＜消化器科＞

①除菌無効胃 MALT リンパ腫の治療 （放射線療法を中心に）

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④胃と腸

⑤第 42 巻 第 8 号別冊 2007

主 題

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放射線療法を中心に

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要旨 胃および十二指腸 MALT リンパ腫の病態を *API2-MALT1* キメラ遺伝子の有無，*H. pylori* 感染の有無，*H. pylori* 除菌治療に対する反応性により 4 群(A，B，C，D)に分類した．*API2-MALT1* 陰性で *H. pylori* 陽性であり除菌治療に反応した群を Group A，反応しなかった群を Group B，*API2-MALT1* 陰性で *H. pylori* 陰性の群を Group C，*API2-MALT1* 陽性の群を Group D とした．除菌治療に反応しなかった Group B，C，D 3 群の臨床病期 I 期の 22 症例(2 例は化学療法併用)に対して放射線治療を実施し全例 CR となった．急性期有害反応は Grade 1 の消化器症状と Grade 1～2 の血液毒性のみであり，晩期有害反応は 1 例に Grade 2 の腎機能障害を認めた．前後対向 2 門照射を多門照射に変更することにより腎機能障害の発生は防ぐことができた．放射線治療は臨床病期 I 期の胃および十二指腸 MALT リンパ腫の治療として有効かつ安全な方法であると考えられる．

Key words **: MALT リンパ腫 *Helicobacter pylori* 除菌 放射線療法 *API2-MALT1*/t(11；18)(q21；q21)**

はじめに

Wotherspoon らは，1991 年に低悪性度の non-Hodgkin B-cell lymphoma である胃 MALT (mucosa-associated lymphoid tissue) リンパ腫に罹患した患者において高率に *Helicobacter pylori* (*H. pylori*) の感染がみられることを報告し[1]，さらに 1993 年には *H. pylori* の除菌の成功により胃 MALT リンパ腫が肉眼的にも組織学的にも退縮したことを報告した[2]．この Wotherspoon らの報告を受けて世界中で胃 MALT リンパ腫に対して *H. pylori* の除菌治療が実施され，その後の検討により *H. pylori* の除菌の成功のみにて約 60～80％の症例において完全寛解 (complete remission；CR) となることが明らかとなり，現在 *H. pylori* 除菌治療が胃 MALT リンパ腫に対する第一選択の治療法であることが広く認められるに至っている．

その一方で，胃 MALT リンパ腫の中にも *H. pylori* の除菌の成功によっても CR とならない症例が存在することが知られていたが，その病因や治療効果の検討によりそれらの特徴がいくつか明らかになってきた．これらの症例においては，従来手術療法が主流であったが，近年欧米では QOL を考慮した非外科的治療としての化学療法・放射線治療 (radiotherapy；RT) の良好な治療成績が報告されており，特に局所治療としての RT に注目が集まっている．

われわれは，本稿において *H. pylori* 除菌治療が無効であった胃 MALT リンパ腫の特徴を明らかにするとともに，これらの症例に対する非外科的治療である RT の有用性を治療成績および有害反応から retrospective に検討し報告する．

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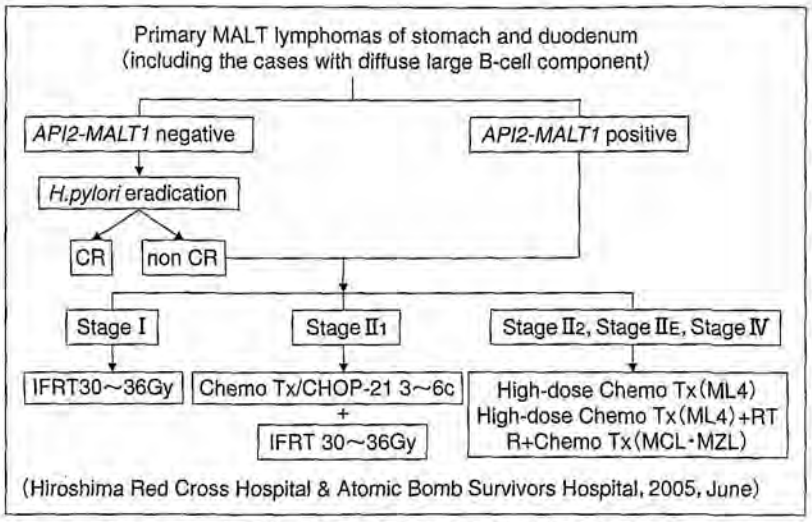


Fig. 1　胃・十二指腸 MALT リンパ腫の非手術治療 protocol.

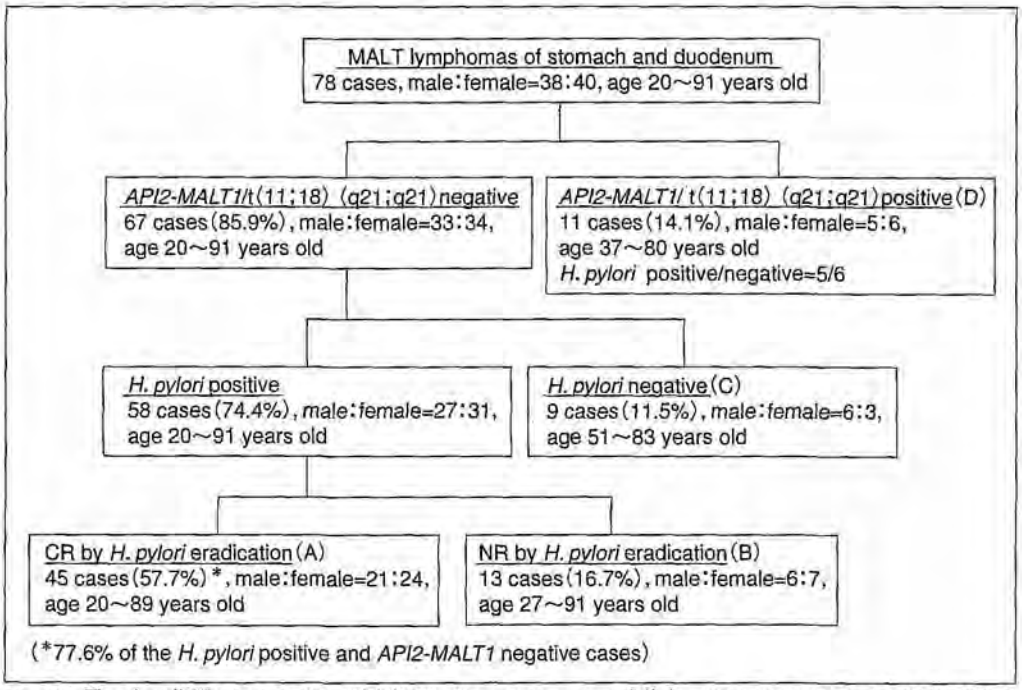


Fig. 2　胃・十二指腸 MALT リンパ腫症例において *H. pylori* 感染と *API2-MALT1* キメラ遺伝子発現の有無より検討した *H. pylori* 除菌治療の効果.

対象と方法

1996 年 4 月～2006 年 5 月に広島赤十字・原爆病院第 6 内科(42 症例)と広島大学病院第 1 内科(36 症例)を受診した胃あるいは十二指腸に原発病巣を有する MALT リンパ腫 78 症例に対して実施した治療 protocol(**Fig. 1**)と，これらの症例に対する *H. pylori* 除菌治療の成績(**Fig. 2**)を示す.

全症例に対してまず *H. pylori* の除菌治療を実施した．*H. pylori* 陰性症例と *API2-MALT1* キメラ遺伝子(*API2-MALT1*)陽性症例は全例において腫瘍の消退はみられなかった．*API2-MALT1* 陰性でありかつ *H. pylori* 陽性であった症例 58 例では，*H. pylori* 除菌治療は全例において成功し 45 例が CR となり 13 例は改善がみられなかった．*H. pylori* 除菌治療成功後 CR となった 45 例を Group A，改善がみられなかった 13 例を Group B，さらに *API2-MALT1* 陰性でありかつ

Table 1 The clinical characteristics affecting response to treatment of primary MALT lymphomas of stomach and duodenum

	Group A (n : 45)	Group B (n : 13)	Group C (n : 9)	Group D (n : 11)	p value					
					A vs. B	A vs. C	A vs. D	B vs. C	B vs. D	C vs. D
Hp infection										
Positive	45 (100)	13 (100)	0 (0)	4 (36.4)	NS	<0.0001	<0.0001	<0.0001	0.0021	0.0195
Negative	0 (0)	0 (0)	9 (100)	7 (63.6)						
Endoscopic appearances										
Superficial	39 (86.7)	5 (38.5)	6 (66.7)	9 (81.8)	<0.0001	0.0607	0.0034	0.3156	0.0411	0.2481
Ulcerative	6 (13.3)	3 (23.0)	2 (22.2)	0 (0)						
Protruding	0 (0)	5 (38.5)	1 (11.1)	1 (9.1)						
Enlarged-folds	0 (0)	0 (0)	0 (0)	1 (9.1)						
Location of lesions										
Stomach	44 (97.8)	9 (69.2)	6 (66.7)	10 (90.9)	0.0037	0.002	0.2711	0.8989	0.3271	0.2431
Stomach and duodenum	1 (2.2)	2 (15.4)	1 (11.1)	1 (9.1)						
Duodenum	0 (0)	2 (15.4)	2 (22.2)	0 (0)						
Infiltrated layers										
M	44 (97.8)	4 (30.8)	5 (55.6)	7 (63.6)	<0.0001	<0.0001	0.0004	0.0813	0.0301	0.7136
SM	1 (2.2)	9 (69.2)	4 (44.4)	4 (36.4)						
Nodal involvement										
Positive	0 (0)	5 (38.5)	0 (0)	2 (18.2)	<0.0001	NS	0.0036	0.0343	0.2761	0.1775
Negative	45 (100)	8 (61.5)	9 (100)	9 (81.8)						
Clinical stage (Lugano)										
I	45 (100)	8 (61.5)	9 (100)	7 (63.6)	<0.0001	NS	<0.0001	0.0505	0.8358	0.064
II_1	0 (0)	1 (7.7)	0 (0)	1 (9.1)						
IV	0 (0)	4 (30.8)	0 (0)	3 (27.3)						
Diffuse large B-cell component										
Negative	42 (93.3)	12 (92.3)	9 (100)	11 (100)	0.8977	0.4254	0.3787	0.3944	0.3474	NS
Positive	3 (6.7)	1 (7.7)	0 (0)	0 (0)						
Prognosis										
NED	44 (97.8)	12 (92.3)	9 (100)	9 (81.8)	0.1509	0.6517	0.0341	0.3944	0.5297	0.2518
AWD	0 (0)	0 (0)	0 (0)	0 (0)						
DOC	1 (2.2)	0 (0)	0 (0)	0 (0)						
TRD	0 (0)	0 (0)	0 (0)	1 (9.1)						
DOD	0 (0)	1 (7.7)	0 (0)	1 (9.1)						

Group A ; CR to *Hp* eradication (*Hp* positive) and *API2-MALT1* negative, Group B : not CR to *Hp* eradication (*Hp* positive) and *API2-MALT1* negative, Group C : not CR to *Hp* eradication (*Hp* negative) and *API2-MALT1* negative, Group D : *API2-MALT1* positive. NED ; no evidence of disease, AWD ; alive with disease, DOC ; death of unrelated causes, TRD ; treatment related death, DOD ; death of disease.

Table 2 Outcomes of radiotherapy in gastric and duodenal MALT lymphoma patients in clinical stage I

Case	S/A	Group	*Hp*	*API2-MALT1*	Primary site of disease	Endoscopical appearance	Depth of invasion (EUS)	Treatment	Outcome	Follow-up period (Months)	Radiotherapy (IFRT)		Toxicity	
											Dose (Gy) / Fraction/ Day	Field arrange-ment	Acute	Late
1	F /27	B	(+)	(−)	Stomach	Ulcerative	M	*Hp* erad/RT	NED	45	30/20/28	4-field	nausea (G1)	
2	F /65	B	(+)	(−)	Stomach, Duodenum	Superficial	SM	*Hp* erad/ ChemoTx/RT	NED (DOD)	85 (60) *	36/20/29	2-field		
3	M/58	B	(+)	(−)	Duodenum	Superficial	M	*Hp* erad/RT	NED	125	36/20/31	2-field		nephropathy (5y : G2, 10y : G3)
4	M/49	B	(+)	(−)	Stomach	Protruding	SM	*Hp* erad/RT	NED	49	39.6/22/30	4-field	abnormal liver function (G1)	
5	M/47	B	(+)	(−)	Stomach	Protruding	SM	*Hp* erad/RT	NED	46	34/17/23	3-field	nausea (G1)	
6	F /51	B	(+)	(−)	Duodenum	Superficial	M	*Hp* erad/RT	NED	37	36/18/25	4-field	nausea (G1)	
7	F /82	B	(+)	(−)	Stomach	Protruding	SM	*Hp* erad/RT	NED	27	30/15/21	4-field	leucopenia (G1)	
8	M/70	B	(+)	(−)	Stomach	Superficial	SM	*Hp* erad/RT	NED	74	44.8/28/39	4-field		
9	M/61	C	(−)	(−)	Stomach	Superficial	M	*Hp* erad/RT	NED	44	30/20/28	4-field		
10	M/83	C	(−)	(−)	Stomach	Protruding	SM	*Hp* erad/RT	NED	31	39.6/22/34	4-field		
11	F /74	C	(−)	(−)	Duodenum	Superficial	M	*Hp* erad/RT	NED	33	36/18/24	3-field	nausea (G1)	
12	M/53	C	(−)	(−)	Stomach	Ulcerative	SM	*Hp* erad/RT	NED	19	34/17/23	4-field	nausea (G1)	
13	M/59	C	(−)	(−)	Stomach	Superficial	SM	*Hp* erad/RT	NED	7	36/18/24	4-field		
14	M/72	C	(−)	(−)	Stomach	Superficial	M	*Hp* erad/RT	NED	5	34/17/23	4-field		
15	F /75	C	(−)	(−)	Stomach	Superficial	M	*Hp* erad/ ChemoTx/RT	NED	58	34/17/24	4-field	leucopenia (G1), thrombopenia (G1)	
16	M/62	C	(−)	(−)	Duodenum	Superficial	M	*Hp* erad/RT	NED	32	36/18/26	4-field	nausea (G1)	
17	F /42	D	(−)	(+)	Stomach	Superficial	M	*Hp* erad/RT	NED	65	30/20/28	4-field	abdominal discomfort (G1)	
18	M/51	D	(+)	(+)	Stomach	Superficial	M	*Hp* erad/RT	NED	64	30/20/28	4-field		
19	F /72	D	(−)	(+)	Stomach	Superficial	M	*Hp* erad/RT	NED	59	30/20/28	4-field	leucopenia (G2)	
20	F /80	D	(+)	(+)	Stomach	Superficial	M	*Hp* erad/RT	NED	42	30/20/28	4-field	abnormal liver function (G1)	
21	F /80	D	(−)	(+)	Stomach	Superficial	SM	*Hp* erad/RT	NED	79	34/17/25	3-field	nausea (G1), leucopenia (G1)	
22	M/49	D	(−)	(+)	Stomach	Superficial	M	*Hp* erad/RT	NED	102	34/17/24	3-field		

Clinical stage of disease according to Lugano classification. S/A ; sex and age, F ; female, M ; male. *Hp* ; *Helicobacter pylori*. M ; restricted to the mucosa, SM ; significant submucosal invasion. erad ; eradication, Chemo Tx ; chemotherapy, RT ; radiotherapy. NED ; no evidence of disease. DOD ; death of disease. * ; 60 か月にて DLBC にて再発後原病死.

H. pylori 陰性であった症例 9 例を Group C, *API2-MALT1* 陽性症例 11 例を Group D とし各群の背景因子を比較検討した(Fig. 2, **Table 1**).

結　果

1. Group A～D の背景因子の比較

Group A はすべての症例が Lugano classification clinical stage(CS)I であり，深達度は，44 例(97.8%)において M にとどまっていた．SM に浸潤していた 1 例の肉眼型は superficial type であった．3 例(6.7%)において diffuse large B-cell lymphoma(DLBCL)の混在を認めるが，いずれも除菌の成功とともに CR となっており，DLBCL の存在は *H. pylori* の除菌による MALT リンパ腫の消退を妨げる要因とは言えなかった．

Group B の 13 例においては，CS II_1 の症例が 1 例(7.7%)，IV の症例が 4 例(30.8%)認められ，リンパ節浸潤を伴う症例も 5 例(38.5%)を占めていた．病変の深達度は SM に浸潤している症例が 9 例(69.2%)と M にとどまるものを大きく上回っており，頸部や腋下リンパ節や他臓器に浸潤のみられる臨床病期の進んだ症例が多く認められた．肉眼型は protruding type が 5 例(38.5%)にみられ，その全例において SM 浸潤を伴っていた．

Group C は 9 例全例が CS I の症例であり，深達度は 4 例(44.4%)において SM への浸潤がみられた．病変占拠部位は十二指腸に病変を有する症例が 3 例(33.3%)を占めており Group A と比較して高率であった．

Group D の 11 例においては，*H. pylori* 感染の有無はその治療効果に影響を与えていなかった．CS I の症例が 7 例(63.6%)，II_1 の症例が 1 例(9.1%)，IV の症例が 3 例(27.3%)を占めており，これまでの報告と同様に肺などの他臓器へ高率に浸潤する傾向が認められた．肉眼型は superficial type が 9 例(81.8%)と多くを占めており，protruding type を 1 例，enlarged-folds type を 1 例に認めた．SM に浸潤していた症例は 4 例(36.4%)でリンパ節浸潤を伴う症例は 2 例(18.2%)であった．CS I の SM 浸潤を有する protruding type の症例は，cyclophosphamide 経口単剤化学療法により治療に伴う肝機能障害にて死亡した．

2. RT の治療効果・転帰・有害反応

H. pylori 除菌治療が無効であった CS I 全 24 症例中 RT を実施した 22 症例の治療効果と転帰と有害反応を **Table 2** に示す．2 例において化学療法が併用されていた．1 例は CHOP×3 cycles と RT の併用にて加療を行った初期の症例(Case 2)であり，1 例は他院にて化学療法(CHOP×6 cycles)を施行され効果がなかった症例(Case 15)であった．20 例は RT 単独で治療された．RT は 10MVX 線を用い，1 回線量 1.5～2.0 Gy で行った．病変の存在する領域を照射範囲とする involved field で，前後対向 2 門照射，3 門照射あるいは 4 門照射を用いて総線量 30～44.8 Gy(中央値 34 Gy)を照射した．放射線(involved field radiotherapy ; IFRT)治療期間は 21～39 日(中央値 27 日)，観察期間は 5～125 か月(中央値 45.5 か月)であった．

RT による急性期有害反応の評価は JCOG (Japan Clinical Oncology Group)の副作用判定基準[3]に従い，RT による晩期有害反応の評価は Toxicity Criteria of RTOG (The Radiation Therapy Oncology Group) and EORTC (The European Organization for Research and Treatment of Cancer)[4]に従った．

RT が実施された 22 例全例において CR となった．胃と十二指腸に病変を有する 1 例(Case 2)においては 60 か月後に十二指腸下行脚の小発赤を呈する DLBCL にて再発した．内視鏡検査・CT scan(頸部～骨盤)・骨髄検査では病変は確認できず，85 か月後に DLBCL の広範な骨髄浸潤を来し死亡した．RT の効果は病変の肉眼型・深達度・病変占拠部位によって影響を受けてはいなかった．CHOP による化学療法により病変の改善がみられなかった 1 例(Case 15)においても RT により CR となった．

急性有害反応は，Grade 3 以上の反応はみられなかった．血液毒性は白血球減少 4 例(Grade 1 : 3 例，Grade 2 : 1 例)，血小板減少 1 例(Grade 1 : 1 例)計 5 例であり，消化器症状は悪心 7 例(Grade 1 : 7 例)，心窩部不快感 1 例(Grade 1 : 1

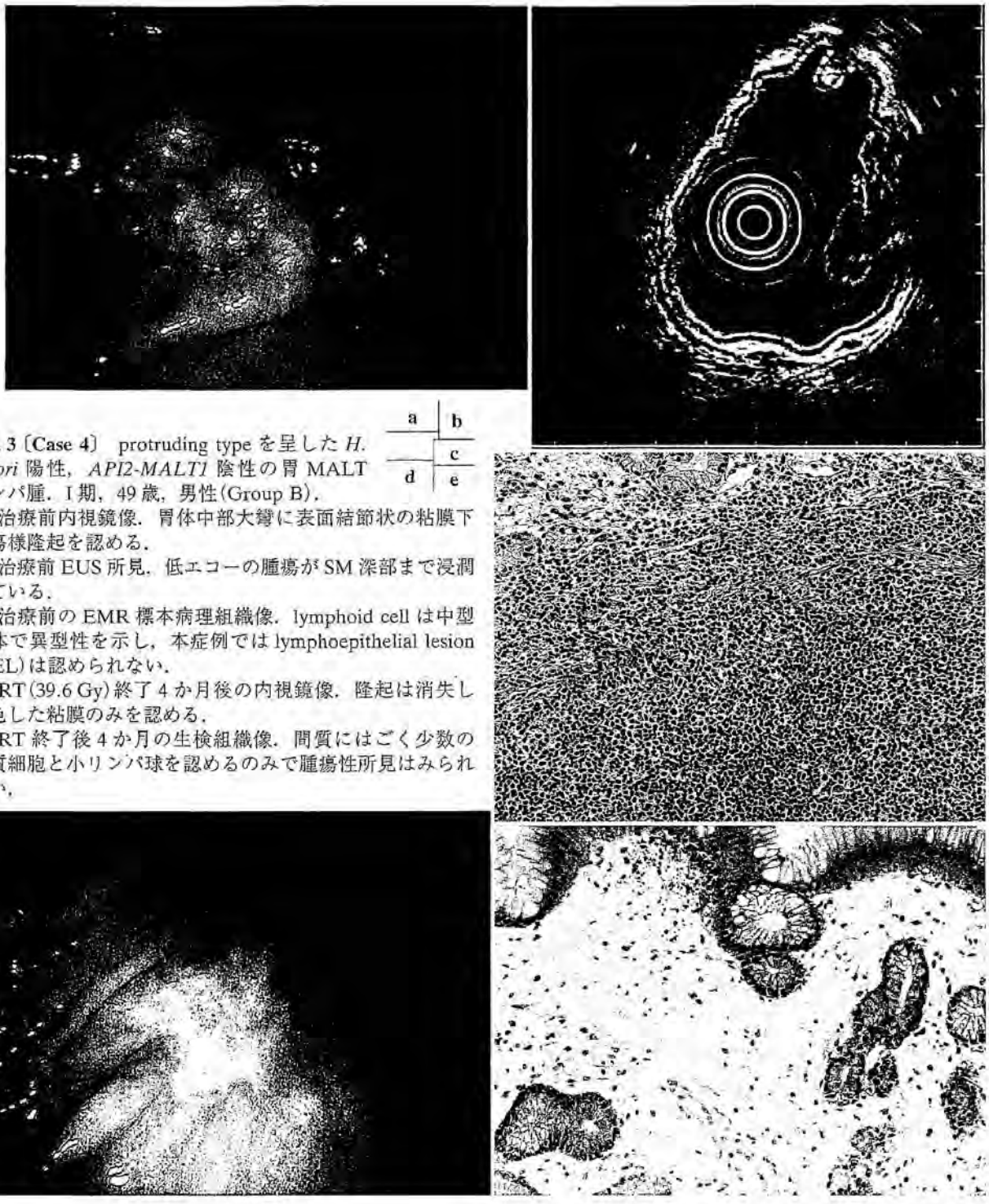


Fig. 3〔Case 4〕 protruding type を呈した *H. pylori* 陽性，*API2-MALT1* 陰性の胃 MALT リンパ腫．I 期，49 歳，男性(Group B)．
a 治療前内視鏡像．胃体中部大彎に表面結節状の粘膜下腫瘍様隆起を認める．
b 治療前 EUS 所見．低エコーの腫瘍が SM 深部まで浸潤している．
c 治療前の EMR 標本病理組織像．lymphoid cell は中型主体で異型性を示し，本症例では lymphoepithelial lesion (LEL)は認められない．
d RT(39.6 Gy)終了 4 か月後の内視鏡像．隆起は消失し褪色した粘膜のみを認める．
e RT 終了後 4 か月の生検組織像．間質にはごく少数の形質細胞と小リンパ球を認めるのみで腫瘍性所見はみられない．

例)，肝機能障害 2 例(Grade 1：2 例)の計 10 例であった．RT による晩期有害反応は 5 年後に Grade 2 の腎機能低下を 1 例に認めた．この腎機能障害は 10 年後には Grade 3 となっており現在引き続き経過観察中である．

3. 症例

Group B，C，D から RT により CR となった症例を各 1 例呈示する．

Group B：Group B の範疇に属する肉眼型が protruding type を呈する症例(Case 4)の RT 前後の内視鏡所見と治療前の EUS 所見を **Fig. 3** に示す．RT により CR となりその後は再発・再燃を認めていない．

Group C：**Fig. 4** は superficial type の肉眼型を呈する *H. pylori* 陰性でかつ *API2-MALT1* 陰性の Group C に分類される症例(Case 13)である．

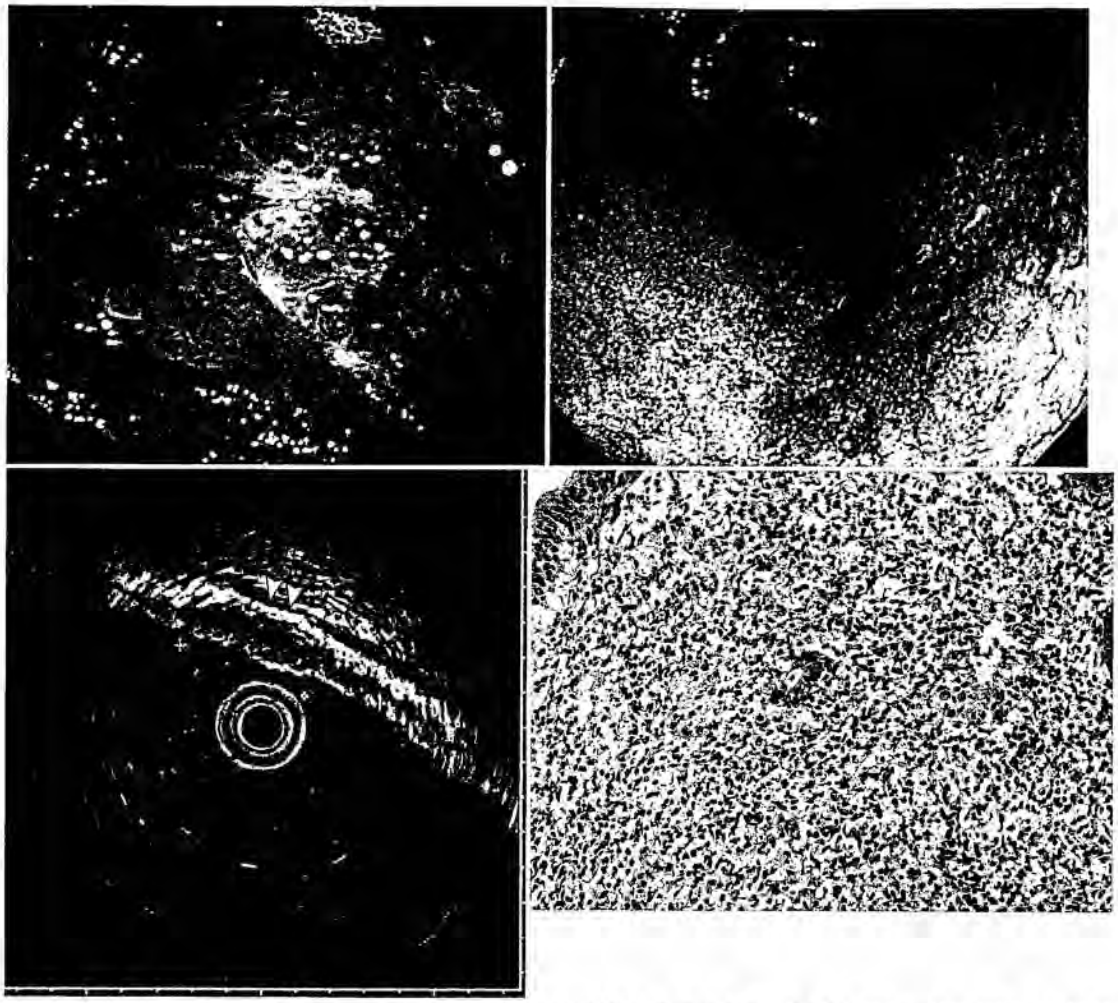


Fig. 4〔Case 13〕 superficial type を呈する病変を噴門部大彎，体下部から胃角部大彎，前庭部大彎に認める *H. pylori* 陰性，*API2-MALT1* 陰性の胃 MALT リンパ腫，I 期，59 歳，男性 (Group C)．
a, b 治療前内視鏡所見．噴門部大彎通常内視鏡像(a)，前庭部大彎インジゴカルミン撒布像(b)．
c 治療前 EUS 所見．矢印の部分に低エコーの腫瘍病変が認められ SM 深部に浸潤している．
d 治療前の生検組織像．中型の異型性を示す lymphoid cell がびまん性，密に増生し，既存の腺管上皮に破壊性に浸潤する LEL を認める．

H. pylori 除菌治療を行ったが病変の退縮は認めず，3 か月後には前庭部の病変の増大を認めた．その後の RT により CR となっている．

Group D：**Fig. 5** は，*API2-MALT1* 陽性で *H. pylori* 陰性の Group D に分類される症例(Case 21)である．肉眼型は superficial type を呈し除菌治療に反応せず，その後の RT にて CR となり再発・再燃を認めていない．

考　案

Southwest Oncology Group (SWOG) が，限局期高悪性度リンパ腫に対する CHOP×3 cycles＋IFRT 45～50 Gy が CHOP×8 cycles と比較し，非再燃生存率・有害反応ともに優れていると報告してから，RT は発生臓器を問わず悪性リンパ腫の local treatment として再認識されている[5]．欧米では，胃悪性リンパ腫においても先行化学療法＋RT が試みられており，現在，病理組織学的悪性度，臨床病期および International Prognostic Index (IPI) を考慮して治療方法が選択されるようになっている．

MALT リンパ腫においては，German Multicenter Study Group は，prospective nonrandomized study にて，切除または非切除で化学療

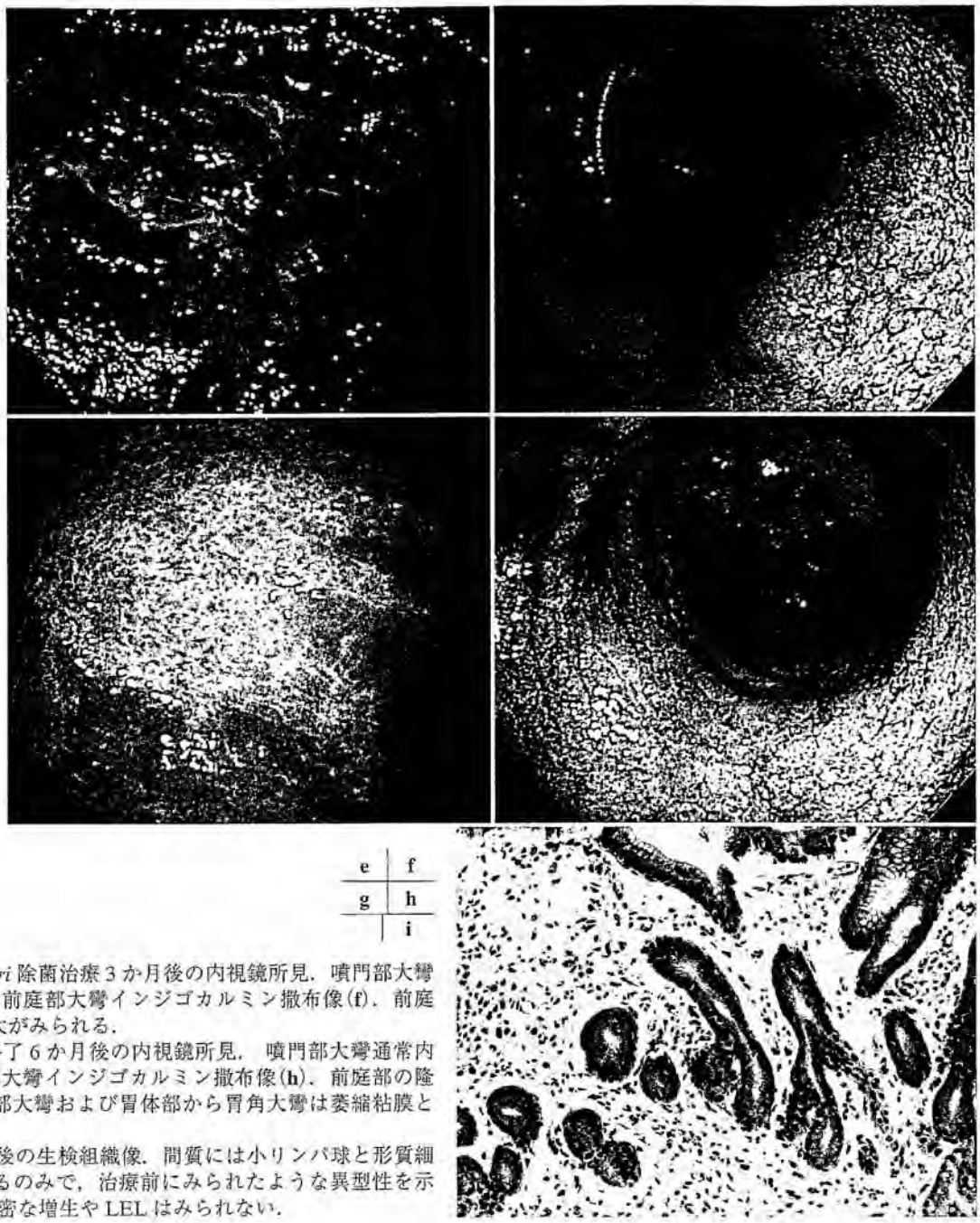
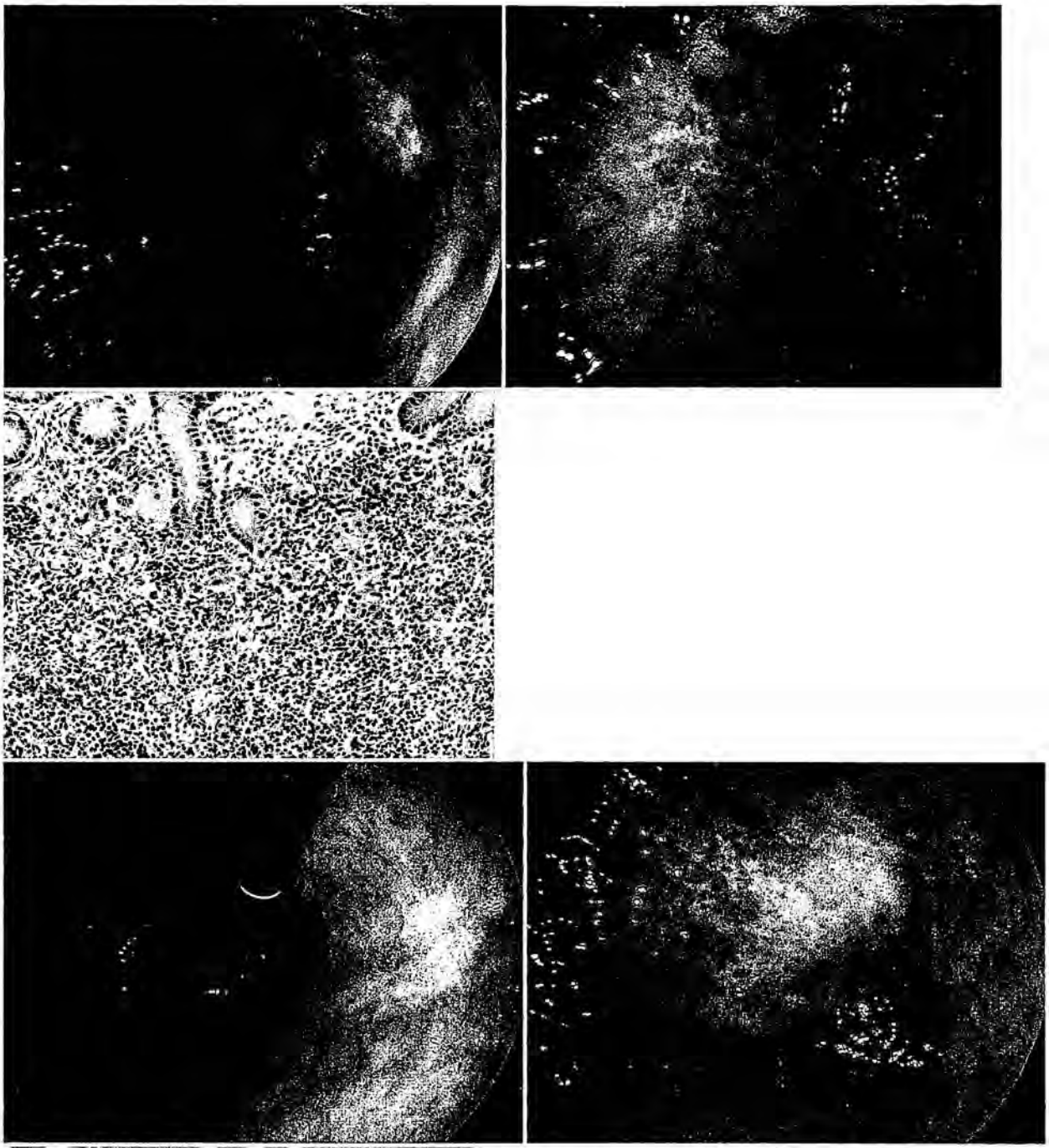


Fig. 4 e, f *H. pylori* 除菌治療3か月後の内視鏡所見．噴門部大彎通常内視鏡像(**e**)，前庭部大彎インジゴカルミン撒布像(**f**)．前庭部の腫瘍病変の増大がみられる．
g, h RT(36 Gy)終了6か月後の内視鏡所見．噴門部大彎通常内視鏡像(**g**)，前庭部大彎インジゴカルミン撒布像(**h**)．前庭部の隆起は消退し，噴門部大彎および胃体部から胃角大彎は萎縮粘膜となっている．
i RT終了6か月後の生検組織像．間質には小リンパ球と形質細胞の軽度浸潤をみるのみで，治療前にみられたような異型性を示すlymphoid cellの密な増生やLELはみられない．

法・RTにて治療された胃悪性リンパ腫における切除群と非切除群間の治療成績を比較検討している[6]．その結果によると，低悪性度リンパ腫の切除群I～II期，非切除群I期に対してはEFRT (extended field radiotherapy)40 Gy単独，非切除群II期ではCOP療法×6 cycles＋EFRT 40 Gyを行い，限局期胃MALTリンパ腫では切除群・非切除群間の生存率に有意差は認められず，外科的治療は不要としており，さらに治療による有害反応の発現頻度も低かったことを報告している．また，限局期胃MALTリンパ腫に対しては，*H. pylori*陽性症例で除菌治療に反応しなかった症例や*H. pylori*陰性症例に対してIFRT 30 Gyが有効であるとの報告もある[7]．

わが国でも1997年に悪性リンパ腫治療研究会が非切除治療された胃原発non-Hodgkin lymphoma 12例を検討し，治療成績(5年非再燃生存率83.3％)およびQOLの点から胃切除は必須とは



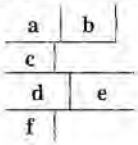


Fig. 5〔Case 21〕 superficial type を呈する病変を胃体中部小彎と胃角前壁に認める．*H. pylori* 陰性，*API2-MALT1* 陽性の胃 MALT リンパ腫．I 期，80 歳，女性(Group D)．

a, b 治療前内視鏡所見．病変部を矢印で示す．胃体中部小彎の病変は褪色した陥凹を呈する(**a**)．胃角前壁の病変はびらんを伴う浅い陥凹を呈する(**b**)．

c 治療前の生検組織像．中型の異型性を示す lymphoid cell が既存の組織を破壊しながらびまん性に密に増生する像を認める．

d, e RT(34 Gy)終了 4 か月後の内視鏡所見．胃体中部小彎の内視鏡像(**d**)，胃角前壁の内視鏡像(**e**)．いずれも萎縮粘膜となり改善している．

f RT 終了 4 か月後の生検組織像．間質には小リンパ球と形質細胞の軽度浸潤をみるのみで，治療前にみられたような異型性を示す lymphoid cell の密な増生はみられない．

考えられないと報告している[8]．その後，欧米での胃悪性リンパ腫に対するRTの良好な治療成績を受けて，1999年12月から厚生省がん研究助成金による「原発性胃悪性リンパ腫に対する非外科治療の適応と有効性の評価に関する研究」班の多施設共同研究による症例登録が開始され，その中間解析結果報告から，MALTリンパ腫症例に対する二次治療としてのRTの効果は短期的には従来の外科手術（胃癌に準じたD2郭清を伴う胃全摘術）と比較し劣るものではないことが報告されている[9]．最終解析の結果とさらなる長期的なデータの蓄積による非外科的治療の位置づけが明確にされることが待たれるところである．

胃悪性リンパ腫に対するRTの主要な急性有害反応は血液毒性および消化器毒性である．われわれの治療例でも22例中5例（22.7％）において血液毒性を，10例（45.5％）において消化器症状を認めたが，いずれもGrade 1～2と軽度であり全例安全にRTを完遂することができた．

一方，胃悪性リンパ腫のRTにおいて問題となる晩期有害反応の1つとして腎機能障害がある[10)11)]．CS Iの胃悪性リンパ腫のRTとして，初期には前後対向2門照射を用いたIFRTが実施されていたことが多く，照射体積内に左腎あるいは症例によっては右腎も含まれるため，晩期有害反応として腎機能障害を念頭に置いて治療を計画する必要があった．Maorらは左側腎体積の1/3以上に少なくとも24 Gyが照射された胃リンパ腫の27例を検討し，両側腎が照射された1例（1/2 bilateral kidney，35 Gy）においてGrade 2の腎機能低下を認めたものの，左側腎の一部あるいは全部が照射範囲に含まれていても重篤な高血圧や腎不全に陥ることはないと報告している[10)]．われわれの施設では初期にRTを実施した十二指腸MALTリンパ腫の1例において腎機能低下を経験している．両側腎体積の50％程度が照射体積に含まれており前後対向2門照射により36 Gyが照射され，5年後にGrade 2であったが，10年後にはGrade 3となっており今後さらに慎重な経過観察が必要と考えられる．このような症例の存在は，今後可能な限り晩期有害反応を回避するためには腎の照射体積を少なくする工夫が必要であることを示している．本症例以後われわれの施設では多門照射を原則として腎を可能な限り照射体積からはずすようにしており，以後腎障害の発生は認めていない．また，われわれは胃・十二指腸原発悪性リンパ腫の全症例にEUSを実施し，固有筋層に深く浸潤するbulky massを認める症例ではRTにより穿孔を生ずる危険性があるので，外科的切除を実施した後に化学療法を行うことにしている．これまで，胃に対するRTの実施による上部消化管出血や胃穿孔などの重篤な有害事象やradiation gastritisは発生していない．

このように装置の進歩や照射方法の工夫により，胃・十二指腸MALTリンパ腫に対してRTは高齢者にも安心して実施できる安全な治療法となっている．また，CS Iの胃MALTリンパ腫に対してCHOPによる化学療法を他院にて実施され再発した症例（Case 15）があることや，CS II_1 の *API2-MALT1* 陽性胃MALTリンパ腫に対してCHOPによる化学療法を実施され無効であったGroup Dの症例がRTにてCRとなっていることより，限局した領域の病変に対するRTの治療効果はCHOPによる化学療法を凌ぐと考えられる．したがって，*H. pylori* の除菌によりCRとならないことが既に報告されているt（11；18）（q21；q21）遺伝子転座を有する胃MALTリンパ腫[12)]や，除菌の成功にもかかわらずCRとなる可能性が乏しい粘膜下層深部を越えて浸潤している胃MALTリンパ腫症例[13)]をはじめとする，Group B，C，Dに分類される症例の中で，CS Iの症例に対する第一選択の治療としてはRTが望ましいと考えられる．

今後は，“RTの晩期毒性”について，現時点ではRTとの関連性が不明である症状も含めてさらなる長期の経過観察にて検討する必要があると考えられる．さらに，欧米に比べてまだ少数であるRTについて多くの症例を集積し，わが国におけるその効果と安全性をより詳細に検討していかなければならないと考える．

今回の検討は，広島赤十字・原爆病院，広島大学大学院分子病態制御内科学，岡山大学大学院病理・病態学の共同研究である．関係諸先生および貴重な症例をご紹介いただいた先生方に深謝いたします．

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Summary

Effect of Radiotherapy on MALT Lymphomas not Responding to *H. pylori* Eradication

Akira Tari [1], *Kouzou Kashiwado* [2], *Hideki Asaoku* [3], *Hiroshi Tani* [1], *Megumu Fujihara* [4], *Yasuhiko Kitadai* [5], *Hiroshi Masuda*, *Tadashi Yoshino* [6]

Gastric and duodenal MALT lymphomas were classified into 4 groups (Group A, B, C, and D) by the existence of *API2-MALT1* chimeric transcript, *H. pylori* infection and its response to *H. pylori* eradication. Cases in group A were *API2-MALT1* negative, *H. pylori* positive which responded to *H. pylori* eradication. Non responders were classified into group B. Cases in group C were *API2-MALT1* negative and *H. pylori* negative. Group D was *API2-MALT1* positive. Twenty two cases of clinical stage I in group B, C and D which did not respond to eradication (2 cases also had chemotherapy) received radiotherapy and all of them achieved complete response. Acute toxicities were only grade 1 digestive symptoms and grade 1～2 hematologic toxicities and late toxicity was seen in only one case as grade 2 nephropathy. Nephropathy was avoided by the multi-field technique instead of the 2-field technique. Radiotherapy can be an effective and safe treatment for gastric and duodenal MALT lymphomas in clinical stage I.

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＜消化器科＞

①Primary follicular lymphoma of the gastrointestinal tract: a retrospective case series.

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④Endoscopy

⑤2007 Dec7

Primary follicular lymphoma of the gastrointestinal tract: a retrospective case series

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Institutions Institutions are listed at the end of article.

submitted 14 August 2007
accepted after revision 7 November 2007

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DOI 10.1055/s-2007-995365
Published online 7 December 2007
Endoscopy 2008; 40: 343–346 © Georg Thieme Verlag KG Stuttgart · New York
ISSN 0013-726X

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Little is known about the clinicopathologic characteristics of primary follicular lymphoma of the gastrointestinal tract (PFLGI). We report our experience with double-balloon enteroscopy (DBE) in patients with PFLGI. Between January 2001 and December 2006, thirteen patients with PFLGI (nine men and four women; mean age, 53.4 years) visited Hiroshima University Hospital. We performed DBE in 11 PFLGI patients to examine the entire small bowel. DBE showed new lesions in the third portion of the duodenum, jejunum, or ileum in nine of these 11 patients (81.8%). The endoscopic finding was nodularity of the involved mucosal surface (small whitish polyps or whitish granules). Seven patients were treated with rituximab plus CHOP chemotherapy (R-CHOP). A complete response was obtained in all patients who received R-CHOP, and no recurrence was seen (mean follow-up period, 22.5 months).

Introduction

The gastrointestinal tract is the most common extranodal site of origin for non-Hodgkin's lymphoma (NHL), accounting for approximately 40% of all extranodal primary NHLs [1]. Mucosa-associated lymphoid tissue-type lymphoma is the most frequent low-grade NHL encountered in the gastrointestinal tract. Primary follicular lymphoma of the gastrointestinal tract (PFLGI) is rare. It represents only about 1.0%–3.6% of all gastrointestinal tract lymphomas [2–4].

Endoscopy now permits direct examination of the esophagus, stomach, proximal small intestine, and colon. However, much of the distal small intestine is located far from both the mouth and anus, rendering it nearly inaccessible endoscopically and making lesions in this region difficult to diagnose. The recent introduction of wireless capsule endoscopy permits painless examination of the entire small intestine, but no capability exists for air insufflation, rinsing luminal surfaces, or biopsy [5–7]. Recently, Yamamoto et al. [8,9] established a new double-balloon insertion method for enteroscopy (DBE), which enables endoscopic inspection of the entire small bowel and some interventions. Therefore, we performed DBE in PFLGI patients to determine the distribution of the initial sites and endoscopic features of PFLGI.

Case series

Twelve of 13 patients had no presenting clinical symptom. They had undergone an upper gastrointestinal endoscopic examination as part of a health checkup, and multiple small whitish polyps or whitish granules were seen in the duodenum (**Fig. 1a, b**). One patient (patient 6) was referred to our hospital because of abdominal discomfort. This patient also underwent upper gastrointestinal endoscopic examination, which revealed small whitish polyps in the duodenum. Biopsy specimens from lesions of the duodenum showed well-circumscribed follicles composed of a monotonous population of predominantly small cleaved cells that were positive for CD20, CD10, and BCL-2 but negative for CD5. The histologic grade in all cases was grade 1, according to the World Health Organization classification system [10]. Ten of the 13 patients had stage I disease, and three patients had stage IV disease according to the criteria of the Lugano International Workshop [11]. These results are shown in **Table 1**.

In all 13 cases, the involved site at initial presentation was the duodenum, especially around the ampulla of Vater. These lesions were detected upon upper gastrointestinal endoscopic examination. Subsequent lower gastrointestinal endoscopy including examination of the terminal ileum was performed in all patients, and this re-

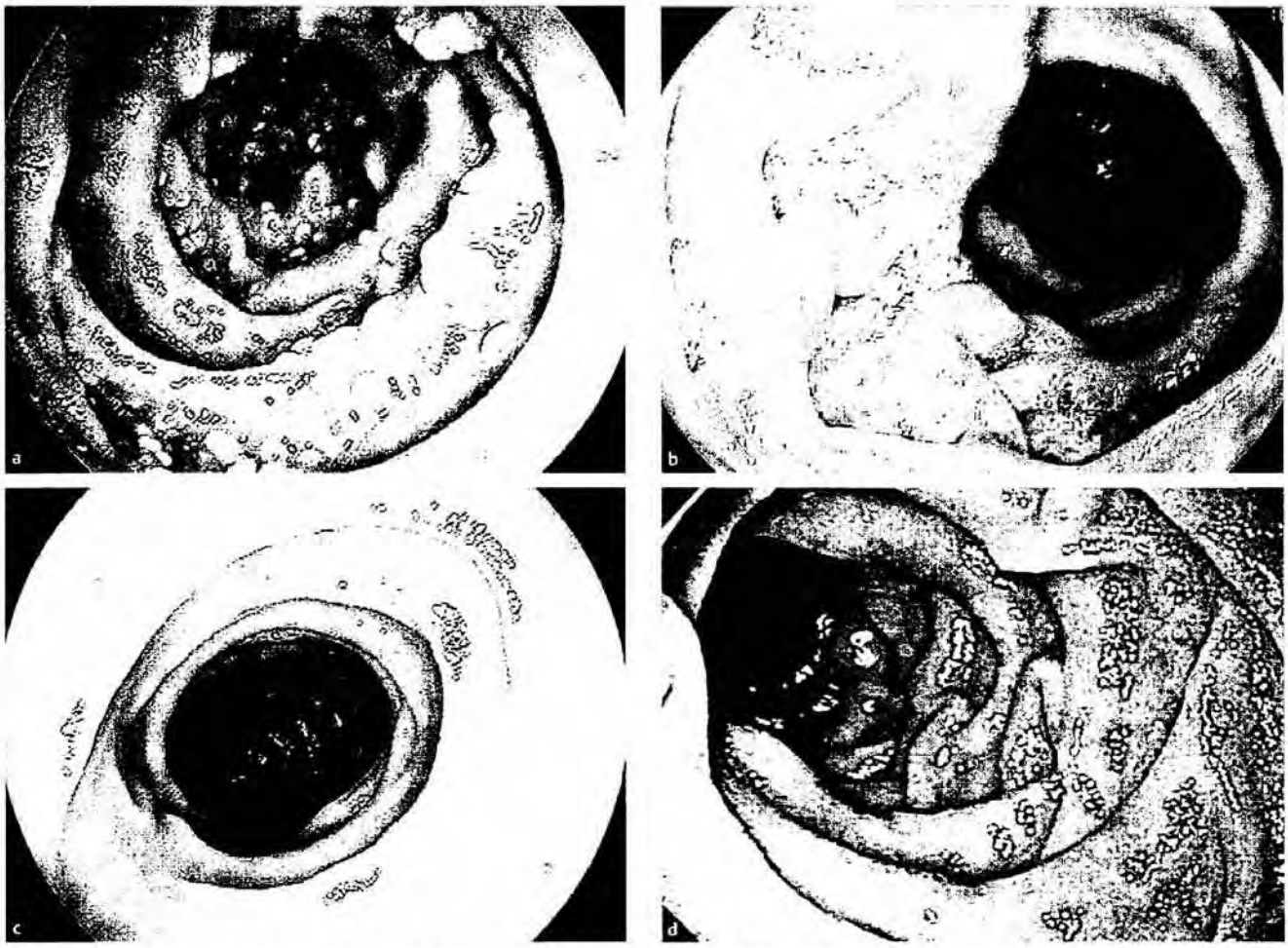

Fig. 1 Upper gastrointestinal endoscopic findings of the primary follicular lymphoma of the gastrointestinal tract. The endoscopic finding was nodularity of the involved mucosal surface, small whitish polyps (**a**, patient 1) or whitish granules (**b**, patient 9). After completion of six cycles of R-CHOP, endoscopic examination revealed disappearance of the whitish polyps or granules in the duodenum (**c**, patient 1; **d**, patient 9). No lymphomatous involvement was seen in this biopsy.

vealed lesions of PFLGI in the terminal ileum in patients 3 and 6. In addition to upper and lower gastrointestinal endoscopy, DBE (EN-450P5 endoscope; Fujinon, Saitama, Japan) was performed in all 11 PFLGI patients who visited our hospital after January 2004. DBE was performed successfully in these 11 patients, and we could examine the entire small bowel. There was no complication related to the procedure. New lesions were identified in the third portion of the duodenum, jejunum or ileum (**Fig. 2**) in nine of the 11 patients (81.8%) by DBE. The endoscopic finding was nodularity of the involved mucosal surface (small whitish polyps or whitish granules). Redness of the Bauhin valve was seen only in patient 3. No imaging analyses detected such involvement. These results are indicated in **Table 1.**

Seven patients (patients 2, 3, 4, 6, 10, 12, and 13) completed the six cycles of R-CHOP. They were to receive six cycles of R-CHOP, one cycle every 3 weeks. Rituximab, 375 mg/m^2, was given intravenously on day 1. Each CHOP cycle consisted of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose, 2.0 mg) given intravenously on day 3 and oral prednisone 100 mg/m^2 given on days 1–5.

After completion of six cycles of R-CHOP, patients were given four cycles of rituximab 375 mg/m^2 every 3 months. After chemotherapy, endoscopy revealed disappearance of the lesions of PFLGI (**Fig. 1c,d**) and absence of lymphoma cells in biopsy specimens from all patients receiving R-CHOP. Three patients (patients 1, 7, 9) did not undergo any treatment after diagnosis ("watch and wait" policy) because of complications such as liver cirrhosis and hepatocellular carcinoma (patient 7) or refusal to undergo aggressive treatment (patient 9). Patient 1 also had liver cirrhosis. The remaining three patients were treated in another institution. None of the 10 patients that were followed up at our institution died of lymphoma. Patient 1 died of liver cirrhosis (mean follow-up period, 22.5 months).

Discussion

▼

Reports focusing on PFLGI are scarce. The largest series was reported by LeBrun et al. [12], who reported the pathologic features of 31 cases of PFLGI. In their series, the small bowel, and more specifically, the terminal ileum, was the site most frequently involved. Yoshino et al. [2] found eight cases of PFLGI in a series of 222 gastrointestinal lymphomas. Five of these eight cases involved the duodenum. Shia et al. [13] also reported a predilection of PFLGI for the duodenum among their 26 patients. Damaj et al. [14] reported a series of 15 cases of PFLGI. The small bowel was again found to be the most common site, with a predilection for the ileum (n = 10). Although LeBrun and Damaj

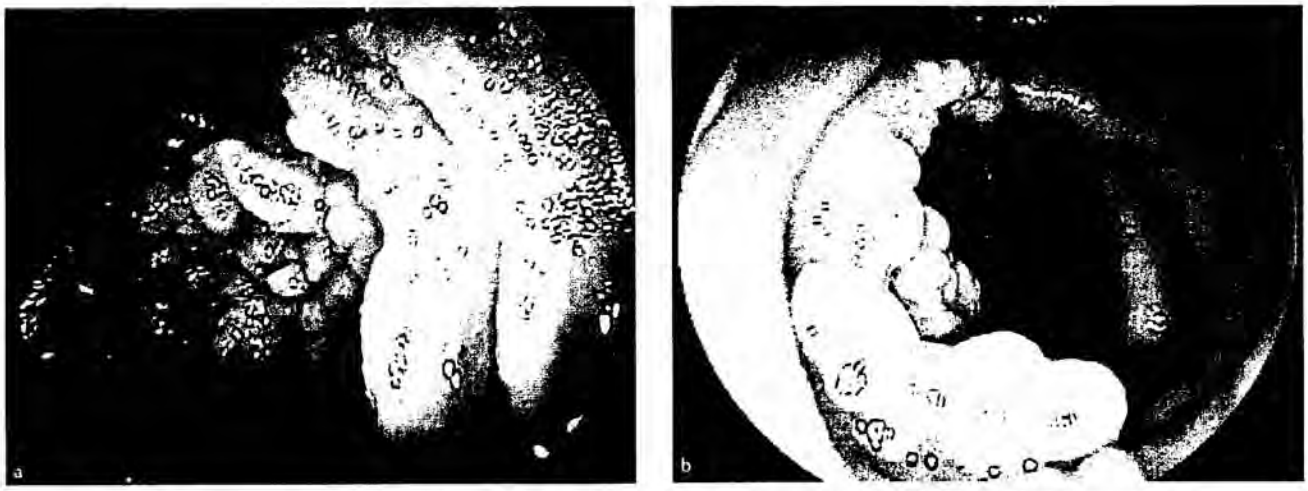

Fig. 2 New lesions in the third portion of the duodenum (**a**) and the jejunum (**b**) (patient 6) were identified by double-balloon enteroscopy.

Table 1 Anatomical distribution of initial localizations and endoscopic findings

					Localization							
Patient	**Age, years**	**Sex**	**Clinical stage**	**DBE**	**Stomach**	**Bulbus**	**2nd**	**3rd**	**Jejunum**	**Ileum**	**Colon**	**Endoscopic findings**
1	74	M	I	No	No	No	Yes	No	NE	NE	No	Multiple whitish small polyps
2	65	M	IV*	No	No	Yes	Yes	Yes	NE	NE	No	Multiple whitish small polyps
3	47	M	I	Yes	No	No	Yes	Yes	**Yes**	Yes	No	Multiple whitish small polyps Whitish granules Redness of Bauhin valve
4	65	M	I	Yes	No	No	Yes	No	No	No	No	Multiple whitish small polyps
5	61	F	I	Yes	No	No	Yes	**Yes**	No	No	No	Multiple whitish small polyps
6	54	M	I	Yes	No	No	Yes	**Yes**	**Yes**	Yes	No	Multiple whitish small polyps
7	70	F	I	Yes	No	No	Yes	No	No	**Yes**	No	Multiple whitish small polyps
8	50	F	I	Yes	No	No	Yes	Yes	No	No	No	Multiple whitish small polyps
9	50	M	I	Yes	No	No	Yes	No	No	**Yes**	No	Whitish granules
10	60	M	I	Yes	No	No	Yes	No	**Yes**	No	No	Multiple whitish small polyps
11	54	M	IV*	Yes	No	No	Yes	No	**Yes**	No	No	Multiple whitish small polyps
12	50	M	I	Yes	No	Yes	Yes	No	**Yes**	**Yes**	No	Whitish granules
13	59	F	IV*	Yes	No	No	Yes	No	**Yes**	No	No	Multiple whitish small polyps

DBE, double-balloon enteroscopy.
Bold entries are new lesions identified by DBE.
2nd, second portion of the duodenum; 3rd, third portion of the duodenum; NE, not examined by DBE.
*Disseminated bone marrow involvement of lymphoma cells.

found a predilection of PFLGI for the terminal ileum, Yoshino and Shia noted a predilection for the duodenum. All 13 patients in our series had lesions in the duodenum, indicating a predilection of PFLGI for the duodenum.

We examined the entire small bowel by means of DBE in 11 of our 13 patients. New lesions that had not been detected by other image analyses were identified by DBE in the distal small intestine in nine of the 11 patients (81.8%). Because accurate diagnosis and accurate staging are essential for the management of this disease, it is necessary to examine the entire small bowel of PFLGI patients by means of DBE.

Most of our patients (12/13) had no clinical symptoms, but small whitish polyps or whitish granules were seen around the ampulla of Vater. Nodularity of the involved mucosa surface around the ampulla of Vater should be a typical endoscopic finding of early-stage PFLGI. We should carefully examine not only the stomach but also the duodenum when performing upper gastrointestinal endoscopy.

No standard therapy has been established for PFLGI, mainly because PFLGI occurs infrequently. Because most patients with PFLGI have multifocal lesions from the duodenum to the ileum as shown in our study, radiation therapy or surgical resection is not considered appropriate. Rituximab is a human–mouse chimeric monoclonal antibody directed against the CD20 antigen. The CD20 antigen is strongly and stably expressed on cells of the B-cell lineage but not on stem cells and is thus an ideal target antigen for antibody therapy of B-cell malignancies. Because the majority of NHLs are of B-cell origin [15], with more than 90% of patients expressing the CD20 antigen [16], rituximab may offer considerable promise to patients with NHL. Czuczman et al. reported the efficacy of R-CHOP. In their study of 40 patients with low-grade NHL, R-CHOP yielded an overall response rate of 100% [17]. In our study, seven patients with PFLGI received R-CHOP, and a complete response was obtained in all cases. Prolonged survival can be expected in such patients, but it is necessary to monitor these patients as long as possible because of the risk of relapse.

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①Immune response to CagA protein is associated with improved platelet count after Helicobacter pylori eradication in patients with idiopathic thrombocytopenic purpura

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⑤2007 Feb;12(1)36-42

Immune Response to CagA Protein is Associated with Improved Platelet Count After *Helicobacter pylori* Eradication in Patients with Idiopathic Thrombocytopenic Purpura

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Keywords
idiopathic thrombocytopenic purpura, *Helicobacter pylori*, gastritis, cytotoxin-associated gene A.

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Abstract

Background: Improvement in platelet counts has been reported after eradication of *Helicobacter pylori* in patients with idiopathic thrombocytopenic purpura (ITP). We examined the levels of serum markers of gastritis and anti-CagA (cytotoxin-associated gene A) IgG antibody in patients with ITP to investigate whether these factors are associated with the platelet response after *H. pylori* eradication therapy.

Materials and methods: One hundred and sixteen consecutive patients with ITP were assessed for *H. pylori* infection by ^{13}C-urea breath test and serum *H. pylori* antibody test. Patients with *H. pylori* infection received eradication therapy. Before and after eradication therapy, we evaluated serum levels of gastrin, pepsinogen (PG)-I, and PG-II and the anti-CagA IgG antibody titer.

Results: *H. pylori* infection was found in 67 (58%) of the 116 patients with ITP. Fifty-two infected patients received eradication therapy, which was successful in 44 patients (85%). Twenty-seven patients (62%) showed an increased platelet count and were identified as responders. The duration of ITP was shorter in responders than in nonresponders ($p = .017$). There was no difference of the levels of gastrin and PGs between responders and nonresponders. Before eradication therapy, the serum anti-CagA antibody titer did not differ significantly between responders and nonresponders. However, reduction in the anti-CagA antibody titer after eradication therapy was significantly greater in responders than in nonresponders ($p = .013$).

Conclusions: *H. pylori* eradication therapy improves the platelet count in *H. pylori*-positive patients with ITP of short duration. Immune response of hosts to CagA protein of *H. pylori* may play a role in the pathogenesis of ITP.

Helicobacter pylori is a Gram-negative bacterium that colonizes in the mucous layer of the human stomach. It causes gastritis and is an important risk factor for gastric ulcer, duodenal ulcer, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma [1]. Several recent reports have suggested that *H. pylori* infection may cause immune diseases not related to the gastric mucosa, including chronic thyroiditis, rheumatoid arthritis, Sjögren syndrome, and idiopathic thrombocytopenic purpura (ITP) [2–5].

ITP is an acquired bleeding disease prevalent in adults, in which autoantibodies bind to the platelet's surface and cause platelet destruction in the reticulo-endothelial system [6]. The pathologic mechanisms that trigger the production of platelet autoantibodies are still poorly understood. Gasbarrini et al. reported that the platelet count was increased in all eight of their patients with ITP after *H. pylori* eradication therapy [5]. After this report, several authors described an improvement in thrombocytopenia among patients with ITP following *H. pylori* eradication [5,7–11], but some studies did not show such improvement [12,13]. The value of *H. pylori* eradication therapy in the management of patients with ITP remains

controversial, and the factors responsible for the different results are not clear. There is a need to clarify any differences in clinical features between *H. pylori* eradication responders and nonresponders.

We investigated the prevalence of *H. pylori* infection and the effects of *H. pylori* eradication on platelet counts in Japanese patients with ITP. We also investigated differences in clinical features, levels of serum markers for gastritis, and anti-CagA (cytotoxin-associated gene A) antibody titers between responders and nonresponders to find factors predictive of platelet recovery.

Methods

Patients

One hundred and sixteen patients with ITP (32 men and 84 women, with a mean age of 54.0 years) who visited Hiroshima University Hospital between April 2001 and November 2005 were enrolled in this study. ITP was diagnosed according to the criteria of the Research Committee for ITP supported by the Ministry of Health and Welfare of Japan (1990). The main criteria are platelet count of less than $10 \times 10^4/\mu L$; no evidence of other hematologic abnormalities in the peripheral blood; bone marrow examination performed to rule out other suspected diseases; no underlying diseases causing the thrombocytopenia; and presence of thrombocytopenia for at least 6 months. Patients who had previously undergone *H. pylori* eradication therapy were excluded from the study. Approval for *H. pylori* eradication therapy in patients with ITP was obtained from Hiroshima University Hospital before the start of the study, and informed consent was provided by all participants according to the Declaration of Helsinki.

Assessment of *H. pylori* Infection

H. pylori infection was diagnosed when results of the ^{13}C-urea breath test (UBT) (Ubit-IR200; Otsuka, Tokushima, Japan) and/or serum *H. pylori* antibody test (E-plate; Eiken, Tokyo, Japan) were positive. Results were considered positive when the levels of labeled CO_2 shown by UBT were greater than 2.5‰ or when the *H. pylori* antibody titer was greater than 10.0 U/mL.

H. pylori Eradication Therapy

Patients with ITP were given antimicrobial therapy only if they tested positive for *H. pylori* infection and agreed to receive eradication therapy by providing informed consent. The *H. pylori* eradication therapy regime consisted of amoxicillin (1500 mg twice daily), clarithromycin (400 mg twice daily), and lansoprazole (60 mg twice daily) for 7 days. To assess the effect of eradication therapy, the UBT was repeated eight or more weeks after the completion of eradication therapy. *H. pylori* infection was considered cured when the level of labeled CO_2 shown by UBT was less than 2.5‰.

Laboratory Studies

The platelet count was determined in each patient immediately before eradication therapy, and counts were monitored for at least 6 months after completion of eradication therapy, being measured every 4 or 8 weeks. To evaluate the effects of eradication therapy, the dose of ongoing medication for ITP was maintained for at least 4 weeks after eradication therapy. Fasting blood serum was obtained at the time of the UBT before eradication therapy and eight or more weeks after therapy, and was stored at −20 °C until assay was performed. Gastrin was measured by radioimmunoassay, as described previously [14]. Serum pepsinogen (PG)-I and PG-II concentrations were determined by radioimmunoassay (Dainabot Co., Ltd, Tokyo, Japan) [14]. ELISA was performed with the use of a CagA kit (*Helicobacter* p120 [CAG A] ELISA; ravo Diagnostika, Freiburg, Germany) according to the manufacturer's instructions. The experiments were performed in duplicate and repeated twice.

Platelet Response Criteria

The hematologic response after eradication therapy was assessed during the final examination in each case, and the effectiveness was determined according to the criteria reported by Fujimura et al. [15], that is, if the initial platelet count was less than $1 \times 10^4/\mu L$ and the count increased more than three times after eradication therapy, the patient was considered a responder. Also, if the initial platelet count was $1 \times 10^4/\mu L$ or greater and less than $3 \times 10^4/\mu L$ and it increased to more than $5 \times 10^4/\mu L$ or if the initial platelet count was $3 \times 10^4/\mu L$ or greater and less than $10 \times 10^4/\mu L$ and it increased to more than $3 \times 10^4/\mu L$ of the initial level, the patient was considered a responder. Partial remission was defined as a platelet count of less than $15 \times 10^4/\mu L$ in responders. Complete remission was defined as a platelet count greater than $15 \times 10^4/\mu L$ after eradication therapy. Patients who did not meet the above-mentioned criteria after eradication therapy were considered nonresponders.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Chi-squared or Fisher's exact test was used for analysis

	H. pylori-positive patients (n = 67)	*H. pylori*-negative patients (n = 49)	*p*-value
Age (years)	57.9 ± 14.3	48.7 ± 17.2	0.002
Male/female ratio	18/49	14/35	0.84
Disease duration (months)	127.4 ± 123.4	119.7 ± 100.4	0.96
Initial platelet count (x 10^4/μL)	3.97 ± 2.93	3.04 ± 2.49	0.067

Table 1 Characteristics of *H. pylori*-positive and -negative patients

of categorical data. Wilcoxon/Kruskal–Wallis analysis was used for comparisons of continuous variables. Serum anti-CagA IgG antibody titers obtained before and after eradication therapy were compared using Wilcoxon signed-ranks test. A *p*-value of < 0.05 was considered statistically significant.

Results

Prevalence of *H. pylori* Infection and Clinical Characteristics of *H. pylori*-Positive Patients

H. pylori infection was detected in 67 (57.8%) of the 116 study patients. The mean age of *H. pylori*-positive patients was greater than that of the *H. pylori*-negative patients (57.9 ± 14.3 years vs. 48.7 ± 17.2 years, $p = .0021$). No significant difference was found in platelet counts, sex ratio, or disease duration between the *H. pylori*-positive patients and the *H. pylori*-negative patients (Table 1).

Platelet Response to Eradication Therapy

Fifty-two patients with *H. pylori* infection received standard eradication therapy, and the bacterium was successfully eradicated in 44 of these 52 patients (84.6%). Complete remission of ITP was achieved in eight (18.1%) of the 44 patients, and partial remission was achieved in 19 of the 44 patients (43.2%), for an overall response rate of 61.4%. No persistent increase in the platelet count was seen in the eradication failure group. One patient in the eradication failure group showed a temporary increase in the platelet count, but the count decreased to less than 3×10^4/μL approximately 4 months after the first course of eradication therapy. Second-line eradication therapy involving metronidazole resulted in a significant increase in the platelet count, which continued for more than 1 year (Fig. 1). Patients in whom eradication therapy was successful showed a significant increase in the platelet count compared to that of patients in whom eradication therapy was not successful (61.4% vs. 0%, $p = .0014$). A diagram of the study population and the various results are shown in Fig. 2.

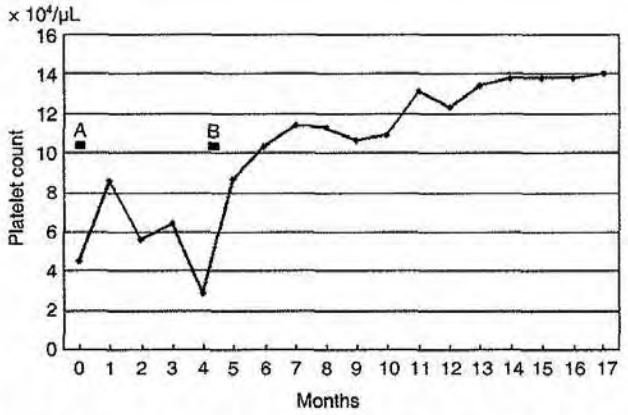

Figure 1 Platelet counts of a patient in the eradication failure group. A temporary increase in the platelet count was observed, but the count soon decreased. After a successful second-line eradication therapy, a significant increase in the platelet count was observed, and this has continued for more than 1 year. (*A*) First-line eradication therapy: amoxicillin (1500 mg twice daily), clarithromycin (400 mg twice daily), and lansoprazole (60 mg twice daily) for 7 days. (*B*) Second-line eradication therapy: amoxicillin (1500 mg twice daily), metronidazole (750 mg thrice daily), and lansoprazole (60 mg twice daily) for 7 days.

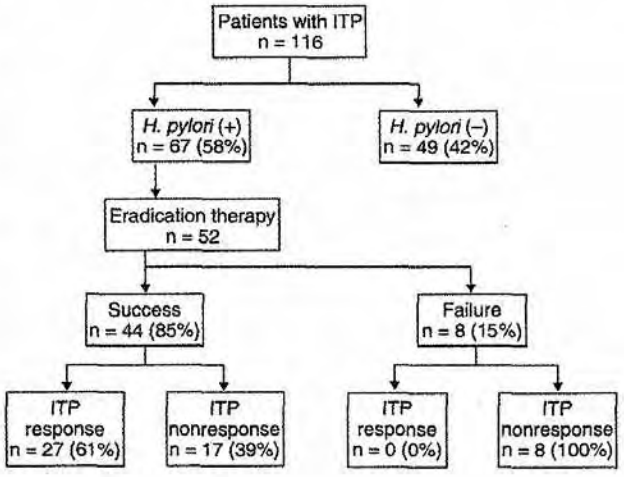

Figure 2 *Diagram of the study population and the various results.* ITP, idiopathic thrombocytopenic purpura.

Table 2 Characteristics of responders and nonresponders in patients with successful eradication

	Responder (n = 27)	Nonresponder (n = 17)	*p*-value
Age (years)	54.9 ± 13.1	59.8 ± 12.0	0.36
Male/female ratio	5/22	6/11	0.29
Disease duration (months)	89.1 ± 71.2	181.0 ± 124.6	0.017
Age at onset (years)	47.9 ± 12.0	45.4 ± 14.4	0.52
Initial platelet count ($\times 10^4/\mu L$)	3.09 ± 2.26	3.89 ± 2.63	0.31
Previous treatment for ITP			
None	8 (29.6%)	6 (35.3%)	0.75
Splenectomy	2 (7.4%)	1 (5.9%)	> 0.99
Steroid	16 (59.2%)	10 (58.8%)	> 0.99
Total dose (g)	3.23 ± 4.06	1.47 ± 2.48	0.23
Immunosuppressive treatment	8 (29.6%)	2 (11.8%)	0.27
Human normal immunoglobulin	7 (25.9%)	2 (11.8%)	
Azathioprine	1 (3.7%)	0	

Clinical Characteristics of Responders and Nonresponders

The 44 patients with ITP in whom *H. pylori* eradication therapy was successful were classified as responders and nonresponders, as described above. Clinical characteristics of these two groups of patients are shown in Table 2. The duration of ITP was significantly shorter in responders than that in nonresponders ($p = .017$). No other factors were associated with the response of platelets to eradication therapy.

Serum Markers of Gastritis in Responders and Nonresponders

We next examined levels of serum markers of gastritis. The gastrin level tended to be higher and the PG-I/II ratio tended to be lower in responders than in nonresponders, but the differences were not statistically significant (Fig. 3).

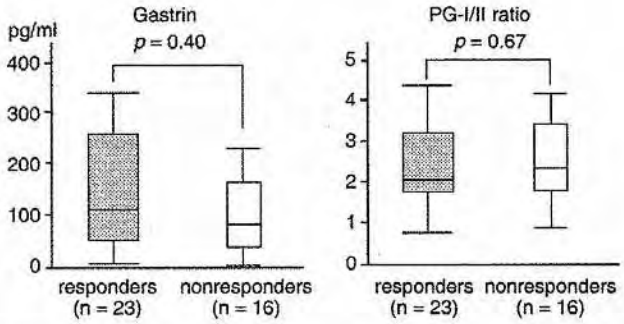

Figure 3 Pretreatment levels of serum markers in responders and nonresponders in whom eradication was successful. The gastrin level tended to be higher and the PG-I/II ratio tended to be lower in responders than in nonresponders, but the differences were not statistically significant.

Serum Anti-CagA IgG Antibody Titers in Responders and Nonresponders

Anti-*H. pylori* IgG and anti-CagA IgG antibody titers were measured by ELISA. Before eradication therapy, no significant difference was found in the anti-*H. pylori* or anti-CagA antibody titer between responders and nonresponders (Fig. 4). The serum anti-*H. pylori* antibody titer decreased significantly after eradication therapy in both responders and nonresponders, indicating that *H. pylori* was successfully eradicated in both groups (Fig. 4A). In contrast, the serum anti-CagA antibody titer decreased significantly after eradication therapy only in responders ($p = .002$) (Fig. 4B). The decrease in the anti-CagA antibody titer after eradication therapy was significantly greater in responders than in nonresponders (11.4 ± 5.3 units vs. 2.26 ± 6.13 units, $p = .013$).

Discussion

Various investigators have examined the effects in *H. pylori* eradication therapy in patients with ITP. The reported effects of *H. pylori* eradication on platelet counts in patients with ITP have varied, with 0% to 100% of patients responding [5,7,8,10–13,15–21]. The prevalence of *H. pylori* infection in healthy persons in Japan is similar to that in Italy, and a good platelet response to *H. pylori* eradication therapy, i.e. approximately 50% to 100% of patients, has been reported in both Japan and Italy [5,7–10,16,18,19]. In contrast, in a study conducted in Spain, Jarque et al. reported that only three out of 23 (13%) patients with ITP in whom *H. pylori* was eradicated showed a significant increase in the platelet count [12]. Michel et al. reported

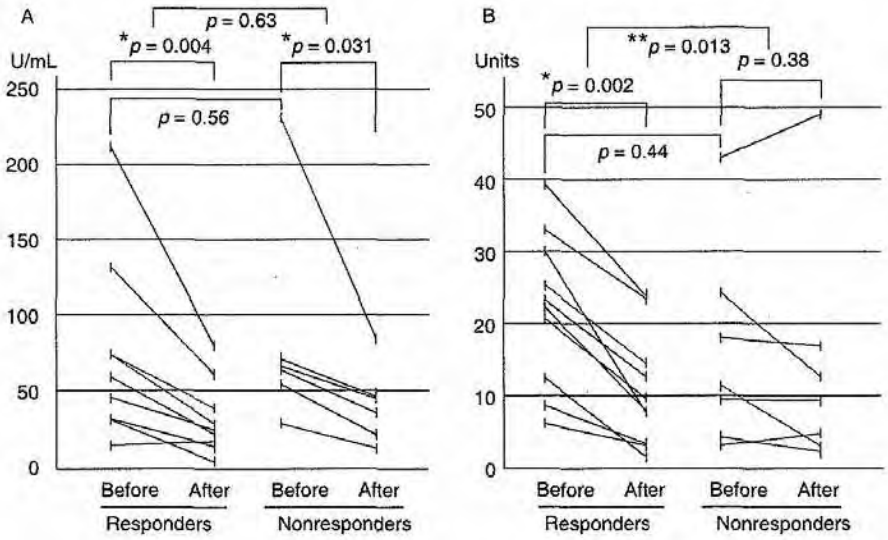

Figure 4 Anti-*H. pylori* IgG (*A*) and anti-CagA IgG (*B*) antibody titers before and after eradication. The *H. pylori* antibody titer decreased significantly after eradication therapy in both responders and nonresponders (*A*). The anti-CagA antibody titer decreased significantly after eradication therapy in responders but not in nonresponders (*B*). Before: before *H. pylori* eradication therapy, after: 8 weeks after eradication therapy. *Statistically significant by Wilcoxon signed-ranks test, **statistically significant by Wilcoxon/Kruskal–Wallis analysis.

that *H. pylori* infection was found in 22% of North American patients with ITP (16/74) and that none of the 14 patients in whom *H. pylori* was eradicated responded [13]. Differences in the characteristics of patients, including the genetic background of the hosts and the strains of *H. pylori*, might contribute to the different effects of eradication therapy.

In the present study, *H. pylori* infection was detected in 67 (57.8%) of the 116 patients, and age was the only factor that differed between *H. pylori*-positive and -negative patients. Asaka et al. reported that the prevalence of *H. pylori* infection in the general population of Japan is approximately 10–40% until 40 years of age, after which it increases to approximately 80%. They also reported the prevalence of *H. pylori* infection in those born before 1949 (aged 40–80 years in 1992) to be higher than in those born after 1950 [22]. Our data also showed the prevalence of *H. pylori* infection among patients with ITP born before 1949 to be higher than that in those born after 1950 (67.2% vs. 44.9%, $p = .022$). The prevalence of *H. pylori* infection in patients with ITP in this study did not differ from that in the general population of Japan.

After eradication therapy, 61.4% of our patients in whom eradication was successful were classified as responders. We examined differences in clinical characteristics between responders and nonresponders in whom eradication was successful. Disease duration was significantly shorter in responders than in nonresponders, consistent with previously reported findings [15,21]. We also investigated serum markers of gastritis in patients with ITP. Ando et al. previously reported that *H. pylori*-infected patients with ITP had a corpus-predominant pattern of gastritis [16], but they were able to obtain mucosal biopsy specimens from only five patients with ITP whose platelet counts were relatively high. It is difficult to obtain mucosal biopsy specimens from patients with a low platelet count because of the risk of mucosal bleeding. Blood sampling can be performed in such patients. If serum markers of gastritis can predict the effect of eradication therapy on platelet counts, evaluation of these serum markers will be useful. The serum level of PG, the precursor of pepsin, is reported to be a reliable marker of atrophic gastritis. Reduction in the area of the fundic mucosa due to gastritis is associated with stepwise reduction in the PG-I/II ratio [23–25]. Gastrin is another popular marker of gastritis. Hypergastrinemia is induced by an increased intragastric pH due to atrophic change of the gastric corpus. In our study, the level of gastrin tended to be higher and the PG-I/II ratio tended to be lower in responders than in nonresponders, suggesting that the platelet counts of ITP patients with atrophic gastritis tend to respond to *H. pylori* eradication therapy.

CagA is the product of the *cagA* gene carried by virulent *H. pylori* strains and is associated with clinical outcomes. Ching et al. reported that positivity for anti-CagA antibody was present in a significantly higher percentage of *H. pylori*-positive patients with peptic ulcer than in patients with nonulcer dyspepsia or in healthy asymptomatic control subjects, and they concluded that anti-CagA antibody can be used as a clinical marker for peptic ulceration [26]. Suzuki et al. reported that, among patients with ITP, the anti-CagA antibody titer was significantly higher in responders than in nonresponders, suggesting that the anti-CagA antibody titer may be a good predictor of platelet recovery after eradication of *H. pylori* [27]. In the present study, we observed no difference in the anti-CagA antibody titer between responders and nonresponders before eradication therapy. However, the decrease in the anti-CagA antibody titer after eradication therapy was significantly greater in responders than in nonresponders.

The anti-CagA antibody titer decreased after eradication therapy in all responders, and the change in the anti-CagA antibody titer with eradication was statistically significant in responders but not in nonresponders (Fig. 4). Therefore, the immune reaction of the host to CagA protein may be prolonged after *H. pylori* eradication in nonresponders. Takahashi et al. showed cross-reactivity between platelet-associated immunoglobulin G (PAIgG) and *H. pylori* CagA protein; PAIgG from *H. pylori*-positive patients with ITP reacted with *H. pylori* CagA protein, and the reaction decreased after successful *H. pylori* eradication, suggesting that molecular mimicry by CagA of an unknown platelet antigen is crucial in the pathogenesis of a subset of ITP cases [18]. In our study, the serum anti-*H. pylori* antibody titer decreased significantly after eradication therapy in nonresponders (Fig. 4A). However, anti-CagA antibody titer did not (Fig. 4B). Therefore, prolonged immune reaction may be specific to CagA protein. Mechanism of this finding has not been elucidated yet, but there is a possibility that anti-CagA antibody may cross-react to unknown platelet antigen and suppress the number of platelet of patients in nonresponder group.

In summary, our study showed that *H. pylori* eradication therapy improves the platelet count in *H. pylori*-positive patients with ITP of short duration. The anti-CagA antibody titer decreased significantly after eradication therapy in responders but not in nonresponders. Therefore, the immune response of hosts to CagA protein may play an important role in the pathogenesis of ITP.

We thank Mr Tetsunori Yoshioka (Hiroshima University Hospital) for UBT assessment, and we thank Ms. Nao Kubota and Ms. Kyoko Kunimitsu (Hiroshima University Hospital) for assessment of PG and gastrin. This work was supported by a grant from the Tsuchiya Foundation, Hiroshima, Japan.

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