clinicopathological characteristics of undifferentiated EGC by reviewing cases that had been treated previously at our institution in order to identify predictive factors of lymph node metastasis and qualify lesions that should be referred for gastrectomy and not EMR.

PATIENTS AND METHODS

Between January 1989 and April 2005, 1,004 patients with EGC underwent gastrectomy as an initial treatment at the National Hospital Organization Shikoku Cancer Center. Among these, 398 patients had undifferentiated EGC. Cases of multiple lesions and cases without regional lymph node dissection were excluded from this study, giving a final total of 332 patients whose clinicopathological features were retrospectively analyzed. They comprised 160 men and 172 women whose mean age was 58.0 years (range, 20 to 87 years), with a mean tumor size of 36.5 mm (range, 1 to 130 mm). Cancer description and histological evaluation of resected specimens were performed in accordance with the Japanese Classification of Gastric Carcinoma.[14]

A set of sections of the stomach parallel to the lesser curvature were made, and the histological classification was based on the predominant pattern of the tumor. Poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma were regarded as undifferentiated. Lymph nodes were cut into two pieces, and the cut surfaces were examined to define the status of the nodes. Lymph node metastasis was identified with use of hematoxylin and eosin staining, and ulceration was defined histologically if fibrosis or deformity in the submucosal layer or deeper was observed.

Tumors were classified macroscopically into two groups: protruded (types 0 I and 0 IIa) or depressed (types 0 IIb, 0 IIc, and 0 III). Lesions showing a combination of these types were classified into a mixed group. The association between each of the nine clinicopathological factors and the presence or absence of lymph node metastasis was examined to identify risk factors predictive of lymph node metastasis.

Univariate analysis was performed with use of the chi-square test. Subsequently, significant factors identified by univariate analysis were included in the multivariate stepwise logistic regression analysis to evaluate the independent risk factors for lymph node metastasis. The odds ratio in the multivariate analysis was defined as the ratio of the probability that an event would occur to the probability that it would not occur. Statistical analyses were performed with use of the Statistical Package for Social Science (SPSS 11.5 for Windows, SPSS, Chicago, IL). Differences of $P < 0.05$ were considered significant.

RESULTS

Univariate Analysis of Risk Factors Predictive of Lymph Node Metastasis

Of the 332 patients with undifferentiated EGC, 45 (14%) had lymph node metastasis. Lymph node meta-

stasis was observed in eight (5%) of the 177 patients with intramucosal cancers and in 37 (24%) of the 155 with submucosal cancers. Nine clinicopathological factors were examined: patient age and gender, tumor size, location, macroscopic type and histological type, presence of ulceration, depth of tumor invasion, and lymphatic-vascular involvement. Univariate analysis revealed that the depth of tumor invasion (submucosa), tumor size (> 30 mm), and lymphatic-vascular involvement (positive) were associated with lymph node metastasis (Table 1).

Multivariate Analysis of Risk Factors Predictive of Lymph Node Metastasis

Only lymphatic-vascular involvement (positive) was shown to have a significant association (odds ratio, 7.4; 95% confidence interval, 2.9–19.0) by multivariate analysis (Table 2).

Survival

Median period of follow-up was 50.5 months (range, 0 to 199 months). Survival curves for patients with and without lymph node metastasis are shown in

TABLE 1. Univariate Analysis of Risk Factors for Lymph Node Metastasis in Patients With Undifferentiated Early Gastric Cancer (EGC)

Factor	Lymph Node Metastasis Positive (%) n = 45	Lymph Node Metastasis Negative n = 287	*P* Value
Age, years			
< 59	19 (11%)	151	
≥ 59	26 (16%)	136	0.256
Gender			
Male	21 (13%)	139	
Female	24 (14%)	148	0.952
Location			
Upper third	6 (17%)	29	
Middle third	30 (13%)	195	
Lower third	9 (13%)	63	0.794
Macroscopic type			
Protruded	3 (33%)	6	
Depressed	40 (13%)	275	
Mixed	2 (25%)	6	0.129
Ulceration			
Negative	23 (15%)	131	
Positive	22 (12%)	156	0.601
Depth of invasion			
Mucosa	8 (5%)	169	
Submucosa	37 (24%)	118	< 0.001
Histological type			.
Poorly differentiated adenocarcinoma	28 (17%)	137	
Signet ring cell carcinoma	15 (9%)	144	
Mucinous adenocarcinoma	2 (25%)	6	0.089
Size of tumor			
< 30 mm	12 (8%)	140	
≥ 30 mm	33 (18%)	147	0.009
Lymphatic-vascular involvement			
Negative	13 (5%)	236	
Positive	32 (39%)	51	< 0.001

Values are number of cases.

413

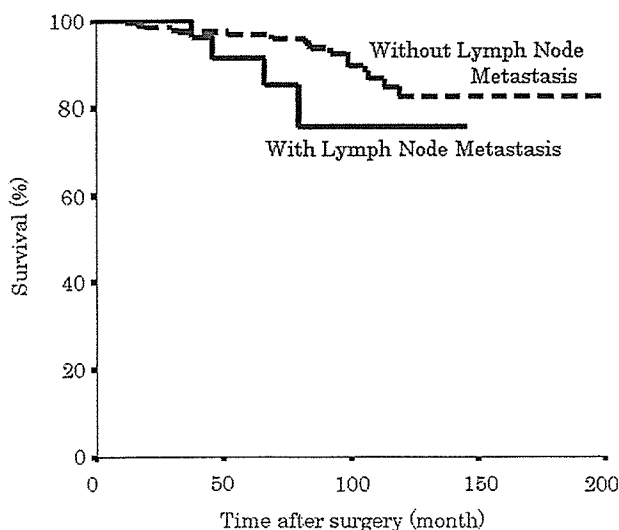**TABLE 2.** Multivariate Analysis of Risk Factors for Lymph Node Metastasis in Patients With Undifferentiated EGC

Factor	Odds Ratio (95% CI)	P Value
Lymphatic-vascular involvement (positive)	7.42 (2.89–19.03)	< 0.001
Size of tumor (≥ 30 mm)	1.98 (0.92–4.22)	0.079
Depth of invasion (submucosa)	1.75 (0.60–5.13)	0.310

CI, confidence interval.

Figure 1. The 5-year survival rate was 96.7% for those without lymph node metastasis and 91.4% for those with lymph node metastasis. There was no statistical difference in overall survival rate between patients with or without lymph node metastasis. Of the patients with lymph node metastasis, three died of recurrence of gastric cancer (one with bone metastasis, one with bone and lymph node metastasis, and one with lymph node metastasis). Of the patients without lymph node metastasis, one died of liver metastasis.

DISCUSSION

EGC has been reported to have a favorable prognosis after gastrectomy.[15] Lymph node metastasis is one of the most important prognostic factors for patients with EGC; the survival rate for patients with lymph node metastasis is significantly lower than for those without it.[3,16] However, the incidence of lymph node metastasis in intramucosal EGC is approximately 3%, whereas that in submucosal EGC is 20%. Excessive gastrectomy and lymphadenectomy may affect perioperative morbidity and mortality.[17] Therefore, minimally invasive treatments such as EMR and laparoscopic wedge resection are considered to be appropriate options for EGC patients without lymph node metastasis.

A new EMR technique that allows complete removal of a large lesion as a single fragment with an insulation-tipped diathermic knife[11] is promising for accurate histological examination of a specimen and subsequent determination of whether local treatment alone will be curative. Although undifferentiated EGC is reported to have more lymph node metastasis than differentiated EGC,[6,7] histological type has no association with survival.[18] Our survival data showed no statistical difference in overall survival rate between patients with or without lymph node metastasis. This may be due to the short follow-up period.

Current application of EMR is limited to differentiated EGC; thus, we sought to expand the use of EMR to undifferentiated EGC by retrospectively examining undifferentiated EGC to determine predictive factors of lymph node metastasis. Univariate analysis revealed three clinicopathological risk factors: depth of invasion, tumor size, and lymphatic-vascular involvement. These factors correlate with those reported previously for both differentiated and undifferentiated EGC by multivariate analysis.[3,4,6-8] Because lymphatic-vascular vessels are less likely to appear in the mucosal layer than in the submucosal layer, it would be reasonable to expect that submucosal tumors would have a more frequent association with lymph node metastasis than intramucosal tumors.

In the present study, multivariate analysis demonstrated that the presence of lymphatic-vascular involvement was the only independent predictive factor for lymph node metastasis, in agreement with previous studies of undifferentiated EGC.[13] Although lymphatic-vascular involvement seems to identify a high-risk population that perhaps should not be offered EMR, this can be determined only after a gastrectomy or EMR. Thus, this pathologic feature is not useful in EMR. There was no proper predictive factor to identify patients with undifferentiated EGC at high risk for lymph node metastasis who should be offered gastrectomy rather than EMR.

In our study, small, undifferentiated EGCs < 10 mm in size without lymphatic-vascular involvement had no lymph node metastasis, but with the narrow range of cases (seven in the mucosa and six in the submucosa), the statistical significance is too limited to make any conclusions. However, our trend is consistent with that described by Gotoda et al,[5] in which zero of 141 patients with undifferentiated intramucosal EGCs < 20 mm in size without ulceration had lymph node metastasis. In our study, one undifferentiated intramucosal EGC < 20 mm (13 mm) in size without ulceration and without lymphatic-vascular involvement had lymph node metastasis. Contrarily, Abe et al reported that lymph node metastasis was found in small, undifferentiated intramucosal EGC (10 mm and 12 mm) without ulceration.[13]

The prognosis for patients with differentiated EGC who undergo EMR is favorable.[19] Still, there is

FIGURE 1. Survival curves for patients with and without lymph node metastasis. There was no statistical difference between them.

some concern about how micrometastasis affects the survival rate; Lee et al[20] reported that patients with micrometastasis had a lower 5-year survival rate than patients without micrometastasis, especially in Stage IA. It is suggested that micrometastasis is missed on conventional histological examination and that immunohistochemical examination is needed. Although there has been no report on the prognosis for patients with undifferentiated EGC treated by EMR, Ishida et al[21] reported that micrometastasis was more frequent in the undifferentiated type than in the differentiated type, and it is feared that cases of small, undifferentiated EGC treated with EMR could potentially recur with lymph node metastasis.

Currently the treatment procedure is decided on the basis of clinical findings, and despite recent improvements in diagnostic techniques, it is sometimes difficult to define the tumor margin and tumor depth by endoscopic examination.[22] The accuracy of determining tumor depth is reported to be significantly lower for undifferentiated tumors than for differentiated tumors and lower for a depressed tumor than for an elevated one.[23] Miyata et al[24] reported that the complete resection rate of EMR for EGC in poorly differentiated adenocarcinoma was lower than in differentiated types.

According to our results, lymphatic-vascular involvement was the only independent predictive risk factor for lymph node metastasis. However, this cannot be confirmed before surgery or EMR. This pathologic factor was not useful to identify patients at high risk for lymph node metastasis who should be offered gastrectomy rather than EMR. Clinical characteristics such as tumor size and depth were not so strong predictors for lymph node metastasis in our study. Therefore, it is prudent to choose EMR as a therapeutic procedure for patients with undifferentiated intramucosal EGCs.

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                                                    415

—症例報告—

早期胃癌に合併した粘膜下腫瘍型
胃 hamartomatous inverted polyp の1例

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片　岡　淳　朗[2)]　松　原　　稔　　鈴　木　誠　祐[1)]

要旨：症例は39歳，女性．内視鏡検査で胃体下部前壁に4cm大の陥凹性病変を，体上部小彎に2cm大の粘膜下腫瘍を認めた．粘膜下腫瘍は超音波内視鏡では細脈管様の無エコー像がみられ，迷入膵が疑われた．幽門側胃切除を施行し，陥凹性病変は印環細胞癌と，粘膜下腫瘍は hamartomatous inverted polyp（HIP）と診断された．HIP はまれな疾患であるが，胃粘膜下腫瘍の鑑別診断において考慮する必要があると思われた．

索引用語：hamartomatous inverted polyp，胃粘膜下腫瘍，超音波内視鏡検査

緒　　言

　胃の hamartomatous inverted polyp（以下 HIP）は粘膜固有層および粘膜下層に限局的に大小の嚢胞状に拡張した腺管構造と粘膜筋板に連なった平滑筋束が樹枝状に増殖した病変である[1)2)]．胃 HIP はこれまでさまざまな画像所見が報告されているが，診断が困難な疾患とされている[3)]．今回われわれは早期胃癌に併存し，迷入膵と鑑別困難であった粘膜下腫瘍型 HIP の1例を経験したので報告する．

Ｉ　症　　例

患者：39歳，女性．
主訴：食欲不振・全身倦怠感．
既往歴：特記すべきことなし．
家族歴：特記すべきことなし．
現病歴：平成15年10月，健康診断目的で近医において上部消化管内視鏡を施行したところ，胃体下部前壁に陥凹性病変を指摘され，精査加療目的にて入院となった．
入院時現症：血圧120/62mmHg，脈拍68/min，整，聴診上心肺に異常なし．眼瞼，眼球結膜に貧血，黄染なし．表在リンパ節触知せず．肝・脾腫

はなく，四肢に浮腫を認めなかった．
　入院時検査成績：軽度の貧血を認める以外異常を認めなかった（Table 1）．
　消化管内視鏡検査：上部消化管内視鏡では胃体下部前壁から胃角にかけて4cm大の浅い発赤調の陥凹性病変を認めた（Figure 1）．胃体上部小彎には2cm大の正常粘膜に覆われた扁平な粘膜下腫瘍を認めた（Figure 2，3）．
　生検所見：陥凹性病変からの生検組織には signet ring cell を認め印環細胞癌と診断された．粘膜下腫瘍からの生検組織は正常の胃粘膜のみが採取されていて，診断には至らなかった．
　超音波内視鏡検査：粘膜下腫瘍様病変に対して超音波内視鏡検査を施行した．低エコーの腫瘍が第2～3層にかけて存在しており，内部に細い脈管と思われる無エコーの集合を認めた．第4層は正常に保たれていた（Figure 4）．これらの所見より粘膜下腫瘍については迷入膵が疑われた．
　腹部 CT 検査所見：腹腔内リンパ節腫大や明らかな遠隔転移等の異常所見は認めなかった．以上の所見から体部前壁の胃癌（深達度 m）と粘膜下腫瘍（迷入膵）と診断した．胃癌については T1，

1）住友別子病院第2内科
2）四国がんセンター内視鏡科

Table 1. 入院時血液生化学検査

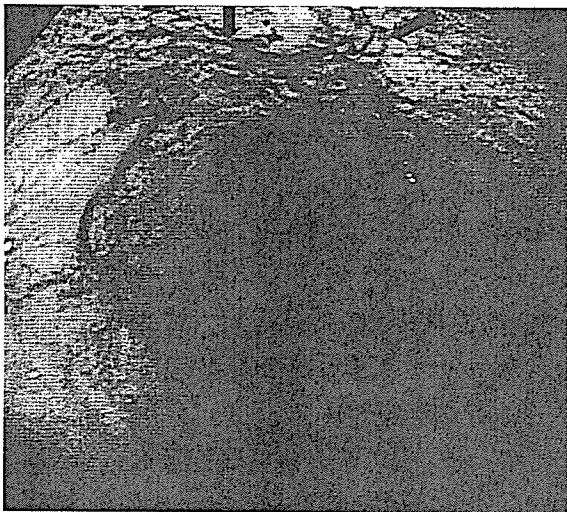|					
WBC	4300 /μl	GOT	24 IU/l	Cr	0.7 mg/dl
Seg	58.1 %	GPT	30 IU/l	BUN	16.7 mg/dl
Mono	6.5 %	LDH	263 IU/l	UA	4.0 mg/dl
Eo	7.4 %	γ-GTP	12 IU/l	Na	144 mEq/l
Baso	0.5 %	ChE	0.59 ΔpH	K	4.1 mEq/l
Lymph	27.5 %	LAP	63 IU/l	Cl	109 mEq/l
		ALP	128 IU/l	Ca	9.1 mg/dl
RBC	401×10⁴ /μl	T.Bil	0.6 mg/dl		
Hb	11.3 g/dl	D.Bil	0.1 mg/dl	CEA	0.5 ng/ml
Ht	33.8 %	T.Cho	188 mg/dl	CA19-9	< 0.6 U/ml
Plt	29.0×10⁴ /μl	T.P	7.5 g/dl		
		Alb	4.4 g/dl	HBsAg	(−)
		ZTT	4.0 Ku	HCVAb	(−)
		TTT	0.5 Ku		

Figure 1. 上部消化管内視鏡検査所見：内視鏡検査で矢印に示す範囲の胃体下部前壁に4cm大の浅い陥凹性病変を認めた.

N0, M0 と診断した. 治療は粘膜下腫瘍様病変を含めた幽門側胃切除および D2 郭清を施行した.

切除病理組織学的所見：陥凹性病変は 4.0×4.5 cm の 0-IIc で，signet ring cell が粘膜層に限局してみられた. 脈管浸襲を認めずリンパ節転移もみられなかった. 粘膜下腫瘍は胃底腺領域に存在し，長径 1.7cm で，粘膜下層を中心に大小不同の嚢胞や拡張した異型のない腺管を多数認めた（Figure 5a）. 拡張した腺管の間には平滑筋束の増生を認めた（Figure 5b）. 粘膜下腫瘍周囲, 癌および癌周囲の粘膜下層には粘膜下嚢胞はみられなかった. 以

上の所見より HIP と診断した. 胃癌については pT1, pN0, M0, H0, P0, CY0, Stage Ia であった. 現在外来経過観察中であるが, 2年後の現在再発を認めていない.

II 考　察

粘膜下の異所性胃腺には胃底腺と幽門腺の境界領域に好発し丈の低い比較的小さな粘膜下隆起が多発するびまん型（いわゆるびまん性胃粘膜下異所腺）と胃体上部や穹隆部など胃底腺領域に好発し比較的大きな腫瘤を形成する孤立型の2つの病態があるとされている[4]. このうち後者の粘膜下異所腺が増生, 貯留, 嚢胞化し孤立性腫瘤を形成するものを胃過誤腫性ポリープや HIP と呼称している[3][5]. Aoki らは孤立型異所性胃腺でいわゆる HIP とされる病変のうち有茎性のものをポリープ型, 無茎性のものを粘膜下腫瘍型と分類している[6]. 本症例は粘膜下腫瘍型と考えられた.

胃 HIP は極めてまれな疾患であり 1990 年から 2004 年まで医学中央雑誌にて検索した範囲では本症例を含めて 13 例のみ[2][3][5]~[14]報告されていた（Table 2）. 平均年齢は 46 歳, 男女比は 5：8 で女性に多く, 主訴は貧血・消化管出血がそれぞれ2例で最も多かった. 無症状のものは本症例を含めて7例であった. 肉眼型はポリープ型が4例, 粘膜下腫瘍型が本症例を含め 10 例であった.

HIP の診断については EUS 診断の有用性が報告されている[8]~[11]. しかしながら杉山ら[8]は第3

(46)

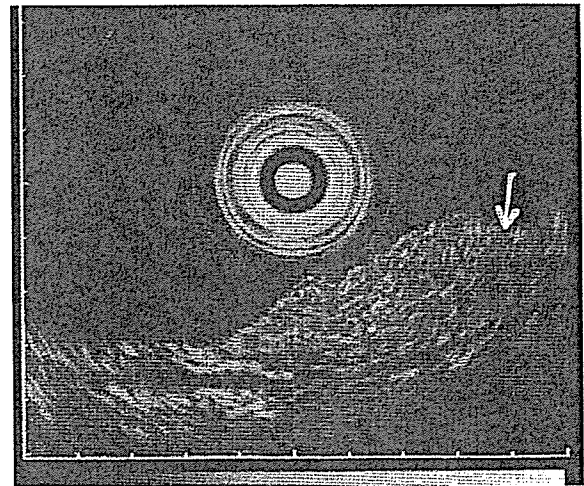Figure 2. 上部消化管内視鏡検査所見：体上部小彎に2cm大の扁平な隆起性病変（矢印）を認めた.

Figure 4. 超音波内視鏡検査所見：低エコーの腫瘍が第2～3層にかけて存在しており，内部に細い脈管様の無エコー域の集簇（矢印）を認めた. 第4層は正常に保たれていた.

Figure 3. 上部消化管内視鏡検査所見：隆起性病変は正常粘膜に覆われており，粘膜下腫瘍（矢印）と診断した.

層のびまん性高エコー腫瘍，松岡ら[11]は粘膜下の大小さまざまな無エコー域の充満する海綿状腫瘍と記載しており，EUS像も症例によって異なり，EUSのみでは確定診断が困難である. Table 2のうち内視鏡でHIPと診断された例は，井上ら[10]，松岡ら[11]が報告した2例のみであった. 日比野ら[3]は病巣内の数個の無エコー域を迷入膵にみられる脈管像と判断し，われわれと同様に術前診断を迷入膵としていた. 胃粘膜下腫瘍のEUS像における細い脈管様の無エコーは迷入膵の導管なのか，あ

るいはHIPの拡張した腺管なのか，症例によって慎重に判断する必要がある. HIPはEUS下穿刺吸引生検を行えば，診断が確定する可能性があるが，腫瘍の組織が採取できていたにもかかわらず，生検組織内に腺窩上皮を多数認めたことから胃粘膜上皮のみが採取されたと誤って診断された報告[3]もあり，あらかじめ粘膜下腫瘍の鑑別診断にHIPを考慮に入れておかないと，EUS下穿刺吸引生検でも診断が困難である.

粘膜下異所性胃腺のうちびまん型では胃癌の合併（特に分化型腺癌）が多く，いわゆるparacancerous lesionとして注意を喚起されており[5][15][16]，近年ヘリコバクターピロリ感染との関連が議論されているが[17][18]，孤立型にも癌が存在し異所性胃腺から癌が発生したとする報告もみられる[19]. Table 2の13例のうち，加藤ら[9]の高分化型腺癌の併存をみた報告と本症例の2例にHIPと胃癌の併存がみられた. さらに本症例では合併した胃癌の組織型は印環細胞癌であり，HIPに分化型腺癌以外の癌が合併した極めてまれな症例と考えられる. 癌とHIPの間に関連があるかどうか現在のところ不明であり，今後さらに症例の集積と検討が必要である.

治療に関してはポリープ型に対しては腫瘍が大きかった1例を除いて内視鏡的切除が行われてい

Table 2. 胃 hamartomatous inverted polyp の本邦報告例（1990〜）

|	著者	年齢	性別	報告年	初発症状	病変の位置	大きさ（cm）	形態	内視鏡診断	胃癌の併存	治療
1	瀧澤ら[7]	48	女	1990	−	体上部小彎	2.5×2.0×1.5	SMT type	粘膜下腫瘍（筋原性腫瘍）	−	手術
2	杉山ら[8]	15	女	1992	心窩部痛	体上部大彎	1.2×1.4	SMT type	記載なし	−	内視鏡的切除
3	加藤ら[9]	73	男	1993	貧血	体中部後壁	1.5×1.4×1.0	SMT type	胃のう胞	+	内視鏡的切除
						体上部大彎	1.5×1.4×1.1	SMT type		−	内視鏡的切除
4	井上ら[10]	67	男	1995	−	体上部大彎	1.0×0.9×0.5	SMT type	胃粘膜下異所腺	−	内視鏡的切除
5	松岡ら[11]	39	女	1995	−	穹隆部前壁	1.8	polyp type	過誤腫様ポリープ	−	内視鏡的切除
6	多田ら[12]	68	男	1996	食欲不振・貧血	残胃吻合部	7×6×4	polyp type	良性ポリープ	−	手術
7	Itoh et al[13]	41	女	1998	心窩部不快感	穹隆部	2.3×1.8×0.9	polyp type	記載なし	−	内視鏡的切除
8	Kubo et al[14]	21	女	2000	消化管出血	穹隆部	記載なし	polyp type	記載なし	−	内視鏡的切除
9	小沢ら[5]	40	女	2000	−	穹隆部大彎	2.5×1.7×0.9	SMT type	HIP またはリンパ管腫	−	内視鏡的切除
10	日比野ら[3]	63	男	2002	−	穹隆部大彎	2.5×2.8	SMT type	迷入膵または筋原性腫瘍	−	手術
11	梅岡ら[2]	41	男	2003	消化管出血	体上部後壁	0.5×0.5	SMT type	粘膜下腫瘍	−	手術
12	Aoki et al[6]	43	女	2004	−	体上部後壁	2.8	SMT type	診断つかず	−	手術
13	自験例	39	女	2005	−	体上部小彎	1.7×1.2	SMT type	迷入膵	+	手術
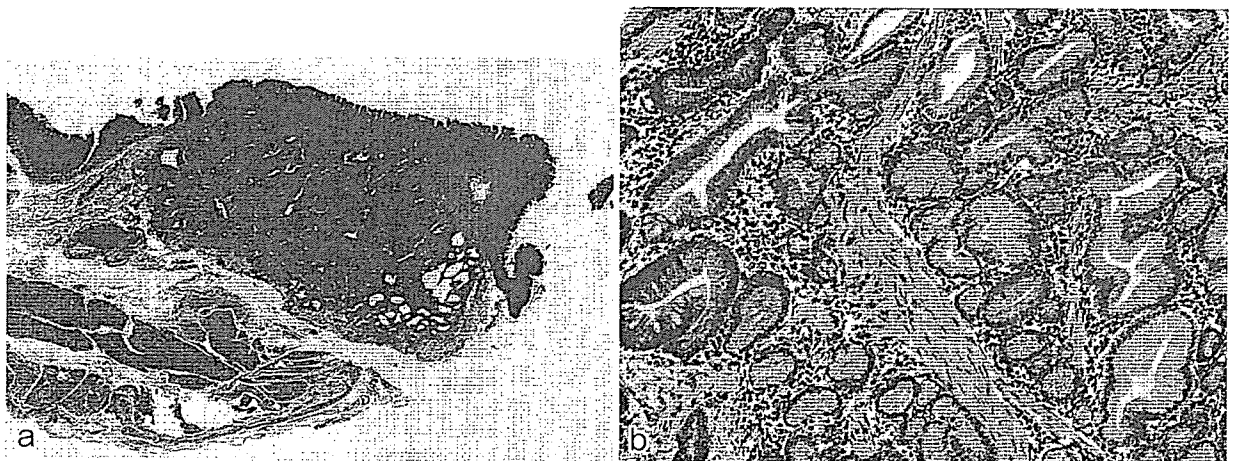
Figure 5. 手術標本組織所見　a：粘膜下層を中心に大小不同の囊胞と拡張した異型のない腺管を多数認めた（HE 染色，×4）．　b：拡張した腺管の間には平滑筋束の増生を認めた（HE 染色，×100）．

る．粘膜下腫瘍型に対しては平滑筋肉腫を否定し得なかった例[7]，出血を繰り返した例[2]，本症例のように胃癌などの他病変に併存した例においては外科手術が行われている．粘膜下腫瘍型に対しては近年急速に普及しつつある切開剥離法（ESD）による内視鏡的切除も有効な治療手段となりうると

思われる[20]．しかし ESD は出血頻度が高い治療法であり，出血の症候を呈した例[2]や内視鏡治療中に出血を生じ，外科手術を行った報告例[7]があることから，粘膜下腫瘍型胃 HIP に内視鏡治療，特に ESD を行う場合は特に出血に注意して慎重に行うべきであると思われた．

結　論

早期胃癌に併存し，迷入膵と鑑別困難であった粘膜下腫瘍型胃 HIP の1例を報告した．胃粘膜下腫瘍の鑑別診断においては HIP を考慮に入れておく必要があると思われた．

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