among liver cirrhosis patients.[13] In addition, the incidence of diabetes in patients having HCV-related liver cirrhosis is higher than that in patients with HBV-related liver diseases.[14]

We recently showed molecular mechanisms for HCV core-induced insulin resistance.[15] HCV core up-regulates the suppressor of cytokine signaling (SOCS) 3, and inhibits insulin signaling by down-regulation of insulin receptor substrate (IRS) -1 and IRS-2 in hepatocytes. Moreover, in an epidemiological survey, we demonstrated that a significant increase in the incidence of diabetes occurs in subjects with high titers of HCV core compared to subjects who are negative for anti-HCV antibody[16] and concluded that HCV infection induces insulin resistance, which causes an increase in the incidence of extrahepatic manifestations in HCV-infected individuals.[17]

In the current study, we surveyed the incidence of abnormal glucose tolerance in patients with or without lichen planus in a study population with HCV-related chronic liver disease, and investigated the relationship between lichen planus and insulin resistance.

Methods

Patients

A total of 105 984 consecutive patients had checkups for chronic liver disease for the first time in the Digestive Disease Center at Kurume University Hospital from April 1988 to August 2005. In the Digestive Disease Center, physicians, surgeons, radiologists, and an oral surgeon hold full-time positions. One of us (M.S.) is a hepatologist and examined 9396 of these 105 984 patients. There were 522 patients who were HCV antibody positive and who thereafter continued with regular hospital visits until April 2006.

Exclusion criteria were the following: (i) other causes of chronic liver disease or disease other than chronic HCV infection; (ii) liver disease related to HBV infection; and (iii) patients treated with interferon therapy at the time of study inclusion.

We examined the presence of extrahepatic manifestations of chronic HCV infection in 87 patients. Informed consent was obtained from all patients after the purpose and methods of the study were explained. The 87 patients were 44 men and 43 women with a mean age of 60.0 $\pm$ 11.5 years.

The patients were monitored for the presence of extrahepatic manifestations of HCV infection such as lichen planus, DM, hypertension, thyroid dysfunction, and extrahepatic malignant tumor as well as liver disease. Biochemical tests were done and insulin values, blood glucose levels, and *Helicobacter pylori* antibody were measured in patient blood samples. Life histories were taken.

Clinical examinations

Patients received oral mucosa and cutaneous medical examinations by an oral surgeon and a dermatologist. The diagnosis of OLP was made on the basis of clinical and histopathological features. Diagnosis of type 2 DM was based on the American Diabetic Association (ADA) criteria of 1997.[18] Persons in whom diabetes was diagnosed before 30 years of age and who used insulin were categorized as type 1 DM and were excluded from our study.

The following definitions of cardiovascular disease were employed. Obesity was defined as a body mass index (BMI) >25 kg/m^2 or higher. Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or higher, or a diastolic blood pressure (DBP) of 90 mmHg or higher according to the criteria of JNC-VI of the International Hypertension Society.[19] Thyroid hormones such as FT3, FT4 and thyroid stimulating hormone were measured for all patients, and thyroid echography examination was performed for some patients. Examination of the upper gastrointestinal tract or lower digestive tract was performed on patients for whom it was deemed clinically necessary.

We also took a history of smoking and alcohol consumption.

Serological assays

Serum samples from the 87 patients were collected and tested for platelets (PLT) and for the following liver function tests: serum ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (γ-GTP), lactate dehydrogenase (LDH), total bilirubin (TBil), direct bilirubin (DBil), thymol turbidity test (TTT), zinc sulfate turbidity test (ZTT), total cholesterol (TC), total protein (TP), and albumin (Alb). Sera were also examined for the presence or absence of HCV or HBV infection. Anti-HCV was measured by a chemiluminescent enzyme immunoassay kit (Lumipulse II HCV, Fujirebio, Tokyo, Japan). HCV RNA in serum was detected using the Amplicore HCV test (Roche, Tokyo, Japan). Hepatitis B virus surface antigen (HBsAg) was assayed using a chemiluminescent immunoassay kit (Architect, HBsAg QT, Dainabot, Tokyo, Japan). Ultrasonographic examination for all patients was performed in order to investigate the shape of the liver and lesions occupying the liver. Computed tomography and liver biopsy were performed in some patients. Most patients underwent endoscopy for detection of esophagogastric varices. We used other possible predictors of liver cirrhosis progression, including serum albumin, TBil, prothrombin time, and PLT.

Plasma glucose levels were measured by a glucose oxidase method for all subjects and serum insulin levels were measured using a sandwich enzyme immunoassay kit (Eiken Chemical, Tokyo, Japan). Insulin resistance (IR) was calculated on the basis of fasting levels of plasma glucose and insulin, according to the homeostasis model assessment (HOMA-IR) method.[20] The formula for the HOMA-IR is: HOMA-IR = fasting glucose (mg/dL) $\times$ fasting insulin (μU/mL)/405.

The presence of serum IgG antibodies against *H. pylori* antibody were measured by the SRL (Tokyo) using E Plate *H. pylori* antibody produced by Eiken Chemical.

Statistical analysis

The chi-squared test and the unpaired Student *t*-test were used for statistical analyses. Differences were judged significant for $P < 0.05$ (two-tailed). This study was approved by the Institutional Review Board/Ethics Committee of our Institution.

Results

Among 87 patients with HCV-related liver diseases, the prevalence of lichen planus was 19.5% (17/87), DM was 21.8% (19/87),

Table 1 Clinical characteristics of 87 patients with HCV-related liver diseases according to presence of lichen planus (LP)

Clinical characteristic	All patients	Group A (with LP)	Group B (without LP)	*P*-value (A *vs* B)
No. subjects	87	17	70	–
Age (years)	60.0 ± 11.5	63.7 ± 10.6	59.1 ± 11.6	NS
Sex (M/F)	44/43	11/6	33/37	NS
BMI (kg/m^2)	22.8 ± 2.9	23.9 ± 2.8	22.5 ± 2.9	NS
Smoking history	32 (36.8)	10 (58.8)	22 (31.4)	0.0356
Alcohol consumption percentage	50 (57.5)	10 (58.8)	40 (57.1)	NS
Diagnosis of liver disease				
Past history of HCV infection	1	0	1	NS
Chronic hepatitis C	69	11	58	
HCV-related liver cirrhosis	9	3	6	
HCV-related HCC	8	3	5	
Comorbidities				
Diabetes mellitus	19 (21.8)	4 (23.5)	15 (21.4)	NS
Hypertension	25 (28.7)	10 (58.8)	15 (21.4)	0.0022
Thyroid dysfunction	18 (20.7)	5 (29.4)	13 (18.6)	NS
Extrahepatic malignant tumor	8 (9.2%)	5 (29.4)[†]	3 (4.3)[‡]	0.0013

Values shown as *n* (%) or mean ± SD. BMI, body mass index; F, female; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; M, male; NS, not significant.

[†]Tumors were: gastric cancer (two), tongue cancer (one), larynx cancer (one), and renal and colon cancer (one). [‡]Tumors were: gastric cancer (one), colon cancer (one), and gallbladder cancer (one).

hypertension was 28.7% (25/87), thyroid dysfunction was 20.7% (18/87), and extrahepatic malignant tumor was 9.2% (8/87).

We compared characteristics of 17 patients who had lichen planus (group A) and 70 patients who did not have lichen planus (group B). The mean age in group A was 63.7 ± 10.6 years; there were 11 men and six women. The mean age in group B was 59.1 ± 11.6 years; there were 33 men and 37 women. Table 1 shows clinical features of groups A and B. The diagnoses of liver diseases in group A were chronic hepatitis C infection (11 patients), HCV-related liver cirrhosis (three patients), and HCV-related HCC (three patients). Those of group B were chronic hepatitis C infection (58 patients), HCV-related liver cirrhosis (six patients), HCV-related HCC (five patients) and past history of HCV infection (one patient) (Table 1).

The prevalence of smoking history ($P = 0.0356$), hypertension ($P = 0.0022$), and extrahepatic malignant tumor ($P = 0.0013$) were significantly higher in group A than in group B (Table 1). Diagnoses of extrahepatic malignant tumors in group A were: tongue cancer (one squamous cell carcinoma), larynx cancer (one squamous cell carcinoma), gastric cancer (one adenocarcinoma, one signet ring cell carcinoma), renal and colon cancer (one renal cell carcinoma). Diagnoses of extrahepatic tumor in group B were: gastric cancer (one adenocarcinoma), colon cancer (one adenocarcinoma), and gallbladder cancer (one adenocarcinoma). Significant differences were not observed for age, sex, BMI, liver disease, alcohol consumption, presence of DM, or thyroid dysfunction between these two groups.

We analyzed for differences between these two groups in liver assays, blood platelets, insulin, blood glucose, HOMA-IR, and presence of *H. pylori* infection. The laboratory data of both groups are shown in Table 2. Prevalence of insulin ($P = 0.0076$) and HOMA-IR ($P = 0.0113$) were significantly higher in group A than in group B (Table 2). Significant differences were not observed for serum AST, ALT, LDH, γGTP, TP, Alb, TBil, DBil, TTT, ZTT, TC, blood platelets, blood glucose, or presence of *H. pylori* infection between these two groups.

Seventeen patients had OLP at a total of 24 sites. The site of occurrence was: buccal mucosa in 13 (76.5%), lower lip in six (35.3%), upper lip in two (11.8%), gingiva in one (5.9%), tongue in one (5.9%), and floor of mouth in one (5.9%) (Table 3). The sites of lichen planus except oral mucosa were lower leg in four (23.5%), antebrachium in one (5.9%), skin extremities in two (11.8%), hypopharynx in one (5.9%), and vulva in one (5.9%). Biopsies of hypopharyngeal lichen planus were performed by an otolaryngologist, and of vulvar lichen planus by a gynecologist. The erosive and reticular variety, respectively, was found to be the prevalent form (Table 3).

Discussion

We performed an epidemiological survey for extrahepatic manifestations and HCC in an HCV hyperendemic area in Japan.[21,22] Anti-HCV positivity among residents of this area in 1990 was 23.6%.[23] We found that the prevalence of extrahepatic manifestations among individuals with HCV infection was higher than among those without HCV,[22] and found an association between HCV core, insulin resistance, and the development of type 2 DM.[16] Recently, we reported that insulin resistance in inhabitants who have an extrahepatic manifestation including OLP with HCV infection shows significantly greater increases than for inhabitants who have neither an extrahepatic manifestation nor HCV infection.[17] By the results of these epidemiological surveys we think that insulin resistance induced by HCV infection causes an increase in the incidence of extrahepatic manifestations in HCV-infected individuals.

In this study, we did long-term follow up for insulin resistance from the standpoint of lichen planus among patients who we identified as having HCV-related chronic liver disease at our hos-

Table 2 Laboratory data of 87 patients with HCV-related liver diseases according to presence of lichen planus (LP)

Laboratory assay	All patients	Group A (with LP)	Group B (without LP)	*P*-value (A *vs* B)
AST (IU/L)	61.1 ± 38.1	60.9 ± 33.5	61.2 ± 39.3	NS
ALT (IU/L)	68.2 ± 46.7	62.4 ± 39.6	69.6 ± 48.5	NS
LDH (IU/L)	216.8 ± 62.8	205.8 ± 72.1	219.6 ± 60.6	NS
γ-GTP (IU/L)	64.1 ± 68.4	63.5 ± 50.0	64.2 ± 72.5	NS
TP (g/dL)	7.7 ± 0.5	7.7 ± 0.5	7.7 ± 0.5	NS
Alb (g/dL)	4.1 ± 0.5	3.9 ± 0.5	4.2 ± 0.5	NS
PLT (/mm^3)	13.8 ± 5.1	12.5 ± 5.0	14.1 ± 5.09	NS
TBil (mg/dL)	1.1 ± 0.6	1.2 ± 0.9	1.0 ± 0.5	NS
DBil (mg/dL)	0.2 ± 0.2	0.2 ± 0.3	0.2 ± 0.2	NS
TTT	16.2 ± 6.7	18.4 ± 4.7	15.8 ± 7.0	NS
ZTT	20.6 ± 6.9	21.8 ± 5.8	20.3 ± 7.2	NS
TC (mg/dL)	172.3 ± 35.8	164.3 ± 41.9	174.1 ± 34.4	NS
Insulin (μU/L)	23.3 ± 42.0	47.3 ± 87.8	17.4 ± 15.4	0.0076
Blood glucose (mg/dL)	97.4 ± 30.1	103 ± 33.2	96.1 ± 29.5	NS
HOMA-IR	7.1 ± 18.8	17.4 ± 40.0	4.6 ± 6.0	0.0113
Helicobacter pylori antibody (*n* (%))	58 (66.7)	10 (58.8)	48 (68.6)	NS

Values shown as mean ± SD. Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DBil, direct bilirubin; γ-GTP, gamma-glutamyl transpeptidase; HOMA-IR, homeostasis model assessment; LDH, lactate dehydrogenase; NS, not significant; PLT, platelets; TBil, total bilirubin; TP, total protein; TTT, thymol turbidity test; TC, total cholesterol; ZTT, zinc sulfate turbidity test.

Table 3 Location of lichen planus in 17 patients with hepatitis C virus-related liver diseases

No	Sex	Age (years)	Liver disease	Lichen planus location			Type
				Cutaneous	Oral	Other	
1	M	71	CH	Antebrachium	–	–	–
2	M	60	CH	Extremities	–	–	
3	F	70	LC	–	Gingiva	–	Erosive
4	M	72	LC	–	Lower lip	–	Reticular
5	F	64	LC	Leg	Buccal mucosa, upper lip, lower lip	–	Erosive
6	M	66	CH	Leg	Buccal mucosa, upper lip, lower lip	–	Erosive
7	M	59	CH	–	Buccal mucosa (reticular)	Pharynx (erosive)	Erosive + reticular
8	M	66	CH	Leg	Buccal mucosa, lower lip	–	Reticular
9	M	57	CH	–	Buccal mucosa	–	Reticular
10	M	50	CH	–	Buccal mucosa, tongue, lower lip	–	Erosive
11	F	77	CH	–	Buccal mucosa	–	Atrophic
12	F	75	CH	–	Buccal mucosa	–	Reticular
13	M	62	HCC	–	Buccal mucosa, lower lip	–	Erosive
14	F	83	HCC	Leg	Buccal mucosa (atrophic)	Vulva (erosive)	Atrophic + erosive
15	M	41	CH	–	Buccal mucosa	–	Reticular
16	M	58	HCC	Extremities	Buccal mucosa, floor of mouth	–	Erosive
17	F	53	CH	–	Buccal mucosa	–	Reticular

CH, chronic hepatitis C; F, female; LC, HCV-related liver cirrhosis; HCC, HCV-related hepatocellular carcinoma; M, male.

pital. Although there was no significant difference in fasting glucose levels and BMI between patients with and without lichen planus, fasting insulin levels and HOMA-IR values, an indicator of insulin resistance, were significantly higher in patients who had lichen planus than in those who did not.

In the present study, insulin levels (17.4 ± 15.4 μU/L) and HOMA-IR values (4.6 ± 6.0) in patients having HCV infection without lichen planus (group B) were higher than the normal range. Normal values for insulin are 3.06–16.9 μU/L, and for HOMA-IR are less than 2. Therefore, the significantly higher insulinemia in patients such as those in group A (among HCV infectious patients) might cause lichen planus.

In Japan, it is known that the prevalence of HCV infection in patients with lichen planus is high;[11] therefore, interferon therapy is often administered to patients with lichen planus and a persistent HCV infection. However, it has been reported that patients cannot

complete interferon therapy because of aggravation of lichen planus.[24,25] The measurement of insulin resistance as well as a search for lichen planus may be useful before performing interferon therapy. A large series of patients with OLP was evaluated for extraoral involvement by Eisen *et al.*[26] They concluded that any patient with OLP should undergo a through history and examination as part of an investigation of potential extraoral manifestations, because a high percentage of patients with OLP develop extraoral manifestations. In our 17 cases of lichen planus, cutaneous lichen planus was diagnosed in seven (41.2%), hypopharynx in one (5.9%), and vulva in one (5.9%). The simultaneous appearance of extraoral and oral lesions was noted among six (35.3%). Because the majority of OLP patients suffer from lichen planus of the genitalia,[27] clinicians should follow OLP patients with sufficient attention to the presence of extraoral manifestations.

Sikuker *et al.* evaluated an association between HCV infection and extrahepatic malignancies. Extrahepatic malignancies were found in 14.6% of anti-HCV positive patients.[28] The incidence of extrahepatic malignant tumor in our subjects was 9.2% (8/87). The insulin-like growth factor family of proteins plays a key role in cellular metabolism, differentiation, proliferation, transformation and apoptosis, during normal development and malignant growth.[29] The hyperinsulinemia that HCV infection causes may induce an extrahepatic malignant tumor as well as HCC.

Many studies have shown that *H. pylori* is involved in the pathogenesis of gastric cancer.[30] The seroprevalence of *H. pylori* is 71% in Japanese aged 50–59 years, and is 81% in those aged 60–69 years.[31] This is almost the same as the seroprevalence of our patients, which was 66.7% (58/87) overall and 82.6% (19/23) in those aged 60–69 years. Seroprevalence of *H. pylori* in our three subjects with gastric cancer was 66.7%. In our study, we did not find an association between *H. pylori* and lichen planus in patients with HCV-infectious liver diseases.

In conclusion, we investigated the association of insulin resistance and lichen planus among patients with HCV-infected chronic liver diseases. The significant factors for development of lichen planus were smoking history, presence of hypertension, extrahepatic malignant tumor, and insulin resistance (HOMA-IR). This supports our previous conclusion that insulin resistance in patients who have an extrahepatic manifestation of HCV infection increases more than insulin resistance of patients who have neither an extrahepatic manifestation nor HCV infection. HCV-infected patients with lichen planus should pay attention to the development of an extrahepatic malignancy. Cooperation with an oral surgeon and a hepatologist is vital for early diagnosis and treatment of any extrahepatic manifestations.

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症例報告

脾辺縁帯リンパ腫の1切除例

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症例は64歳の女性で，熱発，左腰痛を主訴に受診．4年前よりB型慢性肝炎の指摘あり．腹部CTで脾内腫瘍を指摘され，PETでは脾臓に異常集積を認めた．以上より，脾臓原発悪性リンパ腫を疑い組織診断および腫瘍減量目的に膵尾部合併脾臓摘出術が施行された．脾臓は19×15cmと著明な腫大を認め，割面では多発性に白色結節状の腫瘍性病変を認めた．組織学的には，円形から類円形の核を有する中型異型細胞が結節様構造を呈しながら浸潤増殖し，免疫染色では，CD20が陽性であった．以上より，脾辺縁帯リンパ腫（B cell type）と最終診断した．術後早期に全身リンパ節腫脹が出現し，血液内科に緊急入院．入院当日よりTHP-COP療法を開始．全身症状は改善傾向を認め自宅退院となり，手術後13か月現在，外来定期通院中である．本症例は，手術後の急性増悪に対して肝炎の増悪なく化学療法導入に成功した症例である．

はじめに

脾辺縁帯リンパ腫（splenic marginal zone lymphoma：以下，SMZL）は，脾臓において辺縁から白脾髄を取り囲むように進展し，濾胞を消失させ，髄内において小型リンパ球が増殖するB細胞由来の悪性リンパ腫であり，WHOの分類ではmarginal zone lymphomaの一亜型として定義されている[1]．Papadakiら[2]の報告においても，脾辺縁帯のB細胞由来であると示唆され，増殖形態は結節性増殖を示すものが最も多いとされている．また，SMZLは病期の進行が緩徐であるとされており，治療選択は以前まで摘脾が第1選択とされているが，近年化学療法にCD20抗体を追加する方法など多く検討がなされている[3][4]．今回，我々はB型慢性肝炎患者に発症したSMZLに対して脾臓摘出術を行い，術後急速に全身リンパ節腫脹を来した症例を経験したので報告する．

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症　例

患者：64歳，女性

主訴：熱発，左腰痛

既往歴：4年前にB型慢性肝炎を指摘．

家族歴：特記事項なし．

現病歴：平成18年3月頃より発熱（弛張熱型），左腰痛を認め当院受診．腹部超音波検査にて脾腫，脾内腫瘍および腹部リンパ節腫脹を認め血液内科紹介受診となった．

入院時現症：身長154cm，体重54kg，血圧124/80mm/Hg，脈拍76回/分，体温38℃．表在部リンパ節腫脹は認めない．腹部は平坦であるが，脾臓は触知可能であった．

入院時血液検査所見：白血球が異常高値を認めたが，血小板については正常範囲内であった．また，LDHおよびIL2-Rの異常高値が認められた．HBs抗原は陽性であった（Table 1）．

腹部CT所見：動脈相および門脈相で脾腫および脾内腫瘍を認めた．また，脾門部を中心とする腹部リンパ節腫脹がみられた．他の臓器に腫瘍性病変は認めなかった（Fig. 1）．

Table 1　Laboratory date on admission

WBC	18,700 /mm³	BUN	19.1 mg/dl	HBs Ag	(+)
Stab	5 %	Cre	0.62 mg/dl	HBV-DNA	4.7 LGE/ml
Seb	80 %	Na	144 mEq/l	HCV-Ab	(−)
Baso	0 %	Cl	108 mEq/l	VDRL	(−)
Mono	0 %	K	3.8 mEq/l	TPHA	(−)
Lym	8 %				
RBC	387×10⁴ /mm³	CA19-9	8 U/ml	IL2-R	33,848 U/ml
Hb	11.9 g/dl	CEA	1.1 ng/ml		
Ht	35.6 %				
Plt	14.1×10⁴ /mm³	FBS	75 mg/dl		
AST	46 U/l				
ALT	24 U/l	CRP	(4+)		
LDH	1,503 U/l				
ALP	344 U/l				
γ-GTP	37 U/l				
T-Bil	1.2 mg/dl				

Fig. 1　Enhanced abdominal CT showed a nodular lesion in the spleen.

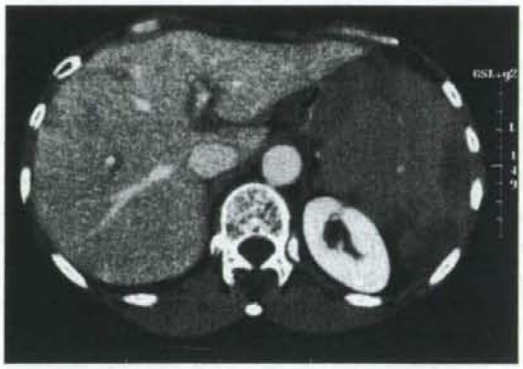
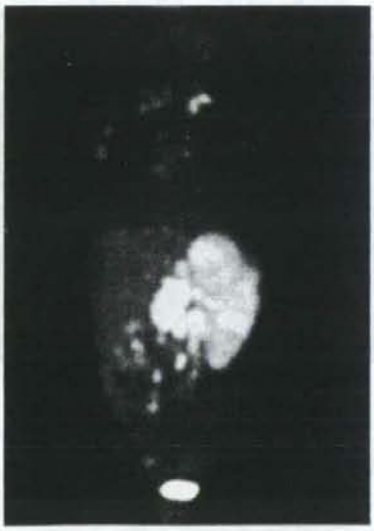


Fig. 2　PET demonstrated FDG uptake of nodular lesion of the spleen (FDG-SUV max 5.6).



PET所見：脾臓および左腸管膜領域に異常集積を認めた(FDG-SUV max 5.6)．また，頸部リンパ節や腋窩リンパ節の異常集積を認めた(Fig. 2)．

以上の所見より，脾臓原発悪性リンパ腫 Stage IV を考えた．治療については，腫瘍減量，組織診断目的に脾臓摘出術を施行した後に化学療法導入予定とした．

手術所見：上腹部正中切開にて開腹した．脾臓は著明な腫大を認めた．腹水はみられなかった．脾門部を中心に腹腔内リンパ節が腫脹しており，脾臓のみの摘出は困難であったため，膵尾部合併脾臓摘出術とした．

病理組織学的検査：脾臓は19×15cmと著明な腫大を認め，割面では多発性に白色結節状の腫瘍性病変を認めた（Fig. 3）．組織学的には，円形から類円形の核を有する中型異型細胞が結節様構造を呈しながら浸潤増殖していた（Fig. 4）．免疫染色では，CD20（+），CD45RO（−），CD10（−）であった(Fig. 5)．また，Flowcytometric analysisではCD19(+)，CD20(+)，κ>>λ，CD25(+)であった．以上より，Splenic marginal zone lym-

Fig. 3 Spleen measuring was 19×15cm. The cutting surface was showed that tumor in the spleen was multiple nodular lesions, white in color (arrow head).

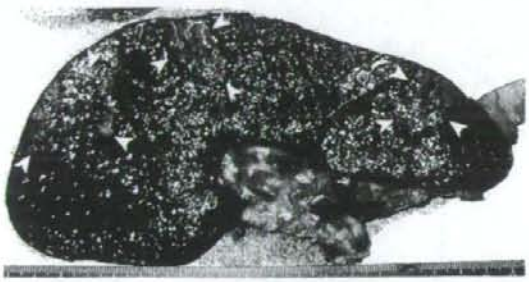
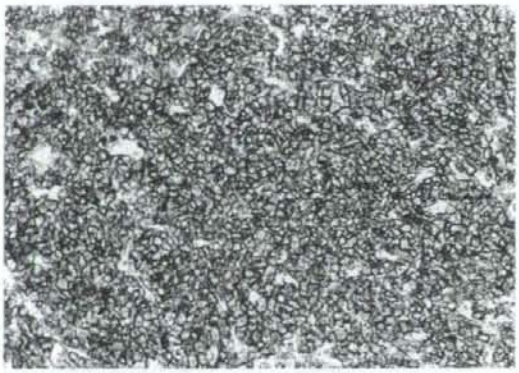


Fig. 4 The tumor was characterised by micronodular infiltration of the spleen (HE stain ×12.5).

phoma（B cell type）と最終診断した．

術後経過：術翌日に左肺に胸水が出現し，胸腔ドレナージ術を施行し，1,200mlの排液を認めたが，胸水細胞診では異型細胞の出現はみられなかった．胸水の改善はないものの，全身状態は比較的安定していたため術後6日目からラミブジン100mgを内服開始となった．術後14日目頃より頸部および腋窩リンパ節の痛みを伴う腫脹および呼吸苦が出現した．また，白血球の異常高値も続いていることから，悪性リンパ腫の骨髄浸潤が考えられ術後24日目に血液内科緊急入院となった．入院直後に胸水穿刺を施行，異型リンパ球の出現を認めたことからSMZLの急性増悪を考え，家族

Fig. 5 The tumor cells were positive for CD20 (CD20 ×100).

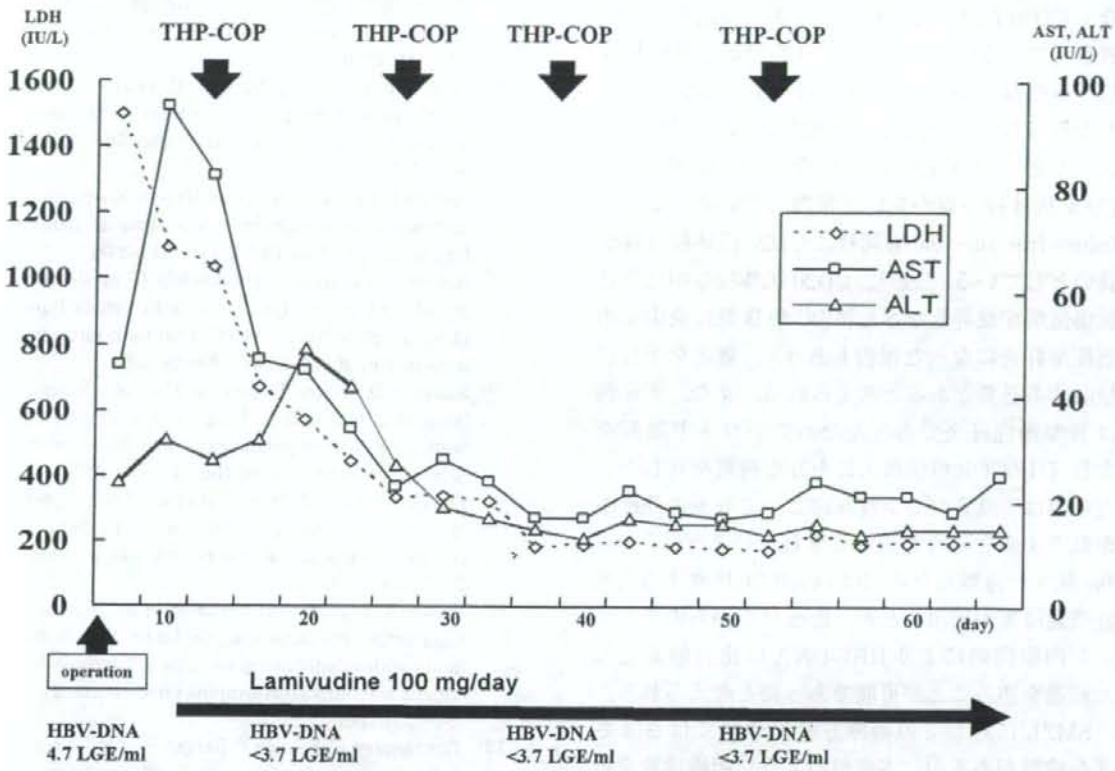


に対して十分なインフォームドコンセントを行い，同意のうえで入院当日よりTHP-COP療法(塩酸グラニセトロン3mg，塩酸ピラルビシン50mg，ビンクリスチン1.4mg，プレドニゾロン100mg)4コースを導入した．導入後，頸部リンパ節腫脹は改善傾向を示し，呼吸状態は安定した．また，初期には肝機能異常は認めたものの，術後早期からのラミブジン投与によりHBV-DNA 4.7LGE/ml（正常値3.7LGE/ml未満）であったのが3.7LGE/ml以下と正常範囲まで低下した（Fig. 6）．THP-COP療法導入後7日目に骨髄穿刺を施行したが，明らかな異型細胞の出現はみられなかった．THP-COP療法4コース終了時のPETでは術前指摘されていた全身のリンパ節の異常集積は指摘されなかった．手術後13か月現在，外来定期通院中である．

考　察

SMZLは，脾臓の辺縁帯B細胞由来の低悪性度Bリンパ腫とされ，我が国では全リンパ腫症例の1%にも満たないと報告されている[5]．また，医学中央雑誌で「悪性リンパ腫」,「Splenic marginal zone lymphoma」をキーワードとして1983年から2007年までについて検索したところ，自験例を含めて9例が報告されているのみで，まれな疾患群として報告されている．近年では，肝疾患と悪性リンパ腫との関係についての検討も報告されており，1994年Ferriら[6]の報告では，B-cell，NHLの50症例中17症例にHCV抗体陽性であったと

Fig. 6　Clinical course



している．SMZL についての HCV の関連については，Arcaini ら[7]は HCV の血清陽性率を伴う SMZL は 19% であったとし，Interferon-α との関連についても近年検討されている[8][9]．また，血清 HBs 陽性を伴う SMZL の報告はあるものの[10]，B 型慢性肝炎との関連については報告が少なく，両者についての因果関係については不明である．

Chacon ら[4]の報告では，主症状として脾腫や全身症状が約半数以上でみられているが，腹痛は 33% と頻度的には低く，脾臓や骨髄の精査で診断されることが多いとされている．また，86.6% の症例で Stage IV であり，無痛性の疾患群であるため早期に発見されることが少ないと考えられる．今回，我々が経験した症例についても，病期が進んできたため自覚症状が出現し発見となったと推察される．

SMZL に対しての治療方針は，以前までは組織診断を目的とした脾臓摘出術を第 1 選択とされてきた[11]．本症例は明らかな表在リンパ節の腫脹がみられず手術以外の組織採取が困難であったことから，組織診断のために手術を施行することも必要であるといえる．一方で，手術翌日から胸水や全身のリンパ節腫脹が出現し，術後 24 日目には異型リンパ球が出現するという急激な進展経過を辿っている．脾臓摘出後の影響についての報告については，Thieblemont ら[12]は脾臓摘出術後においても骨髄浸潤する可能性を示唆し，多変量解析においても脾臓摘出術は独立した予後因子とはなっていないと報告している．また，西森ら[13]の報告でも，術後早期に急激な腹膜播種を生じ死亡していることから，骨髄浸潤のみでなく全身性に進展する可能性があると言える．本症例における急激な進展経過は手術侵襲による影響があった可能性もあり，組織診断を主な目的とする脾臓摘出術においても術後経過に対しては十分な観察が必要である．

現在，SMZLに対しての治療法は手術のみではなくCD20抗体と化学療法を併用する治療法が検討されている[3][4]．Tsimberidouら[3]は，CD20抗体投与単独群は88%，CD20抗体と化学療法を併用した群は83%，化学療法単独群は55%で反応があったとし，3年生存率では95%，100%，55%と，CD20抗体投与群が良いと報告している．また，failure-free survivalも同様にCD20抗体投与群が良いとしている．しかし，CD20抗体投与中に急性腫瘍溶解症候群となった報告[14]やB型肝炎由来の劇症型肝炎になった報告もあり[15]，適応を十分に検討する必要があると考えられる．また，本症例はB型慢性肝炎であったためステロイド製剤を含むTHP-COP療法導入に十分な検討を有した．近年では，ラミブジン投与によって肝炎の発症率が低下するという報告がなされている[11][16]~[18]．今回，我々が経験した症例は，THP-COP療法導入後肝機能障害が出現したが，術後早期からのラミブジン内服開始によりHBV-DNAは比較的安定した経過を辿ることが可能であったと考えられる．

SMZLに対しての治療方針についてはさまざまな検討があるが，本症例のように組織診断を得るための手術を契機に急性増悪を来す可能性があるため，術後化学療法導入時期の検討を含めた集学的治療戦略が必要であると考える．

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A Case of Splenic Marginal Zone Lymphoma

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A 64-year-old seen for fever and lower left back pain and having a 4-year history of chronic hepatitis B was found in abdominal CT to have an intrasplenic tumor and FDG-PET showed abnormal uptake in the spleen. Since these findings suggested primary malignant lymphoma of the spleen, we conducted splenectomy with pancreatic tail resection for histological diagnosis and tumor reduction. Macroscopically, the spleen was 19×15cm, with multiple nodules. Histopathological examination of tumor cells showed medium-sized, abundant pale cytoplasm. The definitive diagnosed Primary malignant lymphoma of the spleen with splenic marginal zone lymphoma. Since generalized lymphadenopathy develops early after surgery, the patient was admitted in an emergency and THP-COP was started on the same day. Systemic symptoms subsequently were reduced, and FDG-PET showed no abnormal uptake in general lymph nodes. As of postoperative 13 months, the patient has followed regularly.

Key words：malignant lymphoma, splenic marginal zone lymphoma, HB virus

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