t-test. When a normal distribution was not evident, the non-parametric Wilcoxon rank sum test was employed. Student's *t*-test was used to compare the thickness of an intraepithelial carcinoma in each categorized group according to parameters such as MVD. The associations of histological parameters with subepithelial invasion were assessed with χ^2 statistics. Spearman's rank correlation tests were employed to assess the relationship between MVD and the thickness of IESCC or the relationship between tumour thickness and tumour size. Values of $P < 0.05$ were considered significant.

Results

HISTOLOGICAL FINDINGS OF NON-NEOPLASTIC LESIONS, DYSPLASIA, SCC *IN SITU* AND INVASIVE SCC ON THE BASIS OF MICROVASCULAR IRREGULARITIES AND THE MATCHED NBI IMAGES

We highlighted several differential diagnostic findings such as IPCL extension upward, IPCL dilation and branching, IPCL diameter expansion, proliferative cell distribution, basal cell palisading, basal cell enlargement, spinous layer retention, superficial layer (parakeratotic-like flat epithelial cell layer) retention, nuclear arrangement, nuclear density and subepithelial solitary cell nest, as shown in Table 3. The microscopic images including H&E staining (A), immunohistochemical staining using CD34 (B) or MIB-1 (C) antibodies are shown in Figures 1–7. The matched NBI images (D), except for Figure 1, are also shown. In Figure 1, as a non-neoplastic and non-inflammatory squamous epithelium, an IPCL was observed and uniform basal cells were arranged in the basal layer, but no microvascular irregularities were observed. In Figure 2, biopsy specimen histology showed an inflammatory lesion. Intercellular oedema and intraepithelial inflammatory cells were recognizable. An upward shift of an almost normal-sized IPCL, but no IPCL irregularity was seen (Figure 2A–C). NBI endoscopy shows inflammatory lesions as an ill-demarcated brownish area. Slight IPCL proliferation and IPCL dilation are obscured by the

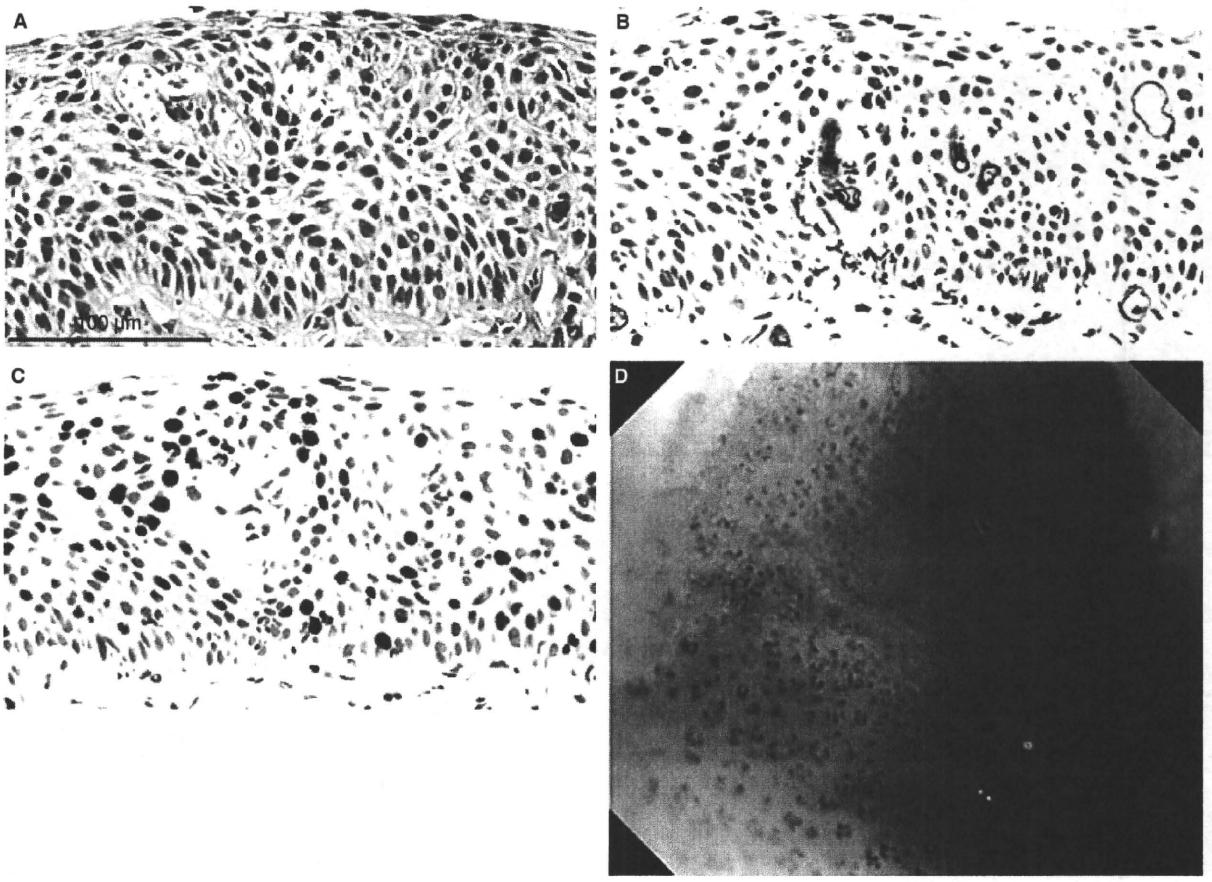

Figure 5. The histology of severe dysplasia from a biopsy specimen. **A**, H&E. **B**, CD34. **C**, MIB-1. **D**, Narrow-band imaging of the hypopharynx (pyriform sinus).

cloudy background mucosa (Figure 2D). Basal cell hyperplasia is shown in Figure 3. Proliferative cells labelled by MIB-1 were localized at the peri-IPCL. Basal cell palisading was preserved and no basal cell enlargement was detected. Spinous and surface layers were also preserved (Figure 3A–C). Figure 3 is presumed be an earlier manifestation of dysplasia, since thickened IPCLs with dilation and branching have shifted to the superficial side of the epithelium (Figure 3A). In contrast to inflammatory lesions, hyperplastic lesions showed small, well-demarcated brownish areas on NBI images with magnification (Figure 3D). Figure 4 shows mild dysplasia. Basal cell palisading was observed, though proliferative cells with enlarged nuclei, proliferating in a lamellar pattern, were limited to the lower third of the epithelial layer (Figure 4A–C). IPCL abnormalities such as IPCL extension upward, IPCL dilation and branching and IPCL diameter expansion were also recognized clearly, as well as basal cell hyperplasia (Figure 4A). The NBI image showed a wider brownish area than Figure 3D. In severe dysplasia (Figure 5), nuclear arrangement polarity was lost and nuclear density was severely increased throughout the intraepithelial layer, although there was maturation of the superficial portion of the epithelium. Microvascular irregularities were more severe than those in mild dysplasia. In the NBI image, dense, irregular IPCLs were recognized as a thicker and whitish epithelial lesion against a well-demarcated brownish area (Figure 5D). In SCC *in situ* (Figure 6), the basal cell palisading was obscure and the superficial maturation of the epithelium was lost. Prominent architectural disarray, marked cytological atypia and increased mitotic figures with pathological forms were recognized. Thickening of the intraepithelial

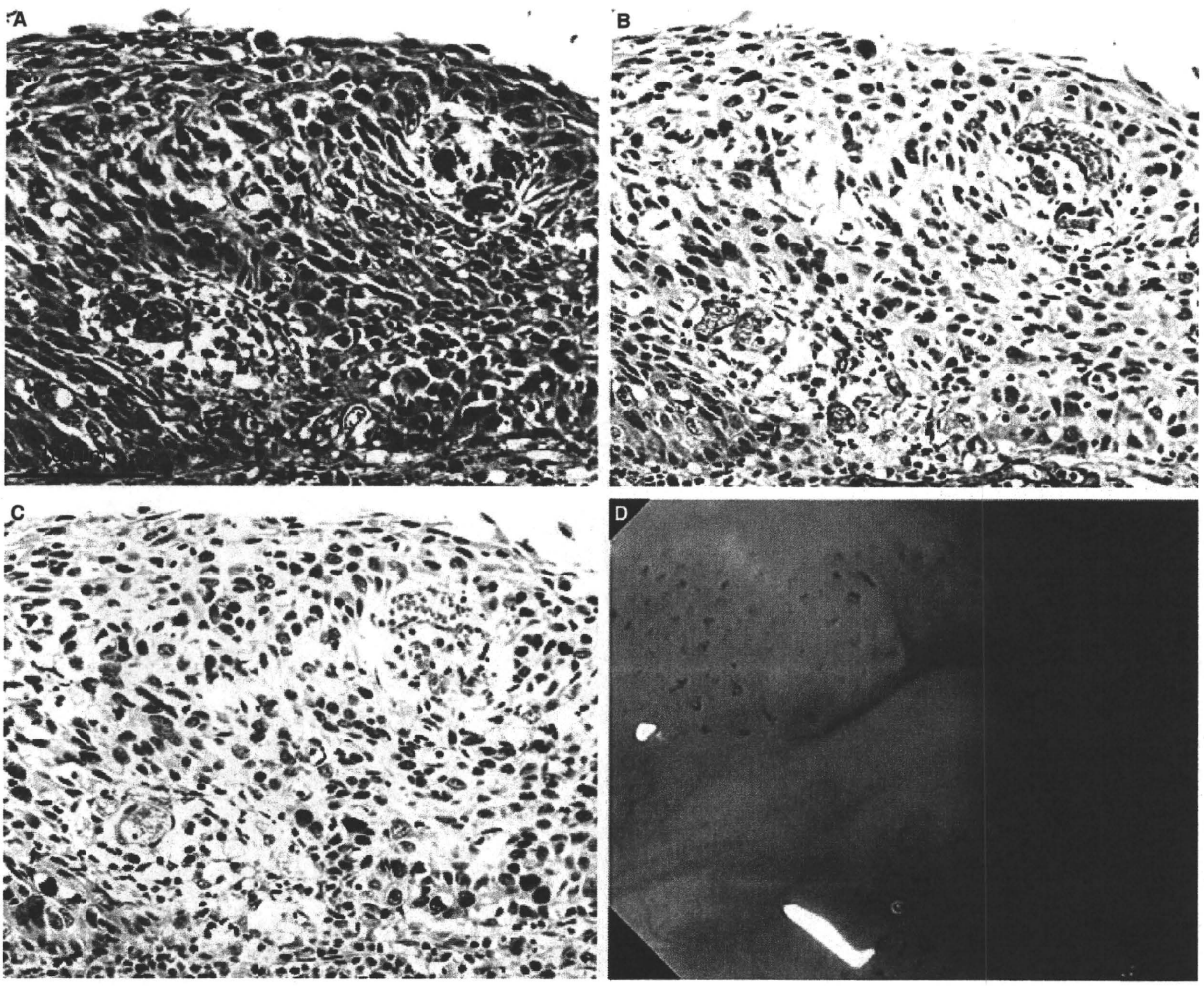

Figure 6. The histology of squamous cell carcinoma *in situ* from an endoscopically resected specimen. A, H&E. B, CD34. C, MIB-1. D, Narrow-band imaging of the hypopharynx (pyriform sinus).

lesion was also recognized as being different from that in severe dysplasia. IPCL dilation and IPCL branching-like petals were clearly recognized. The NBI image (Figure 6D) showed more dilated irregular IPCLs than Figures 4D and 5D. In invasive SCC (Figure 7), IESCC thickening and subepithelial solitary cell nests were recognized (Figure 7A–C). Dilated and branched IPCLs were recognized in the upper area of IESCC accompanied by thickening of IESCC. The NBI image showed a more voluminous and thickened brownish area (Figure 7D).

SUBEPITHELIAL INVASION, IESCC THICKNESSES AND TUMOUR THICKNESS OF INVASIVE SCC

The range of thickness of IESCC was broad: 125–1000 μm. The tumour thickness of invasive SCCs ranged from 300 to 3500 μm. The tumour thickness of all STPSCCs ranged from 125 to 3500 μm.

MVD

To calculate the MVD, immunohistochemistry using CD34 antibody was performed to detect microvessels clearly (Figures 1–7B). The values of MVD ranged from 0.1 to 17.82 (mean ± SD 4.04 ± 3.23).

RELATIONSHIPS BETWEEN HISTOLOGICAL PARAMETERS

There was a significant correlation between MVD and IESCC thickness ($P = 0.0115$, Spearman correlation test $r = 0.25$, Figure 8A). Interestingly, there was

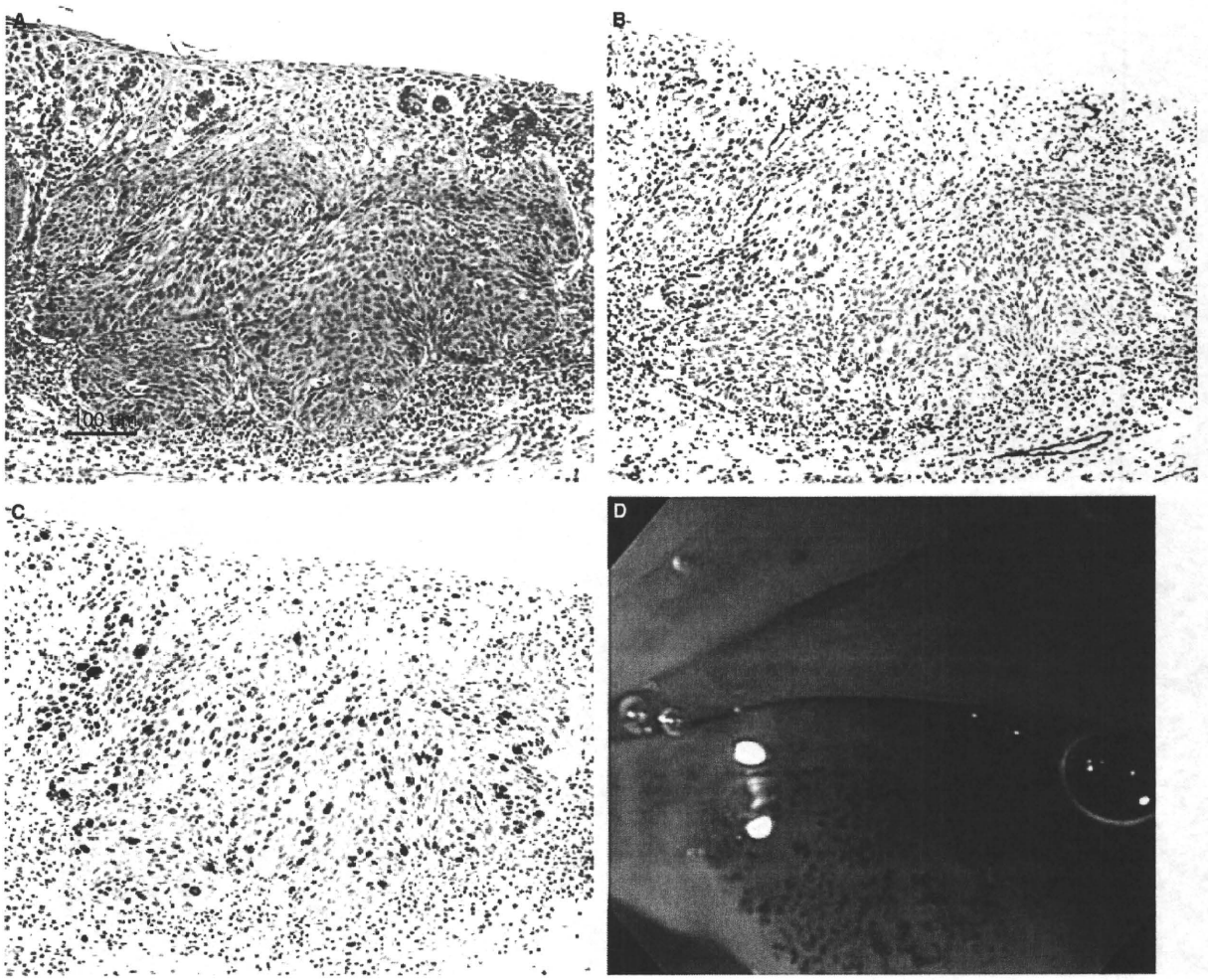

Figure 7. The histology of invasive squamous cell carcinoma from an endoscopically resected specimen. **A**, H&E. **B**, CD34. **C**, MIB-1. **D**, Narrow-band imaging of the oropharynx (lateral wall).

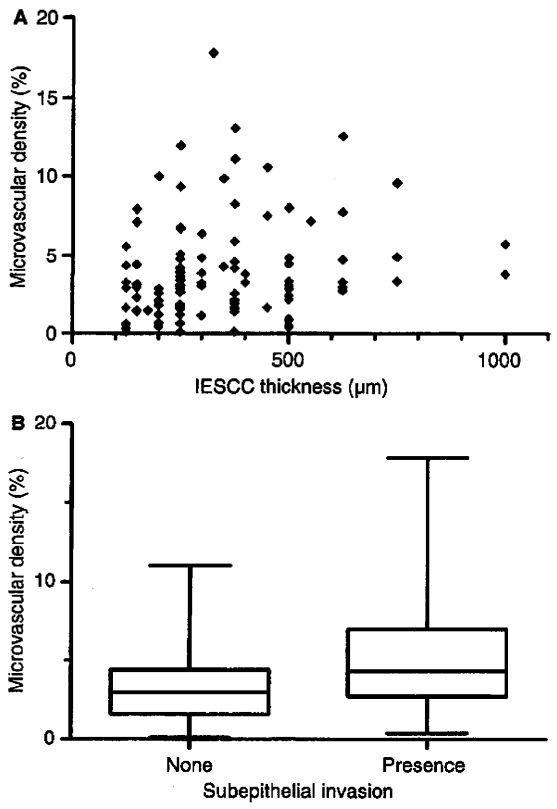

Figure 8. The relationships between intraepithelial squamous cell carcinoma (IESCC) thickness, microvascular density (MVD), and subepithelial invasion. A, The relationship between MVD and IESCC thickness. B, The relationship between MVD and subepithelial invasion. A *P*-value < 0.05 was taken to indicate a statistically significant difference.

significant correlation between MVD and subepithelial invasion ($P = 0.0078$, Figure 8B).

Next, we investigated the relationships between IESCC thickness, tumour thickness, tumour size and subepithelial invasion. There was significant correlation between IESCC thickness and subepithelial invasion ($P < 0.0001$, Figure 9A). There was significant correlation between tumour thickness and subepithelial invasion ($P < 0.0001$, Figure 9B). These correlations suggested that SCC detected by NBI endoscopy shows increased MVD due to microvascular irregularities, which then leads to greater IESCC thickness, resulting in subepithelial invasion.

The cases with subepithelial invasion had significantly larger tumours than those without subepithelial invasion ($P = 0.0013$, Figure 9C). There was significant correlation between tumour thickness and tumour size (Spearman $r = 0.4560$, $P < 0.0001$, Figure 9D).

As described above, there were significant correlations between tumour thickness, MVD and subepithelial invasion. We investigated the relationship between tumour thickness and vessel infiltration, including invasive and non-invasive carcinomas. As shown in Figure 9E, there was significant correlation between tumour thickness and vessel infiltration ($P < 0.0001$). Only one STPSCC (0.96%) showed lymph node metastasis as a late event (Table 2). The tumour thickness in this case was 1750 μm and both lymphatic and blood vessel infiltration were observed in the primary tumour. The mean tumour thickness of STPSCCs resected by EMR/ESD was 1040 μm. Three cases (2.9%) showed local recurrence after EMR/ESD. All three tumours were <20 mm in diameter but showed subepithelial invasion, and one of the three had blood vessel infiltration. The horizontal cut ends of specimens by EMR/ESD were positive for carcinoma cells.

Discussion

The dense microvascular proliferation caused by irregular branching of IPCLs, the upward shift and thickening of IPCLs, which reflect microvascular irregularities detected by NBI endoscopy, were observed pathologically in squamous epithelial lesions of the pharynx. The alterations of microvascular structures represented by IPCL irregularities occurred with architectural or cytological abnormalities in squamous epithelial lesions (Table 3). Based on the current results, we propose four steps to invasive SCC starting with basal cell hyperplasia. In the first step, the upward shift of IPCLs with dilation and branching occurs in basal cell hyperplasia (Figure 3). In the second step, density of IPCL increases in mild dysplasia (Figure 4). In the third step, microvascular irregularities increase with branching of IPCLs (Figure 5). Moreover, marked IPCL proliferation with irregular branching is observed throughout the intraepithelial layer. Thickening of intraepithelial lesions becomes apparent (Figure 6). Finally, in the fourth step, dilated and branched IPCL increases in intraepithelial lesions, accompanied by increasing MVD, resulting in subepithelial invasion (Figure 7).

The results of the present study suggest that IESCC thickening by increased MVD plays an important role in the early stage of subepithelial invasion (Figures 8 and 9). On the other hand, the average value of MVD of dysplasia (including mild and severe) was 2.9, which was lower than the average value of MVD of IESCC (4.0). The value of MVD of single basal cell hyperplasia was 2.1. This suggests that MVD increases step by step from basal cell hyperplasia through dysplasia to

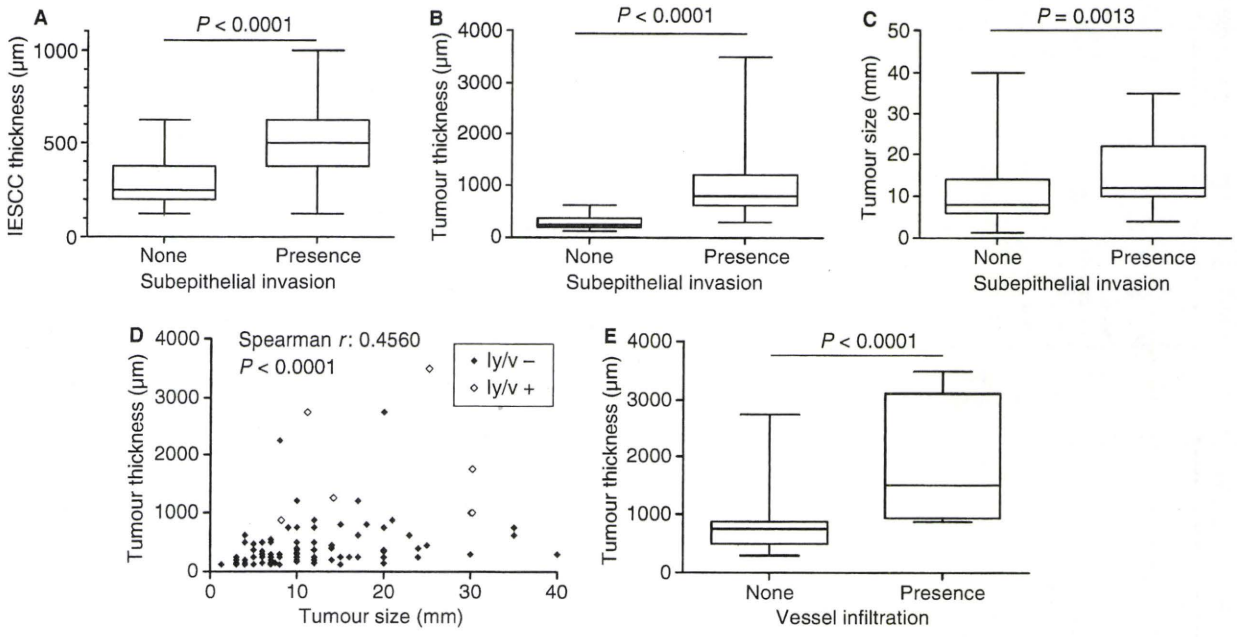

Figure 9. The relationships between intraepithelial squamous cell carcinoma (IESCC) thickness, tumour thickness, tumour size, subepithelial invasion, and vessel infiltration. **A**, The relationship between IESCC thickness and subepithelial invasion. **B**, The relationship between tumour thickness and subepithelial invasion. **C**, The relationship between tumour size and subepithelial invasion. **D**, The relationship between tumour thickness and tumour size. Black and white diamond symbols represent a case without lymphatic and venous infiltration and a case with lymphatic or venous infiltration, respectively. **E**, The relationship between tumour thickness and vessel infiltration in superficial-type pharyngeal squamous cell carcinomas (STPSCCs) with subepithelial invasion (n = 29). A P-value <0.05 was taken to indicate a statistically significant difference.

carcinoma. An interesting previous report examined MVD in epithelial proliferative lesions of breast.[12] In florid ductal hyperplasia usual type, atypical ductal hyperplasia and atypical lobular hyperplasia, MVD values were intermediate between normal glandular structures and neoplastic lesions. Moreover, the MVD of higher-grade-type intraductal carcinoma was higher than that of lower-grade-type intraductal carcinoma. These findings suggest that an increase in blood supply is necessary for any type of epithelial proliferation, and higher MVD values are associated with a higher risk of progression to invasiveness in pre-invasive breast cancer as in intraepithelial squamous lesions in the present study. However, because the number of precursor lesions in the present study was small, further detailed analysis is needed in the future.

There were a few tumours showing remarkable intraepithelial spreading without either subepithelial invasion of the STPSCC or thickening of IESCC. The five tumours without subepithelial invasion were > 20 mm (20 mm <), and these tumours were categorized as T2 in the International Union Against Cancer classification.[13] The cases were assumed to be good candidates for endoscopic resection of STPSCC. As shown in Figure 9E, there was significant correlation between tumour thickness and vessel infiltration in STPSCC. However, as shown in Figure 9E, the greater the tumour thickness, the higher rate of vessel infiltration that was observed. These results suggest that the T factor incorporating tumour thickness may be reasonable, as well as being a qualified risk factor, for clinicians when contemplating additional treatments such as lymph node dissection or selecting intense follow-up after EMR/ESD.

Multiple STPSCCs at oropharyngeal and hypopharyngeal mucosal sites were identified in 30 patients (43.5%) in the current study. This means that the same patient would need additional EMR/ESD. Numerous EMR/ESD can cause future stenosis of the pharynx. From the view of a preventive strategy, it is important to identify the abnormal proliferative factor influencing IPCL in STPSCC, and further future analyses are necessary.

The chance of diagnosing an early squamous epithelial lesion with microvascular irregularities detected by NBI endoscopy has improved and facilitates an understanding of the pathological features necessary for appropriate diagnosis. The present study has

shown microvascular irregularities to be associated with carcinogenesis of SCC. A better understanding of the pathogenesis of squamous epithelial lesions and early invasion of SCC should facilitate appropriate diagnosis and treatment of STPSCC.

Acknowledgements

We thank Ms Mai Okumoto for her excellent technical assistance in immunohistochemistry. This study was supported in part by a Grant-in-Aid for Cancer Research (19-10) from the Ministry of Health, Labour, and Welfare of Japan and a Grant-in-Aid for the Third Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare of Japan.

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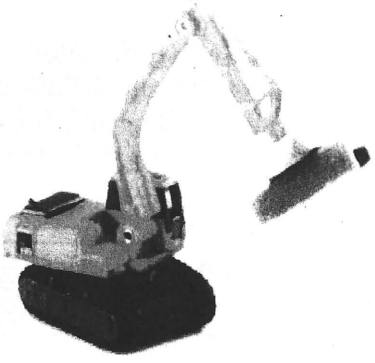
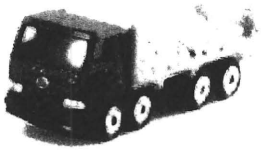
消化管診療のトピックス＆トレンド





インタビュー
第6回日本消化管学会総会学術集会会長
飯田 三雄氏
「消化管学のさらなる発展に寄与したい」

特集 炎症性腸疾患を鎮める あの手この手

レポート
IBSの発症原因に新仮説が続々

診療アップデート
「小腸の内視鏡診断と治療」ほか

学会トピックスWIDE
胃シンチでFDの運動機能を評価

日本消化管学会監修

咽頭・食道癌の最新知見

アルコールの発癌性にWHOが警鐘

アルコール飲料に含まれるエタノールが代謝される過程で産生されるアセトアルデヒドが、WHOでClassIの発癌物質として認定された。日本人の約半数はアセトアルデヒドの代謝酵素が低活性型もしくは不活性型であるため、飲酒による発癌リスクが高いと考えられている。

消化管疾患の知識

武藤 学（京都大学医学部消化器内科准教授）

2009年10月に世界保健機関（WHO）の下部組織である国際がん研究機関（International Agency for Research on Cancer:IARC）の会合が行われ、この会で初めて、アルコール飲料が代謝される際に発生するアセトアルデヒドが食道・頭頸部癌のClass Ⅰの発癌物質、つまり最も明らかな癌の原因物質であることが認定された。筆者もこの会議に参加し、2週間以上かけて様々な発癌物質を再評価する場に立ち会った。ヒトの体内で代謝によって産生される物質が発癌物質と認定されたのはこれが初めてのことだ。

食道癌と頭頸部の扁平上皮癌は多発または重複しやすく、このことは半世紀以上前から“フィールド癌化説（field cancerrization）”という理論で知られていた。アセトアルデヒドが食道・頭頸部の共通した発癌物質であることは、この現象からも説明がつく。

本稿では、近年、明らかになってきた、アルコールによる食道咽頭癌発生のメカニズムや、多発・重複癌が発生しやすい理由を紹介したい。

ALDH2の低活性型と不活性型はハイリスク

図1はアルコールの代謝過程だ。摂取されたアルコール飲料（エタノール）は、主に肝臓のミトコンドリアでアルコール脱水素酵素（ADH）によってアセトアルデヒドに代謝される。さらに、アセトアルデヒドは、アルデヒド脱水素酵素（ALDH）によって酢酸に代謝される。

アセトアルデヒドの代謝では、ALDHの一種のALDH2という酵素がアセトアルデヒドを主に除去する役割を担っている。そのため、飲酒後のアセトアルデヒドの血中濃度は、ALDH2活性型の人に比べ、ALDH2不活性型ヘテロの遺伝子型の酵素をもつ人（低活性型）は約6倍、ALDH2不活性型ホモの遺伝子型の酵素をもつ人（不活性型）は約19倍にも上昇する（表1）。

日本人の約半数は、ALDH2低活性型、もしくはALDH2不活性型である。これらの遺伝子型を持ってい

図1●アルコールの代謝過程

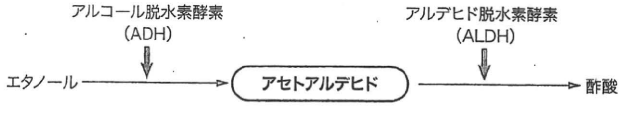


表1●飲酒後のアセトアルデヒドの相対血中濃度（武藤氏による）

ALDH2-活性型/活性型	1
ALDH2-活性型/不活性型	6
ALDH2-不活性型/不活性型	19

図2●食道・のどの癌化のメカニズム（武藤氏による）

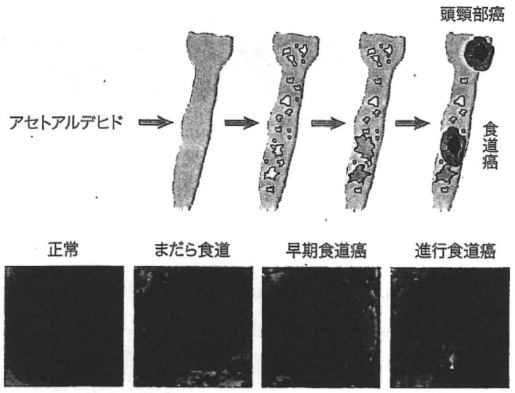


表2●頭頸部癌/食道癌症例におけるまだら食道（multiple LVL）発生予測因子

因子	相対危険度（95% CI）	p
ALDH2不活性型遺伝子を持つ人（大半が低活性型）	5.8（2.9-11.6）	<0.0001
低活性ADH3遺伝子	2.8（1.1-6.7）	0.019
男性	2.3（0.5-12.2）	0.32
60歳以上	1.5（0.8-2.8）	0.27
たばこ指数（1日本数×年数）≧1000	1.0（0.5-1.8）	0.88
1日摂取アルコール量≧80g	0.9（0.5-1.8）	0.84

M Muto, et al. Carcinogenesis 2005 ;26 ;1008-12.

る人は、飲酒により顔面紅潮や動悸を起こすので、この反応によって9割以上の人のALDH2遺伝子型を大まかに判別することができる。ALDH2不活性型の人は極端にお酒に弱いため、お酒は全く飲めない。しかし、ALDH2低活性型の人は飲酒を繰り返すうちにある程度お酒が飲めるようになる。こうした人がアルコール飲料を飲むと食道癌になりやすいことが実際の報告からも明らかになっている。

ALDH2活性型の人の場合でも、1日1合の日本酒換算量を飲む場合を基準とすると、2合飲むと食道癌のリスクは5倍、3合飲むと10倍のリスクになる。一方、ALDH2低活性型の人が1日1合の日本酒換算量を飲む場合は、ALDH2活性型の人が1日1合の日本酒換算量を飲む場合に比べて、食道癌のリスクは5倍、2合飲むと食道癌のリスクは実に50倍以上、3合飲むと80倍にもなる（Yokoyama A, Muto M, et al. Carcinogenesis 2002;23:1851-9）。

“まだら食道”が食道癌に進展

内視鏡検査を行うと、ヨード染色にて大小不同のヨード不染帯を多発するいわゆる“まだら食道”を来す患者に遭遇することがある。このまだら食道は、放置すると上皮内腫瘍が出現し、扁平上皮癌へと移行し、2～3年もすれば進行癌になる（図2）。

我々の調査で、このまだら食道はALDH2不活性型遺伝子を持つ人で出現しやすいことが明らかになった（表2）。頭頸部癌もしくは食道癌の患者におけるまだら食道の発生予測因子を調べたところ、ALDH2活性型の人に比べて、ALDH2不活性型とALDH2低活性型の人の相対危険度は5.8と、年齢や喫煙より高いことが分かった。ALDH2不活性型遺伝子を持つ人のほとんどは、ALDH2低活性型だった。病変が広範にわたるまだら食道から発癌すると、冒頭のように頭頸部や食道に多発・重複癌が発生するというわけだ。

写真1●全身麻酔下内視鏡的咽頭粘膜切除術（提供：武藤氏）

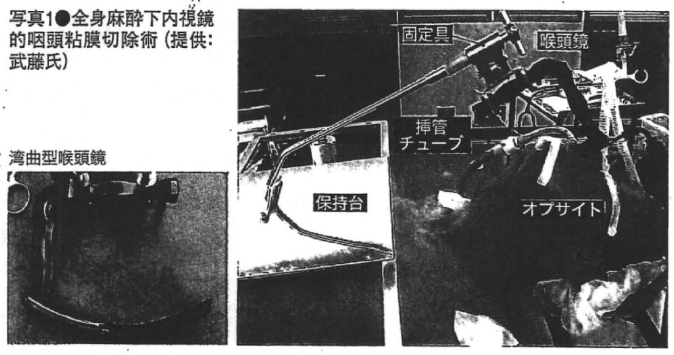
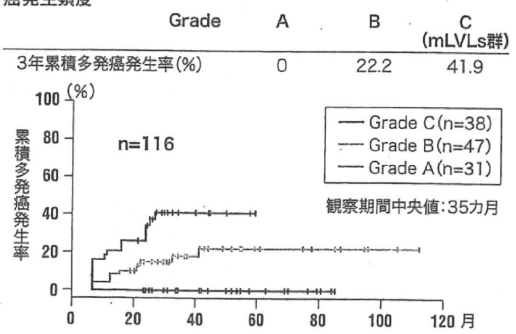
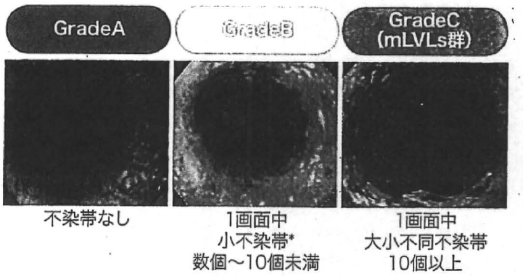


図3●食道癌EMR例におけるヨード不染帯の程度別の食道内多発癌発生頻度





*小不染帯とは5mm以下のヨード不染帯を示す

堅田親利、武藤学ほか. 胃と腸 2007;42(9):1355-63.

頭頸部癌の早期発見が可能になった

多発・重複癌発生メカニズムが明らかになったことに加え、Narrow Band Imaging (NBI)や拡大内視鏡といった内視鏡技術の進歩により、これまで極めて困難といわれていた頭頸部、特に咽頭・喉頭の扁平上皮癌の早期発見が可能になった。早期発見した咽頭・喉頭の表在癌に対しては、低侵襲である全身麻酔下での内視鏡的切除が行われるようになった。

我々は、川崎市立病院耳鼻咽喉科の佐藤靖夫氏らが開発した湾曲型喉頭鏡を用いて、全身麻酔下の内視鏡的切除術を行っている (写真1)。通常、内視鏡で見ると左右の梨状陥凹はつぶれているが、湾曲型喉頭鏡を用いると喉頭が持ち上がり、食道入口部まで見える。視野が確保されやすくなり、非常に内視鏡切除術が行いやすい。

4分の3周以上の病変は7割が再狭窄

まだら食道から移行した食道癌は、病変が広範囲に及ぶため、治療に難渋することが多い。食道癌の治療は、内視鏡的治療や外科的切除、抗癌剤治療、放射線など、ステージ別に様々な選択肢がある。中でも内視鏡的粘膜切除術 (Endoscopic mucosal resection:EMR) や粘膜下層剥離術 (Endoscopic submucosal dissection:ESD) は、低侵襲で根治性のある治療法として広く行われているが、周在性が大きい病変や全周性の病変では、治療後の食道狭窄を来すため適応にならない。

EMR後の粘膜欠損の周在性と食道狭窄の頻度を調べると、粘膜欠損が4分の3までの場合は、食道の再狭窄を来した患者はいなかったが、4分の3周以上の病変を取った場合には狭窄率は一気に跳ね上がり、約7割の人で狭窄が起きていた。3cm以上の長い病変になると狭窄はほぼ100%近い値になる。

ヨード不染帯の程度によって再発率に大きな違い

食道癌の外科手術例における10年以内の2次癌の発生リスクを部位別にみると、胃癌の相対危険度が2.0、肺癌が3.24であるのに対し、頭頸部癌は実に34.9と突出して多くなっている。まだら食道から移行した食道癌は、内視鏡により病変を取り除いても、その後、異時性の癌が発生する可能性が高い。

EMR後の食道癌における異時性の食道内多発癌の発生率は、ヨード不染帯の数が多くなるに従って高くなる (図3)。筆者は、GradeBやGradeCの患者には半年から1年に1回程度の検査が必要と考える。また、逆に、不染帯がない患者は3年に1回程度の検査でよい可能性がある。

エタノールの代謝産物のアセトアルデヒドには発癌性があり食道癌を来しやすい。アセトアルデヒドによる食道癌は、多発性の病変や重複頭頸部癌を伴うため、治療方針に難渋したり、再発率が高いといった課題が残る。そのため、飲酒により顔面紅潮などを起こすALDH2低活性型・不活性型と考えられる人は、過剰なアルコール摂取を控えることが重要である。

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BRIEF ARTICLE

Endoscopic diagnosis of cytomegalovirus gastritis after allogeneic hematopoietic stem cell transplantation

Yasuo Kakugawa, Masahiro Kami, Takahisa Matsuda, Yutaka Saito, Sung-Won Kim, Takahiro Fukuda, Shin-ichiro Mori, Tadakazu Shimoda, Ryuji Tanosaki, Daizo Saito

Yasuo Kakugawa, Takahisa Matsuda, Yutaka Saito, Daizo Saito, Division of Endoscopy, National Cancer Center Hospital, Tokyo 104-0045, Japan
Masahiro Kami, Division of Exploratory Research, Institute of Medical Science, University of Tokyo, Tokyo 108-0071, Japan
Sung-Won Kim, Takahiro Fukuda, Shin-ichiro Mori, Ryuji Tanosaki, Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo 104-0045, Japan
Tadakazu Shimoda, Clinical Laboratory Division, National Cancer Center Hospital, Tokyo 104-0045, Japan
Author contributions: Kakugawa Y participated in the design of the study, data acquisition and interpretation, performed endoscopic examinations, and wrote the first draft of the manuscript; Kami M managed the therapy of patients, participated in the design of the study, and contributed to the writing of the manuscript; Matsuda T and Saito Y performed endoscopic examinations, and contributed to the writing of the manuscript; Kim SW, Fukuda T, Mori S and Tanosaki R managed the therapy of patients, and contributed to the writing of the manuscript; Shimoda T made the pathological diagnosis and contributed to the writing of the manuscript; Saito D participated in the design of the study and contributed to the writing of the manuscript; all authors read and approved the submitted version of the manuscript.
Correspondence to: Yasuo Kakugawa, MD, Division of Endoscopy, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. yakakuga@ncc.go.jp
Telephone: +81-3-35422511 Fax: +81-3-35423815
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Abstract

AIM: To clarify the endoscopic and clinical findings of cytomegalovirus (CMV) gastritis after allogeneic hematopoietic stem cell transplantation (allo-SCT).

METHODS: Between 1999 and 2005, 523 patients underwent allo-SCT at our hospital, and 115 of these patients with gastrointestinal symptoms underwent esophagogastroduodenoscopy.

RESULTS: CMV gastritis was diagnosed pathologically in seven patients (1.3%) with the other 108 patients serving as controls. Six of the seven patients developed positive CMV antigenemia, and five complained of abdominal pain. Development of abdominal pain preceded CMV antigenemia in four of the five patients. Endoscopic examination showed oozing (n = 2), erosion (n = 6), and redness (n = 5) in the seven patients with CMV gastritis, while the control patients showed oozing (n = 3), erosion (n = 24), and redness (n = 100). Erosion and oozing were more frequently documented in patients with CMV gastritis compared with the controls, and the differences were statistically significant (P = 0.0012 and 0.029, respectively). CMV inclusion bodies were documented in 12 of 14 biopsy specimens obtained from erosive lesions, while they were identified in 4 of 15 biopsy specimens obtained from lesions other than erosions (P = 0.0025).

CONCLUSION: This study suggests that erosion and oozing, as well as abdominal pain, are useful indicators in the diagnosis of CMV gastritis following allo-SCT.

Key words: Cytomegalovirus gastritis; Hematopoietic stem cell transplantation; Cytomegalovirus antigenemia; Esophagogastroduodenoscopy; Graft-versus-host disease

Peer reviewer: Dr. Herwig R Cerwenka, Professor, Department of Surgery, Medical University of Graz, Auenbruggerplatz 29, A-8036 Graz, Austria

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INTRODUCTION

Cytomegalovirus (CMV) disease is a serious complication after allogeneic hematopoietic stem cell transplantation (allo-SCT)[1], which is widely accepted as a curative therapy for advanced hematological malignancies including leukemia and malignant lymphoma. CMV disease can involve many organs and the gastrointestinal (GI) tract is a common target[2].

CMV antigenemia is one of the most widely used methods to detect CMV reactivation in a variety of clinical settings[3]; however, it is of limited value in predicting and diagnosing GI CMV disease[4]. GI CMV disease is usually diagnosed based on pathological examination of endoscopically obtained mucosal biopsy specimens. Few reports have been published regarding endoscopic examination in diagnosing CMV gastritis after allo-SCT[5-7]. This study aimed to investigate endoscopic findings of CMV gastritis after allo-SCT in addition to its clinical features.

MATERIALS AND METHODS

Study patients

Between January 1999 and September 2005, 523 patients underwent allo-SCT at the National Cancer Center Hospital in Tokyo, Japan. Among them, 115 patients with GI symptoms underwent esophagogastroduodenoscopy (EGD). Written informed consent was obtained from all patients before EGD. We retrospectively reviewed records of medical, endoscopic and pathological examination in the 115 EGD patients. CMV gastritis was diagnosed pathologically in seven patients (1.3%) by hematoxylin-eosin staining and immunohistochemical staining with an anti-CMV antibody. The other 108 patients served as controls.

Endoscopic procedure

All EGD patients orally received 100 mL of a solution containing 1 g of pronase and 1 g of sodium bicarbonate to remove mucus and bubbles on the gastric mucosa before EGD. Antiperistaltic agents (scopolamine butylbromide 20 mg or glucagon 1 mg) and sedatives (pethidine hydrochloride 17.5-35 mg or midazolam 2-3 mg) were injected intravenously. Conventional endoscopic instruments (GIF Q240; Olympus Co, Ltd, Tokyo, Japan) were used, and biopsy specimens were obtained endoscopically from severely involved areas. When abnormal findings were not found, biopsy specimens were obtained from normal appearing areas.

Pathological examination

Biopsy specimens were fixed immediately in a 10% buffered formalin solution and subsequently stained with hematoxylin-eosin. All tissues were examined by expert pathologists. Diagnosis of CMV gastritis was based on histological identification of CMV inclusion bodies by hematoxylin-eosin staining and immunohistochemical staining with an anti-CMV antibody. Diagnosis of graft-versus-host disease (GVHD) was determined in accordance with a report published previously[8].

Management of CMV

All patients were monitored at least once a week for CMV reactivation by CMV antigenemia assay using monoclonal antibody against C7-HRP (Teijin, Tokyo, Japan) after engraftment.

A patient was considered to be infected with CMV when CMV antigenemia assay detected CMV in the blood. A patient was considered to have CMV disease when CMV was demonstrated in biopsy specimens by hematoxylin-eosin staining and immunohistochemical analysis. Ganciclovir was initiated when either more than 10 cells per 50000 cells were positive according to the CMV antigenemia assay in patients transplanted from related donors, a single cell per 50000 cells was positive in patients transplanted from unrelated donors, or a patient was diagnosed as having CMV disease[9].

Management of GVHD

Acute GVHD was graded according to the consensus criteria[10,11] and all patients with grades II-IV acute GVHD were treated with 0.5-2.0 mg/kg per day of methylprednisolone.

Statistical analysis

Univariate analysis using Fisher's exact test was performed to compare differences in patient characteristics, clinical features, and endoscopic findings between the seven patients with CMV gastritis and the other 108 patients who had GI symptoms, but did not have CMV gastritis. Values of $P < 0.05$ were considered significant.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. There was a significant difference in the number of patients given tacrolimus with methotrexate as GVHD prophylaxis between the two groups ($P = 0.018$).

Clinical features

Five of the seven patients with CMV gastritis complained of abdominal pain, while 31 of the 108 control patients complained of abdominal pain ($P = 0.030$) (Table 2). The pain was localized in the upper abdomen in all four patients with CMV gastritis whose medical reports provided the specific location of their pain (Table 3). Three patients required significant analgesia (morphine hydrochloride for one and pentazocine hydrochloride for the other two). Abdominal pain improved with ganciclovir in four of the five patients with abdominal pain, and the remaining patient (Case 1) died of bacterial pneumonia without any improvement in CMV gastritis.

Watery diarrhea was found in four of the seven patients with CMV gastritis, and was complicated by intes-

Table 1 Patient characteristics with and without CMV gastritis

Variables		Patients with CMV gastritis (n = 7)	Patients without CMV gastritis (n = 108)
Median age (range)		47 (26-62)	45 (18-69)
Gender	Male/female	5/2	65/43
Underlying diseases	Acute leukemia	1	41
	Chronic leukemia	2	15
	Malignant lymphoma	3	21
	Myelodysplastic syndrome	1	22
	Others	0	9
Preparative regimens	Myeloablative/reduced-intensity	2/5	48/60
Stem cell sources	Marrow/peripheral blood/cord blood	3/3/1	39/64/5
GVHD prophylaxis	CSP alone/CSP + MTX/CSP + MMF/FK506 + MTX/FK506 Alone	2/3/0/2[a]/0	36/64/2/2[a]/4

CMV: Cytomegalovirus; GVHD: Graft-versus host disease; CSP: Cyclosporine; MTX: Methotrexate; MMF: Mycophenolate mofetil; FK506: Tacrolimus. [a]P = 0.018.

Table 2 Clinical features in patients with and without CMV gastritis

Variables			Patients with CMV gastritis (n = 7)	Patients without CMV gastritis (n = 108)
Gastrointestinal symptoms at EGD		Nausea	2	60
		Vomiting	1	26
		Abdominal pain	5[a]	31[a]
		Abdominal discomfort	2	23
		Hematemesis	1	2
		Tarry stool	2	6
		Watery diarrhea	4	32
		Appetite loss	0	40
CMV	Median onset of CMV gastritis	Days (range)	63 (33-167)	NA
	CMV antigenemia (C7-HRP) at EGD	Positive/negative/not done	6[b]/1/0	28[b]/71/9
		Median number of positive cells per 50 000 (range)	8[d] (0-143)	0[d] (0-167)
	Involved organs of CMV diseases	Esophagitis/duodenitis/enterocolitis/pneumonitis/retinitis	1/2/1/0/0	0/0/4/0/0
GVHD		Positive (clinical grade: Ⅰ/Ⅱ/Ⅲ/Ⅳ)	7[c] (2/2/3/0)	65[c] (45/10/9/1)

EGD: Esophagogastroduodenoscopy; NA: Not applicable. [a]P = 0.030, [b]P = 0.0026, [c]P = 0.044, [d]P = 0.0023.

Table 3 Clinical features of CMV gastritis

	Demographics	Gastrointestinal symptoms			CMV antigenemia assay	
	Age (yr), gender, diagnosis	Any symptoms	Abdominal pain		Onset (d)	Level at EGD (cells per 50000)
			Onset (d)	Localization in abdomen		
Case 1	34, male, CML	Abdominal pain, tarry stool	81	Upper abdomen	88	8
Case 2	43, female, MDS	Nausea, abdominal pain, tarry stool, hematemesis, watery diarrhea	53	No description	69	2
Case 3	60, male, AML	Abdominal pain, watery diarrhea	62	Upper abdomen	73	143
Case 4	48, female, ML	Abdominal pain, watery diarrhea	36	Upper abdomen	31	10
Case 5	47, male, ML	Abdominal pain, watery diarrhea	30	Upper abdomen	32	4
Case 6	62, male, CML	Abdominal discomfort	NA	NA	47	32
Case 7	26, male, ML	Nausea, vomiting, abdominal discomfort	NA	NA	NA	0[i]

[i]CMV antigenemia remained negative throughout clinical course. CML: Chronic myelocytic leukemia; MDS: Myelodysplastic syndrome; AML: Acute myelocytic leukemia; ML: Malignant lymphoma.

tinal GVHD in three of these four patients. Watery diarrhea improved with ganciclovir in a patient with CMV gastritis who had no evidence of intestinal GVHD.

All seven patients with CMV gastritis had GVHD, while 65 of the 108 control patients had GVHD (P = 0.044) (Table 2). Five of the seven patients with CMV gastritis had grade Ⅱ-Ⅳ GVHD that was being treated by corticosteroids.

CMV antigenemia assay

Six of the seven patients with CMV gastritis and 28 of the 108 controls showed positive CMV antigenemia (P =

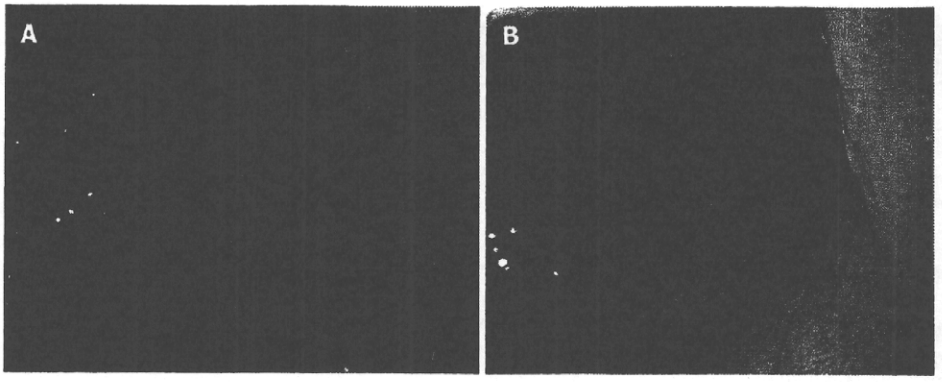

Figure 1 Erosion (Case 6). Multiple erosions are clearly shown in gastric body. A: Before indigo carmine dye spraying; B: After indigo carmine dye spraying).

Table 4 Endoscopic features in patients with and without CMV gastritis

Variables	Patients with CMV gastritis (n = 7)	Patients without CMV gastritis (n = 108)
Atrophic mucosa	3	36
Redness	5	100
Edema	2	9
Orange peel appearance	2	21
Mucosal sloughing	1	6
Erosion	6[b]	24[b]
Ulceration	0	2
Oozing	2[a]	3[a]

[a]P = 0.029, [b]P = 0.0012.

0.0026) (Table 2). The median number of positive cells in the CMV antigenemia test among the seven patients with CMV gastritis was 8 cells per 50 000 cells (range, 0-143) at the time of EGD.

Development of abdominal pain preceded the CMV antigenemia in four of the five patients who complained of it, and the median interval between onset of abdominal pain and the first positive CMV antigenemia was 7 d (range, -5 to 16 d) (Table 3).

Endoscopic findings

Erosion was observed in six of the seven patients with CMV gastritis and in 24 of the 108 control patients (P = 0.0012) (Table 4). The erosive lesions were located in the antrum (n = 2), body (n = 2), and antrum-body (n = 2) of the stomach. Two of the six patients had a solitary erosion, and the other four patients had multiple erosions of various sizes. Erosions were flat in four patients and raised in the other two. A representative example of erosion is shown in the accompanying figure; multiple erosions are clearly shown in the gastric body (Figure 1).

Oozing was observed in two of the seven patients with CMV gastritis and in three of the 108 control patients (P = 0.029). Oozing was located in the antrum with erosion (Case 3), and in the antrum-body with mucosal sloughing (Case 2).

Pathological findings

Detailed information regarding pathological findings is shown in Table 5. CMV inclusion bodies were documented in 12 of 14 biopsy specimens obtained from erosive lesions, while they were identified in 4 of 15 biopsy specimens obtained from lesions other than erosions (P = 0.0025) (Table 5).

Outcomes

Four patients died, and CMV disease was not the primary cause of death in any of them (Table 5). Two died from recurrences of their primary diseases, one died of bacterial pneumonia and one died of renal failure.

DISCUSSION

The present study clarifies the endoscopic findings of CMV gastritis following allo-SCT in addition to its clinical features. CMV gastritis was diagnosed pathologically in seven patients (1.3%) among 523 patients who underwent allo-SCT at our facility. The incidence is comparable to a previous study (1.7%)[12]. None of the seven patients died of CMV gastritis, while three patients complained of significant abdominal pain requiring analgesia which impaired their quality of life. CMV gastritis was a clinically important complication after allo-SCT.

No detailed information on clinical features of CMV gastritis has been previously reported. In the present study, abdominal pain was a common symptom of CMV gastritis. The pain was localized in the upper abdomen in all four patients whose medical reports provided the specific location of their pain. Ganciclovir administration improved abdominal pain in these four patients, supporting the likelihood that this symptom was attributable to CMV gastritis. Clinicians should pay particular attention to upper abdominal pain following allo-SCT as a possible symptom of CMV gastritis.

The association between watery diarrhea and CMV gastritis may be minimal as it remained unclear whether such diarrhea was due to CMV gastritis or overlapping intestinal GVHD. In the present study, ganciclovir improved symptoms in only one of four patients with diarrhea. In contrast, CMV gastritis was complicated by intestinal GVHD in three of those four patients. Our observations suggested that watery diarrhea in patients with CMV gastritis was more likely due to intestinal GVHD rather than the CMV gastritis itself.

Endoscopic findings characteristic of CMV gastritis

Table 5 CMV inclusion bodies and response to ganciclovir of CMV gastritis

	Positive specimens with CMV inclusion bodies/total specimens in EGD biopsy				Response to ganciclovir		Outcome	
	Total	Erosions	Mucosal sloughing	Other findings or normal mucosa	Abdominal pain	CMV antigenemia assay	Outcome	Cause of death
Case 1	1/2	1/2	None	0	Continued	Continued	Death	Bacterial pneumonia
Case 2	2/2	None	2/2[1]	0	Improved	Turned negative	Death	Recurrence of primary disease
Case 3	2/3	2/3[1]	None	0	Improved	Turned negative	Death	Renal failure
Case 4	5/7	4/4	None	1[2]/3	Improved	Turned negative	Alive	NA
Case 5	1/5	1/1	None	0/4	Improved	Turned negative	Alive	NA
Case 6	4/7	3/3	None	1[2]/4	NA	Turned negative	Alive	NA
Case 7	1/3	1/1	None	0/2	NA[3]	NA[4]	Death	Recurrence of primary disease
Case 7		26, male, ML		Nausea, vomiting, abdominal discomfort	NA	NA	NA	0[1]

[1]Oozing was accompanied in these findings; [2]The patient was not given ganciclovir, but CMV gastritis improved spontaneously; [3]The patient was not given ganciclovir, and CMV antigenemia remained negative throughout clinical course; [4]The patient was not given ganciclovir, and CMV antigenemia remained negative throughout clinical course.

after allo-SCT have not been fully investigated, but the present study indicates that erosion and oozing might be useful markers for early diagnosis of CMV gastritis. Vascular endothelium infected with CMV narrows vessels and induces local ischemia[13] eventually resulting in erosions and oozing. In fact, most CMV inclusion bodies were obtained from erosion sites. Erosions from CMV gastritis developed in all stomach sites and varied in size. Endoscopists should suspect CMV gastritis and obtain multiple biopsies whenever erosions are found in any stomach site.

In contrast, none of the seven patients with CMV gastritis had punched out ulcers which had previously been considered characteristic of GI CMV disease[14-16]. In the present study, early EGD might have enabled early diagnosis of CMV gastritis before progression to ulcers. In two patients (Cases 4 and 6), CMV inclusion bodies were identified pathologically from normal mucosa as well as erosions. This result demonstrates the necessity of biopsy even if only normal findings are identified when EGD is performed.

CMV antigenemia reflects the severity of CMV reactivation[3,17], but the clinical significance of CMV antigenemia remains unknown in the diagnosis of GI CMV disease because of the wide variation in positive findings, ranging from a low of 21%[4] to a high of 73%[18]. In this study, CMV antigenemia was positive in six of the seven patients with CMV gastritis. This result supports the usefulness of CMV antigenemia in the diagnosis of CMV gastritis. It should be noted that abdominal pain preceded CMV antigenemia in four of the five patients with positive CMV antigenemia and abdominal pain. Our observations suggest that elaboration of physical and endoscopic examinations is even more important than detection of CMV antigenemia in the early diagnosis of CMV gastritis.

Patients with GVHD, and patients given corticosteroids for treatment of GVHD, carry a high risk of CMV disease[19]. In this study, such increased risk was confirmed as all seven patients with CMV gastritis also had GVHD and five of them had grade II-IV GVHD that was being treated by corticosteroids. GVHD, by itself and also accompanied by corticosteroid administration, are exacerbating factors in the existence of CMV gastritis.

The present investigation was a retrospective study based on our examination of medical records as well as endoscopic and pathological findings. The small size of the study does not exclude the possibility of unrecognized bias. Since EGD was not conducted in all allo-SCT recipients, underestimation of the frequency of CMV gastritis is a possibility. Consequently, further prospective evaluation is warranted to clarify the endoscopic findings for early diagnosis of CMV gastritis.

The results of this study suggest that endoscopic and clinical findings are useful indicators in the diagnosis of CMV gastritis following allo-SCT. Use of EGD is warranted for the establishment of an early diagnosis of CMV gastritis following allo-SCT.

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COMMENTS

Background

Cytomegalovirus (CMV) disease is a serious complication after allogeneic hematopoietic stem cell transplantation (allo-SCT), which is widely accepted as a curative therapy for advanced hematological malignancies including leukemia and malignant lymphoma. CMV disease can involve many organs and stomach is a common target.

Research frontiers

Few reports have been published regarding endoscopic examination in diagnosing CMV gastritis after allo-SCT. In this study, the authors demonstrate the endoscopic findings of CMV gastritis after allo-SCT in addition to its clinical features.

Innovations and breakthroughs

The present study indicated that erosion and oozing might be useful markers for early diagnosis of CMV gastritis.

Applications

Endoscopists should suspect CMV gastritis and obtain multiple biopsies whenever erosions are found in any stomach site when performing esophagogastroduodenoscopy in patients after allo-SCT.

Peer review

Although it does not really break new ground, this is an interesting manuscript on an important topic. The study presented here is a retrospective one with a small number of affected patients (7), but it offers some insight into this complex problem.

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〈トピックス〉

大腸用カプセル内視鏡

角川康夫　　斎藤　豊

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東京医学社　　〒113-0033 東京都文京区本郷3-35-4
電話 03(3811)4119(代表)

〈トピックス〉

大腸用カプセル内視鏡

角川康夫*,** 斎藤 豊**

要旨 本邦で承認されているカプセル内視鏡は，小腸用カプセルのみであるが，欧州では大腸用カプセル内視鏡(PillCam® COLON)もすでに認可され，臨床現場に登場している。この大腸カプセル内視鏡は，大きさが31×11 mmで，カプセルの両端にレンズが備わっており4フレーム/秒の頻度で撮影される。これまでの研究によると，6 mm以上の大腸ポリープの感度はおよそ60%前後である。この感度は腸管前処置に大きく依存しており，洗浄度が良好な場合には感度は大幅に上昇する。また，35フレーム/秒の頻度で撮影される新しい大腸カプセル内視鏡PillCam® COLON 2が2009年暮れに初めて論文紙上で公表され，6 mm以上の大腸ポリープの感度が89%になったと報告された。大腸カプセル内視鏡の進歩には目覚ましいものがあり，本邦でも一刻も早い登場が待ち望まれる。

key words: 大腸カプセル内視鏡，PillCam® COLON，PillCam® COLON 2

はじめに

本邦で承認されているカプセル内視鏡は，小腸用カプセルのみであるが，欧州では大腸用カプセル内視鏡(PillCam® COLON)も2006年にすでに認可され，臨床現場に登場してきている。

本稿では，大腸カプセル内視鏡につき，これまでに海外から報告された論文を中心に，現状と今後の展望につき紹介する。

Ⅰ．大腸カプセル内視鏡：PillCam® COLON

1．特徴

大腸カプセル内視鏡(**図1b**)は電源が入った3分後にいったん電源は切れ，およそ1時間45分後に再び点灯し撮影が再開するようプログラミングされている。大きさは31×11 mmで，従来の小腸用カプセル内視鏡PillCam® SB(図1a)に比べ長径が5 mmほど長い。ビデオカメラのレンズがカプセルの両端にあり，それぞれ1秒あたり2枚ずつ画像を撮影するため，合わせて1秒間に4枚の内視鏡画像が得られることになる。撮影時間はおよそ6～8時間である。各レンズは従来の小腸カプセル内視鏡PillCam® SBに比べ視野角が140度から156度に拡がり，また自動調光機能も備わったため，撮影される範囲や深度が大幅に広がった。

2．大腸ポリープの感度および影響を与える因子

大腸カプセル内視鏡：PillCam® COLONに関する代表的な4本の研究の概略を供覧する(**表1**)[1~4]。これらの研究によると，6 mm以上の大腸ポリープの感度はおよそ60%前後である。このなかで最も規模の大きいEuropean multicenter studyでは，6 mm以上の大腸ポリープの感度は64%と報告されており，advanced adenomaに限定すると，その感度は73%になると述べている[4]。さらに，彼らは腸管前

Capsule endoscopy for the colon

* 国立がんセンターがん予防・検診研究センター検診研究開発部 ** 同 中央病院内視鏡部
〔〒104-0045 東京都中央区築地5-1-1〕

a|b

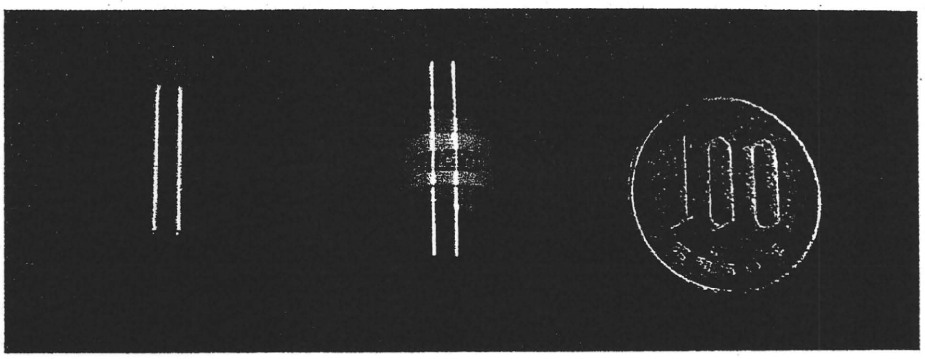

図 1　大腸カプセル内視鏡：PillCam® COLON
aは小腸カプセル内視鏡PillCam® SBで，bが大腸カプセル内視鏡PillCam® COLONである。大きさは31×11 mmで，両端にレンズが備わっている。視野角が156度に拡がり，自動調光機能も備わったため，撮影される範囲や深度が大幅に広がった。

表 1　大腸カプセル内視鏡の感度，特異度（海外の報告から）

	Eliakim Rら[1]	Schoofs Nら[2]	Sieg Aら[3]	Van Gossum Aら[4]
発表年	2006	2006	2009	2009
ジャーナル	Endoscopy	Endoscopy	AJG	NEJM
参加国	イスラエル	ベルギー	ドイツ	European Union
施設数	3施設	1施設	1施設	8施設
症例数	91	41	38	332
平均年齢（歳）	57	56	56	58.5
Polyp≧6 mm				
感　度（%）	58	60	64	64
特異度（%）	83	73	Not Reported	84

AJG：American Journal of Gastroenterology，NEJM：New England Journal of Medicine

表 2　大腸カプセル内視鏡の腸管前処置方法（海外の報告から）

	Eliakim Rら[1]	Schoofs Nら[2]	Sieg Aら[3]	Van Gossum Aら[4]
前日　夕方	PEG 2 *l*	PEG 3 *l*	PEG 3 *l*	PEG 3 *l*
当日　午前	PEG 1 *l*	PEG 1 *l*	PEG 0.5 *l*	PEG 1 *l*
0 H	大腸カプセル内服			
2 H	NaP 30 m*l*＋Water 1 *l*	NaP 45 m*l*＋Water 1 *l*	NaP 22 m*l*＋Water 0.5 *l*	NaP 45 m*l*＋Water 1 *l*
4～6 H	NaP 15 m*l*＋Water 0.5 *l*	NaP 30 m*l*＋Water 1 *l*	NaP 22 m*l*＋Water 0.5 *l*	NaP 30 m*l*＋Water 1 *l*
8 H	Bisacodyl坐薬10 mg	Bisacodyl坐薬10 mg	—	Bisacodyl坐薬10 mg
総水分摂取量	4.5 *l*	6 *l*	4.5 *l*	6 *l*

PEG：polyethylene glycol，NaP：sodium phosphate

処置がその感度に大きく影響すると述べており，腸管の洗浄度が良好な場合には88%まで上昇することを報告している。逆に洗浄度が不良の場合には，その感度は44%に留まる。そのため，よりintensiveな腸管前処置にすべし，といった論調が少なくない。

3．腸管前処置

しかし，大腸カプセル内視鏡の腸管前処置はこれまでの方法（**表2**）[1~4]では，いずれも被検者にかかる負担が少なくない。いずれも検査前日から禁食となり，夕方にはポリエチレングリコール（PEG）の服用が要求される。さらに，検査当日にもPEGの服

表 3　大腸カプセル内視鏡における腸管洗浄度と体外排出率(海外の報告から)

	Eliakim R ら[1]	Schoofs N ら[2]*	Sieg A ら[3]	Van Gossum A ら[4]
腸管洗浄度				
Excellent	40 % } 84%	30 % } 88%	Cleansing level: 1.9	Not Reported } 72%
Good	44 %	58 %		Not Reported
Fair	11 %	6 %		Not Reported
Poor	4 %	3 %		Not Reported
体外排出率	78 %	83 %	84 %	93 %

腸管洗浄度がExcellentあるいはGoodをAdequate，FairあるいはPoorをInadequateと定義される。
*なお，Schoofsらの腸管洗浄度については，大腸カプセル内視鏡が再点灯した時点でBauhin弁の口側に位置していた症例(97%)についての検討結果である。

用が必要とされ，その後にやっと大腸カプセル内視鏡検査を開始することができる。

しかし，このままでは小腸通過に何時間も要するため，カプセルを大腸まで押し流す目的でリン酸ナトリウム(NaP)が用いられる。これをBoosterと呼び，現在はBooster ⅠとBooster Ⅱの2回に分けて行うことが一般的で，このときに水も同時に飲むため，結果的に1～2 *l*程度の水分が負荷されることとなる。最後に坐薬(Bisacodyl)を用いて最終排便を行い，カプセル内視鏡検査は完了する。

2日間で負荷される水分はおよそ4.5～6 *l*に及ぶ。禁食も2日間に及ぶ。これでは，本来侵襲の少ないことが最大の売りであるはずのカプセル内視鏡のメリットは大きく損なわれてしまう。

このような腸管前処置方法により洗浄度がadequate(excellentあるいはgood)になった割合は72～88%，またカプセル内視鏡の検査時間内の体外排出率は78～93%であった(**表3**)[1~4]。良好な洗浄度および体外排出率を維持しつつ，かつ被検者の負担をいかに軽減させていくかが今後の課題である。

4．本邦における研究について

筆者らは第3次対がん10か年総合戦略研究事業の斎藤　豊班「新しい内視鏡診断機器の臨床への応用と，これらを用いた診断精度の向上に関する調査研究」の一環として，大腸カプセル内視鏡の多施設共同研究(国内6施設)を研究者主導により行っている。本研究の目的は，被検者の侵襲をできるだけ減らし，かつこれまでと同等の洗浄度および体外排出率が確保された腸管前処置方法の探求である。**表4**は筆者らが考案したスケジュールの概略であるが，PEGの服用は当日だけに限定し，かつ前日の食事(低残渣食)を朝昼晩ともに可能にした点などがこれまでの方法と異なる大きな特徴である。

表 4　被検者の負担を軽減した新しい腸管前処置方法(概略)(現在，多施設共同研究で検討中)

当日	
午前	PEG 2 *l**
0 H	大腸カプセル内服
2 H	Magnesium citrate 50 g/Water 900 m*l*
5～6 H	Magnesium citrate 50 g/Water 900 m*l*
8 H	Bisacodyl suppository 10 mg(排便がない場合)

*：洗浄が不十分な場合は，個別に効能書きの範囲内で追加投与を行う。詳細な方法はここでは割愛する。
PEG：polyethylene glycol

また，この方法できれいにならない場合は，効能書きの範囲内で追加投与も可能とし，これにより腸管内がinadequate(fairあるいはpoor)となる被検者の割合を減少させるよう工夫した。Boosterは本邦では液状のNaPは市販されていないため，クエン酸マグネシウム(magnesium citrate)で代用することとした。

図2は本研究中に観察された大腸病変の1例であるが，大腸カプセル内視鏡でも十分明瞭にLST-NGを描出できている(図2b, c)。

Ⅱ．新しい大腸カプセル内視鏡：PillCam® COLON 2

新しくバージョンアップされた大腸カプセル内視鏡PillCam® COLON 2(**図3a**)が2009年暮れに初めて論文紙上で公表された[5]。これはデータレコーダー