, AST, ALT, lipid profile, fasting blood glucose and uric acid, and ophthalmologic examination costs 5,900 pesos. The author thinks that only wealthy people can re-

ceive such preventive medical services in the Philippines. Both private hospitals have air-conditioning systems for their buildings.

It may be planned that these public hospitals are rebuilt, with the new buildings having web systems for connections between clinics, laboratories, radiography, and so on. In this case, preventive health care centers will coexist in these public hospitals and achieve preventive health care for all people in the Philippines.

Secondly, it is important to solve the funding problem. The author received several questions about funding after the Philippine-Japan Medical Seminar and the meeting at DoH. People wanted to know if they could get funding from the Japan International Cooperation Agency (JICA) or other funds provided by the Japanese government or not. Therefore, it is necessary to discuss the details of these projects with each hospital and provide them with sufficient funding.

Conclusion

The Japan Society of Ningen Dock should promote high-level preventive health care systems in order to achieve greater longevity and reductions in total medical costs in the Philippines and other countries, and cooperate with MEJ in achieving these goals.

Conflict of Interest

There are no conflics of interest associated with this report.

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Acknowledgments

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I sincerely thank their kind cooperation.

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The Regulations of the International Society of Ningen Dock

Article 1
Name
The name of the association shall be the International Society of Ningen Dock.

Article 2
Office
The Society has its principal office in Japan Society of Ningen Dock.

Article 3
Aims
The Society, an organization of Japan Society of Ningen Dock for international operations, aims to contribute to global health promotion by enhancing the development of ningen dock as a medical check-up system.

Article 4
Tasks
The Society conducts the following tasks to achieve the aims described in the preceding section.
1. Holds congress (World Congress on Ningen Dock), board meetings, lectures, and committee meetings
2. Publishes journals and news magazines
3. Communicates and cooperates with related academic societies both in Japan and overseas
4. Promotes research activities in ningen dock and related fields
5. Does whatever is necessary to achieve the aims of the Society

Article 5
Membership
1. The Society consists of the following members
   1) Regular member
      A regular member shall be a member of the International Society of Ningen Dock who agrees to the aims of the Society, and has expert knowledge, techniques, or experience in the areas associated with the Society.
   2) Supporting member
      A supporting member shall be a person, a corporation, or a group that agrees to the aims of the Society, and supports its programs.
   3) Honorary member
      An honorary member shall be recommended, from those who have significantly contributed to the areas associated with the Society, by the executive board.
2. Those who want to apply for regular or supporting membership of the Society shall submit the prescribed application form with the membership fee.
3. The board meeting will process applications mentioned in the preceding section, and promptly notify the applicants of its decision.

Article 6
Officials
1. The Society shall appoint the following honorary advisors and officials.

Honorary advisor: Number not decided
Congress president: 1
President: 1
Vice president: 3 (from Japan : 2, overseas: 1)
Board members: up to 25 (from Japan : 15 or less, overseas : 10 or less)
Auditor: 2

Article 7
Honorary advisor
1. An honorary advisor shall be appointed by the president from those who have contributed to the development of the Society for a long period, and approved by the executive board.
2. Honorary advisors shall be eligible to attend the board meeting, and to express opinions; honorary advisors will not have voting rights.

Article 8
Congress president
1. The congress president shall be recommended by the executive board and appointed by the president.
2. The congress president shall represent the Society and host the World Congress on Ningen Dock as a scientific meeting.

Article 9
President
1. The president shall be selected by and from among board members and delegated by the president of Japan Society of Ningen Dock.
2. The president shall preside the Society.

Article 10
Vice president
1. The vice president shall be appointed, from among board members, by the president.
2. The vice president shall assist the president. In the case of accident, one of the vice presidents will be appointed by the president and will temporarily take over the duties.

Article 11
Board members
1. Board members from Japan shall be selected among candidates from regular members at Japan Society of Ningen Dock.
2. Overseas board members shall be selected at the recommendation of the executive board.
3. Board members execute duties for the Society under the orders from the president.
4. Board members, together with the president and the vice president, comprise the executive board.

Article 12
Board meeting
1. The president will call a board meeting on an as-needed basis, and serves as the chairman of the meeting.
2. The board meeting will pass resolutions on important matters of the Society.
3. The board meeting shall have the right to start proceedings if the majority of all the board members (including a letter of proxy) attend the meeting.
4. The board meeting shall pass resolutions with the majority votes of attendances.

Article 13
Auditor
Auditors shall audit accounts of the Society, and report to the board meeting.

Article 14
Commissioner
For the aims of successful programs of the Society, the president will set up committees and divisions through the resolutions of the executive board, and delegate the commissioners to regular members or other members of the Society.

Article 15
Accounting
1. The fiscal year for the Society starts on April 1 every year and ends on March 31 the following year.
2. Expenses required for the Society shall be covered by the following revenues.
   1) Membership fees
   2) Grants
   3) Donations
   4) Others

Article 16
Modification of rules
The rules of the Society can be amended by the resolution of the executive board.

Article 17
Miscellaneous provisions
Detailed regulations necessary for the enforcement of the rules of the Society are defined elsewhere by the president with the approval of the executive board.

Article 18
Additional clause
The Regulations of the International Society of Ningen Dock will come into effect on September 15, 2006.

Detailed Regulations of the International Society of Ningen Dock

Detailed regulations of the International Society of Ningen Dock are defined as follows:

(Detailed regulations on members)

Article 1

1. Members shall pay the following annual membership fee; honorary members will be exempt from membership fee.
   1) Regular member : 2,000 yen
   2) Supporting member : from one unit (unit: 20,000 yen)
2. Annual membership fee paid shall not be refunded for any reason.
3. Members with foreign citizenship shall pay a 3-year membership fee of 50 dollars.

Article 2

Members will be given priority in the following events :

1) Participation in scientific meetings hosted by the Society;
2) Contributions of articles to and receipt of the journal of the Society.

Article 3

Members shall lose their memberships in the event of the following:

1) Withdrawal from membership;
2) Adjudication of incompetence or quasi-incompetence;
3) Death or adjudication of disappearance, or dissolution of the group in the case of a member of a supporting group;
4) Delinquency in payment of membership fee for over three year.

Article 4

Those intending to withdraw from the Society must submit the notice of withdrawal in the prescribed form to be approved by the executive board.

Article 5

The Society can expel a member to whom either of the following would apply, with a resolution of the executive board:

1) Those who violate their duty as members of the Society;
2) Those who damage the honor of members of the Society or act against the aims of the Society.

Article 6

Those who satisfy Sections 1 and 2 of Article 5 of the Regulations of the International Society of Ningen Dock will be accepted as members of the Society.

(Detailed regulations on officials)

Article 7

1. The president will be selected from the board members of Japan Society of Ningen Dock.
2. In principle, the majority of board members from Japan will be selected from among the board members of Japan Society of Ningen Dock.

3. Overseas board members will essentially be selected from Asia, Pacific Rim, North America, or Europe.

Article 8

1. The term of the congress president will be from the end of the congress of which he/she is in charge to the next congress.
2. The term of board members will be six years (two terms of three years).

(Detailed regulations on congress and board meeting)

Article 9

Congress and board meeting will be held as follows :

1) The title of the congress will be World Congress on Ningen Dock.
2) In principle, the congress and the board meeting will be held once every three years; with the resolution of the executive board, however, the congress and the board meeting will be held as needed.
3) The congress and the board meeting will be held at the same time.
4) The name of the congress president and the location of the next congress will be announced.

Article 10

1. Those who want to take part in the congress shall pay the participation fee, which is defined separately.
2. Participation fee for the congress will be defined accordingly by the congress president.
3. Only regular members shall be allowed to present the results of their studies, except those who have been approved by the congress president.

(Enforcement of the detailed regulations)

Article 11

1. The detailed regulations will come into effect on September 15, 2006.

INSTRUCTIONS TO AUTHORS

Ningen Dock International
Official Journal of Japan Society of Ningen Dock

Ningen Dock is the official journal of Japan Society of Ningen Dock, in which original articles, case reports, and review articles in both Japanese and English are published. Ningen Dock accepts only manuscripts that are original work in the field of ningen dock and related areas not previously published or being considered for publication elsewhere, except as abstracts. The manuscripts published in Ningen Dock will appear on the website of our society.

If the manuscript concerns a clinical study, it must be in accordance with the Declaration of Helsinki of 1964 (subsequent revisions included). Therefore, for a manuscript whose content is epidemiological or clinical research, the approval of the facility's Institutional Review Board (IRB) or the Ethics Committee of Japanese Society of Ningen Dock must have been obtained for the study described. Also, in the text, it should be indicated that informed consent has been obtained from subjects. Additionally, for case reports, it should be stated that adequate care has been taken to ensure the privacy of the subject concerned.

Online submission system

Ningen Dock uses an online submission system called ScholoarOne Manuscripts.
Please access http://mc.manuscriptcentral.com/ningendock
This site is only in Japanese at this time.

Preparation of manuscript

All manuscripts must be written in English with MS-Word, Excel, PowerPoint and/or a common graphic format. Authors who are not fluent in English must seek the assistance of a colleague who is a native English speaker and is familiar with the field of the manuscript.

The title, abstract, text, acknowledgments, references, tables, and figure legends should begin on separate sheets, with pages numbered, and be typed double-spaced using the 12-point font size in MS-Word.
Files for submission should be prepared in English in a Microsoft Word or other file format that may be uploaded to the online system.

Available formats for files to be uploaded: doc (docx), xls (xlsx) ppt (pptx), jpg, tiff, gif, ai, eps, psd File names must consist of alphanumeric characters and an extension.

Example file names: Manuscript.doc, Fig 1 .jpg, Table 1 .xls, etc.

Please indicate the version of Microsoft Office used in a cover letter accompanying the uploaded files.

All measurements should be expressed in SI units. Less common abbreviations should be spelled out at first usage and the abbreviated form used thereafter.

Title page

Titles should be concise and informative. Include the full names of authors, names and addresses of affiliations, and name and address of a corresponding author to whom proofs are to be sent, including a fax number, telephone number and e-mail address.

Abstract

The abstract should not exceed 250 words, and should be arranged under the following subheadings: Objective, Methods, Results, Conclusions, and have up to 4 keywords.

Types of articles

Original articles: An original article should not exceed 3,000 words, and should be arranged as follows: Abstract, Objective, Methods, Results, Discussion, (Conclusion), (Acknowledgments), and References.

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Review articles: Review articles should not exceed 4,000 words. Review articles are usually by invitation. However, articles submitted without an invitation may also be considered by the Editorial Board.

References

References should be numbered consecutively in order of appearance in the text and cited in the text using superscript numbers. For example, according to the study by Sasamori[1)]. For journals, the names and initials of the first three authors, followed by "et al" if there are other coauthors, the complete title, abbreviated journal name according to Index Medicus, volume, beginning and end pages, and year should be included. For books, the names and initials of the first three authors, followed by "et al" if there are other coauthors, the complete title, book name, edition number, beginning and end pages, name and city of publisher, and year should be included. Examples of references are given below.

Journal: Ishizaka N, Ishizaka Y, Nagai R, et al: Association between white cell count and carotid arteriosclerosis in Japanese smokers. Atherosclerosis 2004; 175: 95-100.

Book: Kaplan NM: Measurement of blood pressure. In: Kaplan NM(ed), Kaplan's Clinical Hypertension. 7th ed., Lippincott William & Wilkins, Philadelphia, 2002, 25-55.

Tables

Tables should be cited in the text, and numbered sequentially with Arabic numerals. Each table should be given a number and a brief informative title, and should appear on a separate page. Explain in footnotes all abbreviations used.

Figures

Figures should be cited in the text, and numbered sequentially with Arabic numerals. A brief descriptive legend should be provided for each figure. Legends are part of the text, and should be appended to it on a separate page. Color figures can be reproduces if necessary, but the authors will be expected to contribute towards the cost of publication.

Conflict of Interest (COI)

All authors are required to disclose any conflict of interest (COI) on the form designated by the Japan Society of Ningen Dock.

If no author has any COI, this should be indicated in the manuscript.

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The corresponding author will receive PDF proofs, the author should correct only typesetting errors. After correcting, page proofs must be returned promptly.

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Thirty reprints of each paper are free, and additional reprints are available at charge in lots of 10, but for a minimum order of 50. Reprints should be ordered on submission of the manuscript as follows: For example, "I order 100 reprints: 30 (free) + 70."

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Categories of manuscript:

- ☐ Original article (not more than 3,000 words)
- ☐ Case report (not more than 2,000 words)
- ☐ Review article (not more than 4,000 words)

Typing:

- ☐ Manuscript on A4 paper with wide margins
- ☐ Type double space using 12-point

Title page:

- ☐ Title of paper
- ☐ Full names of authors and affiliations without title of MD, PhD, etc
- ☐ Full name and address of a corresponding author including fax number, telephone number and e-mail address.
- ☐ Running title not more than 50 characters.

Abstract:

- ☐ Not more than 250 words.
- ☐ Arranged in the order of Background, Methods, Results, and Conclusion.
- ☐ Up to four key words.

Text of paper:

- ☐ Manuscript is arranged in the order of Objective, Methods, Results, Discussion, (Conclusion), (Acknowledgments), and References.
- ☐ Measurements are expressed in SI units.
- ☐ Abbreviations are spelled out at first usage.

References:

- ☐ References are numbered consecutively in order of appearance in the text and cited in the text using superscript numbers.
- ☐ Format is consistent with examples in Instructions for Authors.

Tables:

☐ Each table is given a number and a brief informative title, and appears on separate page.

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Abbreviations

1	**1,5-AG**	1,5-anhydroglucitol	61	**hCG**	human chorionic gonadotropin
2	**17-OHCS**	17α-hydroxycorticosteroid	62	**HCV**	hepatitis C virus
3	**95% CI**	95% confidence interval	63	**HDL-C**	high-density lipoprotein cholesterol
4	**α-GI**	α-glucosidase inhibitor	64	**HLA**	histocompatibility [leucocyte] antigen
5	**β_2-MG**	β_2-microglobulin	65	**HPLC**	high-performance liquid chromatography
6	**γ-GTP**	γ-glutamyl transpeptidase	66	**Ht**	hematocrit
7	**A/G ratio**	albumin-globulin ratio	67	**ICD**	International Classification of Disease
8	**ABI**	ankle-brachial index	68	**ICU**	intensive care unit
9	**ACTH**	adrenocorticotropic hormone	69	**IFG**	impaired fasting glucose
10	**ADL**	activities of daily living	70	**IGT**	impaired glucose tolerance
11	**AFP**	α-fetoprotein	71	**IMT**	intima-media thickness
12	**ALP**	alkaline phosphatase	72	**LAP**	leucine aminopeptidase
13	**ALT**	alanine aminotransferase	73	**LDH**	lactate dehydrogenase
14	**Apo (a)**	apolipoprotein (a)	74	**LDL-C**	low-density lipoprotein cholesterol
15	**APTT**	activated partial thromboplastin time	75	**Lp(a)**	lipoprotein (a)
16	**AST**	aspartate aminotransferase	76	**LPL**	lipoprotein lipase
17	**BMI**	body-mass index	77	**MCH**	mean corpuscular hemoglobin
18	**CA125**	carbohydrate antigen 125	78	**MCHC**	mean corpuscular hemoglobin concentration
19	**CA19-9**	carbohydrate antigen 19-9	79	**MCV**	mean corpuscular volume
20	**cAMP**	cyclic adenosine 3', 5'-monophosphate	80	**METs**	meatbolic equivalent
21	**CAPD**	continuous ambulatory peritoneal dialysis	81	**MetS**	metabolic syndrome
22	**CBC**	complete blood cell count	82	**MMG**	mammography
23	**Ccr**	creatinine clearance	83	**MRA**	magnetic resonance angiography
24	**cDNA**	complementary deoxyribonucleic acid	84	**MRI**	magnetic resonance imaging
25	**CEA**	carcinoembryonic antigen	85	**mRNA**	messenger RNA
26	**cGMP**	cyclic guanosine 3', 5'-monophosphate	86	**MRSA**	methicillin-resistant *Staphylococcus aureus*
27	**ChE**	cholinesterase	87	**MSW**	medical social worker
28	**CKD**	chronic kidney disease	88	**NMR**	nuclear magnetic resonance
29	**COI**	conflict of interest	89	**PET**	positron emission tomography
30	**COPD**	chronic obstructive pulmonary disease	90	**PSA**	prostate-specific antigen
31	**CK**	creatinine kinase	91	**PTH**	parathyroid hormone
32	**CRP**	c-reactive protein	92	**PWV**	pulse wave velocity
33	**CT**	computed tomography	93	**QOL**	quality of life
34	**CVA**	cerebrovascular accident	94	**RBC**	red blood cell
35	**D-Bil**	direct bilirubin	95	**RF**	rheumatoid factor
36	**DBP**	diastolic blood pressure	96	**RI**	radioactive isotope
37	**DNA**	deoxyribonucleic acid	97	**RIA**	radioimmunoassay
38	**DRG**	diagnosis-related group	98	**RNA**	ribonucleic acid
39	**dsDNA**	double stranded deoxyribonucleic acid	99	**SBP**	systolic blood pressure
40	**EBM**	evidence-based medicine	100	**SD**	standard deviation
41	**ECG**	electrocardiogram	101	**SEM**	standard error of the mean
42	**eGFR**	estimated glomerular filtration rate	102	**STD**	sexually transmitted disease
43	**EIA**	enzyme immunoassay	103	**T-Bil**	total bilirubin
44	**ELISA**	enzyme-linked immunosorbent assay	104	**T_3**	triiodothyronine
45	**EPO**	erythropoietin	105	**T_4**	thyroxine
46	**ESR**	erythrocyte sedimentation rate	106	**TC**	total cholesterol
47	**FBG**	fasting blood glucose	107	**TG**	triglyceride
48	**FDA**	Food and Drug Administration	108	**TIA**	transient (cerebral) ischemic attack
49	**FEV**	forced expiratory volume	109	**TIBC**	total iron binding capacity
50	**FEV_1**	forced expiratory volume in one second	110	**tPA**	tissue plasminogen activator
51	**FEV_1%**	forced expiratory volume % in one second	111	**TPHA**	*Treponema pallidum* hemagglutination assay
52	**FPG**	fasting plasma glucose	112	**TSH**	thyroid stimulating hormone
53	**FSH**	follicle stimulating hormone	113	**TTT**	thymol turbidity test
54	**FT3**	free triiodothyronine	114	**UCG**	ultrasonic echocardiography
55	**FT4**	free thyroxine	115	**UIBC**	unsaturated iron binding capacity
56	**FVC**	forced vital capacity	116	**UN**	urea nitrogen
57	**GFR**	glomerular filtration rate	117	**VLDL**	very-low-density lipoprotein
58	**GH**	growth hormone	118	**WBC**	white blood cell
59	**Hb**	hemoglobin	119	**WHO**	World Health Organization
60	**HbA1c**	hemoglobin A1c	120	**ZTT**	zinc sulfate (turbidity) test

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6-41 Akasaka 9-chome, Minato-ku, Tokyo 107-0052 Japan
Phone : +81-3-3475-5618 Fax: +81-3-3475-5619
E-mail: info@jaacc.jp

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Masaharu Nara
President
Japan Society of Ningen Dock

FAX: +81-3-3265-0083

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TEL: +81-3-5911-3355
FAX: +81-3-5911-3356


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