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BRIEF ARTICLE

Endoscopic diagnosis of cytomegalovirus gastritis after allogeneic hematopoietic stem cell transplantation

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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

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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 50 000 cells were positive according to the CMV antigenemia assay in patients transplanted from related donors, a single cell per 50 000 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[1]

[1]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 =

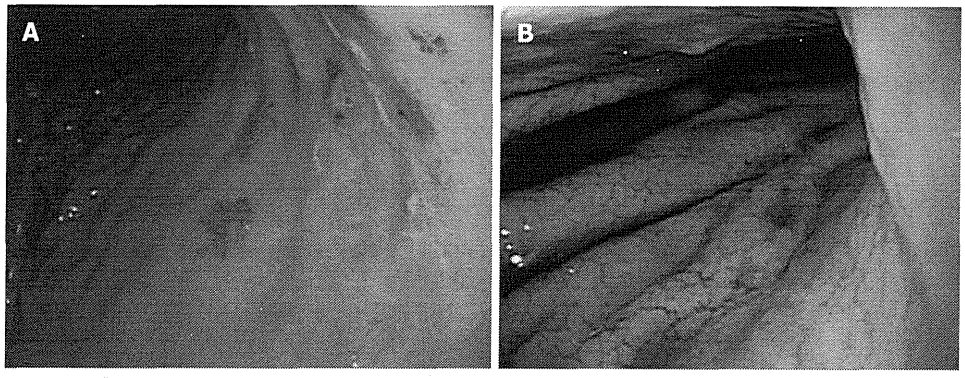

Figure 1 Erosion (Case 6). Multiple erosions are clearly shown in gastric body. A: Before indigo carmine dye spraying; B: After indigo carmine dye spraying).

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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Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms

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Abstract

Background

Capillary patterns (CP) observed by magnifying Narrow Band Imaging (NBI) are useful for differentiating non-adenomatous from adenomatous colorectal polyps. However, there are few studies concerning the effectiveness of magnifying NBI for determining the depth of invasion in early colorectal neoplasms. We aimed to determine whether CP type IIIA/IIIB identified by magnifying NBI is effective for estimating the depth of invasion in early colorectal neoplasms.

Methods

A series of 127 consecutive patients with 130 colorectal lesions were evaluated from October 2005 to October 2007 at the National Cancer Center Hospital East, Chiba, Japan. Lesions were classified as CP type IIIA or type IIIB according to the NBI CP pattern classification. Lesions were histopathologically evaluated. Inter and intraobserver variabilities were assessed by three colonoscopists experienced in NBI.

Results

There were 15 adenomas, 66 intramucosal cancers (pM) and 49 submucosal cancers (pSM): 16 pSM superficial (pSM1) and 33 pSM deep cancers (pSM2-3). Among lesions diagnosed as CP IIIA 86 out of 91 (94.5%) were adenomas, pM-ca, or pSM1; among lesions diagnosed as CP IIIB 28 out of 39 (72%) were pSM2-3. Sensitivity, specificity and diagnostic accuracy of the CP type III for differentiating pM-ca or pSM1 (<1000 μm) from pSM2-3 (≥1000 μm) were 84.8%, 88.7 % and 87.7%, respectively. Interobserver variability: $\kappa = 0.68, 0.67, 0.72$. Intraobserver agreement: $\kappa=0.79, 0.76, 0.75$

Conclusion

Identification of CP type IIIA/IIIB by magnifying NBI is useful for estimating the depth of invasion of early colorectal neoplasms.

Background

Following complete surgical resection it has been found that colorectal cancers confined to the intramucosal layer (pM) or invading less than 1000μm into the submucosa (pSM1), with no lymphovascular invasion or signs of poor differentiated histology do not have lymph node (LN) metastasis. In contrast, lesions invading more than 1000μm into the submucosa (pSM2-3) have a 6-12% LN metastatic rate [1, 2, 3]. Therefore, in vivo estimation of the depth of invasion in early colorectal lesions may be important for an adequate therapeutic strategy.

Several studies on the adenoma-carcinoma sequence have demonstrated a gradual increment in microvessel density and a reduction in the apoptosis process during the progression from low dysplasia to high dysplasia and cancer [4]. In addition it is well recognized that angiogenesis performs a critical role in the development of solid tumors [5, 6] and that detailed characterization of lesions using advanced optical imaging techniques is possible. We therefore developed in the late nineties the NBI system as an in vivo approach for visualizing microvascular anatomy or microvessels morphologic changes in superficial neoplasia [7, 8, 9].

By using this narrow spectrum, contrast in the microvascular architecture on the surface of the lesions is markedly improved [10, 11]. In accordance with our previous investigations, the microvascular architecture (capillary pattern: CP) was classified into three types (CP type I, II and III) [9, 11, 12]. Our observations demonstrated that the CP assessed by magnifying NBI is useful for differentiating small colorectal non-neoplastic from neoplastic polyps [13] and is highly accurate at distinguishing between low-grade dysplasia and high-grade dysplasia/invasive cancer, and thus can be used to predict the histopathology of colorectal neoplasia [14]. However, its usefulness in estimating the depth of invasion of early colorectal neoplasms (pM, pSM1 or pSM2-3) is still unclear. The aim of this study was to clarify the diagnostic accuracy of magnifying NBI for assessing the depth of invasion of T1 colorectal cancer.

Methods

Patients

A total of 127 consecutive patients with 130 lesions endoscopically diagnosed as NBI CP type IIIA /IIIB who underwent endoscopic or surgical resection at the National Cancer Center East Hospital (NCCEH) from October 2005 to October 2007 were analyzed. The protocol was approved by the medical ethics committee of our hospital, and written informed consents for diagnosis and treatment were obtained from all patients prior to the procedures. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Cases judged as NBI CP III but with familial adenomatous polyposis (FAP), and inflammatory bowel disease (IBD) were excluded from the study. CP type III lesions with an obvious appearance of advanced cancer were also excluded.

Colonoscopy procedure using the RGB sequential illumination based NBI system

Bowel preparation consisted of 2 to 3L of polyethylene glycol solution in the morning before the procedure, as previously reported [15]. Hyoscine methobromide (10-20 mg IV) was administered if there were no contraindications, and light sedation with diazepam (3-5 mg IV) was used in selected subjects. All procedures were performed up to the cecum using high-definition colonoscopy (CF-H260AZI [with a magnifying power of 75 at maximum]; Olympus, Optical Co., Ltd., Tokyo, Japan) with NBI magnification. A videoendoscope system (EVIS LUCERA SPECTRUM; Olympus, Optical Co., Ltd., Tokyo, Japan) and a digital image filing system (nexus sif; Fujifilm, Tokyo, Japan) was used. In NBI mode using this system, the center wavelengths of the dedicated trichromatic optical filters are 540 and 415 nm, with bandwidths of 30 nm Optional enhancement setting was set at enhancement mode A5 and color mode 3. Lesions were classified macroscopically based on the Paris classification of superficial gastrointestinal lesions [2]. Next, lesions were observed in NBI and each CP were evaluated by magnifying NBI view in real time. For larger lesions, the highest quality NBI image from the macroscopically worst area (e.g. large nodule, depression and reddened area) was evaluated.
In lesions identified as CP type IIIA, snare polypectomy, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD) were performed. In lesions identified as CP type IIIB, surgical or endoscopic resection was performed.

Capillary pattern classification

Following conventional white light observation all cancer lesions were evaluated by magnifying NBI. Based on the surface characteristics of the meshed capillaries, CP type III were defined as demonstrating irregular and unarranged pattern in a mesh-like microvascular architecture and exhibiting at least one of the following: irregular size, complicated branching, disrupted irregular winding when compared to the regular small caliber capillaries observed in adenomatous polyps (CP type II) [Figure 1] [9, 11, 14].

Moreover, CP type III lesions were further classified into two groups: types IIIA or IIIB.

Capillary pattern type IIIA

CP type III lesions clearly show visible microvascular architecture and high microvessel density with lack of uniformity, blind ending, branching and curtailed irregularly. [Figure 2A].

Capillary pattern type IIIB

CP type III lesions show a clear distinction between normal/cancerous mucosa on the surface (demarcated area) and the presence of a nearly avascular or loose microvascular area. [Figure 2B]

Histological examination

All resected specimens were retrieved and immediately fixed in 10% buffered formalin solution and examined histologically using hematoxylin and eosin staining. Histopathological diagnosis was determined according to the Vienna classification [16]. Non-pedunculated lesions with a vertical invasion length of less than 1000μm in the submucosal layer were classified as pSM1, and those with invasion of more than 1000μm were classified as pSM2-3 [2]. Pedunculated lesions were categorized according to Haggitt's classification [17]. Pedunculated lesions with head invasion were classified as pSM1, and those with stalk invasion were classified as pSM2-3.

Image evaluation

In an independent sub-study, inter- and intraobserver variabilities of the NBI CP type III for estimating the depth of early colorectal cancer were assessed by three colonoscopists experienced in NBI (YS, TM, HI). All 130 lesions were evaluated. The best magnifying NBI image of each lesion was selected. All selected images were arranged randomly for pattern assessment by the three readers who were blinded to the histological diagnosis of the lesions. All readers diagnosed the image of one pattern one day, and diagnosed another pattern one week later. The obtained data was not used for evaluating diagnostic accuracy of the lesions.

Clinical data evaluation

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the CP type III for estimating the depth of invasion of early colorectal cancer was calculated according to the pathological report. Inter and intraobserver variabilities were calculated using kappa statistics.

Results

Clinicopathologic features of colorectal lesions

A total of 130 early colorectal lesions in 127 patients were analyzed. The clinicopathological data is shown in Table 1. According to the macroscopic types, there were 85 (65.4%) flat elevated and depressed lesions and 45 (34.6%) polypoid and protruded lesions. The mean lesion size was 17 mm (range 5-80 mm). There were 81 (62.3%) lesions located in the left colon and rectum and 49 (37.7%) lesions located in the right and transverse colon. Histologically, there were 15 adenomas, 66 pM, 49 submucosal cancers (pSM): 14 pSM1 and 33 pSM2-3. Among lesions diagnosed as CP IIIA 86 out of 91 (94.5%) were adenomas, pM, or pSM1; while among lesions diagnosed as CP IIIB 28 out of 39 (72%) were pSM2-3.

Diagnostic accuracy, NPV and PPV of CP type IIIA and type IIIB

Sensitivity, specificity and diagnostic accuracy of the CP type IIIA / IIIB for differentiating pM or pSM1 (<1000 μm) from pSM2-3 (≥1000 μm) were 84.8%, 88.7% and 87.7%, respectively. The accuracy of CP type IIIA (NPV) was 94.5% (86/91), and that for lesions of CP type IIIB (PPV) was 71.8% (29/39) [Table 2].

Image evaluation

The calculated interobserver variability of HI-YS, HI-TM, and YS-TM was $\kappa = 0.68$, 0.67, and 0.72, respectively. Intraobserver agreement of HI, YS, and TM was $\kappa = 0.79$, 0.76, 0.75, respectively (Table 3).

Discussion

We previously demonstrated that NBI with magnification is a simple and reliable method to differentiate non-adenomatous from adenomatous colorectal polyps less than 10 mm (sensibility 96%, specificity 92, overall accuracy 95) [13] and, low grade adenomatous polyps from high grade adenomas or early colorectal neoplasms (Sensitivity 90%, specificity 97, overall accuracy 95) [14].

Based on the clinical observation and detailed characterization of lesions based on changes in the pattern and size of microvessels using magnifying NBI, we have described three different types of CP: CP type I (non-neoplastic lesion), CP type II (adenomatous lesion) and CP type III (cancerous lesion) [9]. The initial studies on CP type III lesions showed that within this group, there were lesions invading the intramucosal or the superficial submucosal layer, which require endoscopic treatment and lesions invading deeply into the submucosal layer, which require surgical treatment. These two subgroups could be differentiated from each based upon their respective CP patterns [17,18]. Concurrent to this study, we performed a pilot study using magnifying NBI to predict the depth of invasion of early colorectal lesions at the National Cancer Center Hospital, Tokyo. From the results of this investigation the following factors were found significantly more frequently in pSM2-3 lesions compared to pM-pSM1 lesions ($P<0.001$): wide caliber, irregular caliber, tortuousity, irregularity, short length and non-dense arrangement. Multivariate analysis, however, revealed that irregularity and non-dense arrangement remained as independent factors [19]. These results supported the reliability of our classification. Consequently, we evaluated the efficacy of subdividing CP type III lesions into two groups (CP type IIIA / Type IIIB) and demonstrated that this may provide an effective in vivo method to predict the depth of invasion of colorectal neoplasms.

In this study, the overall diagnostic accuracy of the CP type IIIA classification to differentiate pM or pSM1 from pSM2-3 (87.7%) was quite similar to results obtained by magnifying chromocolonoscopy (87%) [20]. On the other hand, the sensitivity of using CP IIIA/IIIB to differentiate pM/pSM1 from pSM2-3 lesions (84%) was quite similar when compared to that obtained by the non-invasive/invasive pattern using MCC (85%) [21]. The specificities however, differed markedly (88% and 99%) in these two studies. Possible reasons for these differences are the inclusion of more than 3000 thousand adenomatous lesions in the study and due to the learning curve for estimating depth using NBI in early colorectal neoplasms.

When the NBI results were analyzed, it was found that 5 out of 91 (5.5%) lesions judged as CP type IIIA were ultimately classified as pSM2-3 in the pathological report. On the other hand, 11 out of 39 (28.2%) lesions diagnosed as CP IIIB were demonstrated to be pM or pSM1 according to the pathological report. Therefore the 71.8% positive predictive value (PPV) of CP was lower than the 86.5% PPV associated with using the pit pattern classification [21]. However diagnosis using pit pattern classification is time consuming due to the need to spray indigo carmine and crystal violet. An advantage of NBI is the

ability to diagnose lesions without using any dye solution. Fundamentally, it is suggested that the lesion showing CP type IIIA is recommended for endoscopic treatment. In contrast, when a lesion is classified as CP type IIIB it is then necessary to perform Kudo's pit pattern observation using dye method or EUS assessment. Consequently, accurate pit pattern analysis and sufficient skills in magnifying colonoscopy are basic fundamentals required for accurate NBI diagnosis of depth of invasion in colorectal lesions [22].

In the sub-study, the rate of diagnostic agreement among the three observers was not excellent but good without variability (according to inter and intraobserver agreement rates). Some difficulties may relate to the study design in which the assessment was undertaken using only one image per lesion making the judgment difficult. Huang et al. reported a mean kappa value for inter and intraobserver agreement rate using pit pattern analysis of 0.716 and 0.810, respectively [23]. Considering that analysis of pit pattern has been performed for many years, the inter and intraobserver agreement rates associated with NBI reported in this study may indicate acceptable results. However, further multicenter research with endoscopists of different abilities and interobserver and intraobserver variability studies are necessary to validate these results.

The primary limitation of this study was that the NBI CP appearance was judged by a single endoscopist well experienced in magnifying NBI colonoscopy. Another point worth mentioning is that endoscopic judgment of the interobserver and intraobserver studies was carried out by experienced examiners. This means that the effectiveness of classifying CP by NBI deserves further validation studies including less experienced endoscopists.

Conclusions

This study has demonstrated that the CP (Type IIIA/Type IIIB) evaluated by magnifying NBI may be an effective in vivo alternative method to predict the depth of invasion of colorectal neoplasms without the application of any dye solution. However, additional comparative research with MCC may be necessary to validate the results of this study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The study was planned by HI, TM, FE, YS, TU, K-IF, KK, YS participated in the design and coordination of the study. OA and TF analyzed a pathologic finding. HI collected the clinical data and wrote the manuscript. HI, TM and YS performed the statistical analyses. All authors have read and approved the final the manuscript.

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Figures

Figure1 - Capillary pattern classification

Figure2 - Capillary pattern type IIIA, IIIB (magnifying NBI image at full max 75 times)
A : Capillary pattern type IIIA
B : Capillary pattern type IIIB

Tables

Table 1 - Clinicopathological features of CP III lesions

No. of patients/lesions	**127/130**
Sex (Male/Female)	**81/46**
Mean age (y [range])	**65.3 [41-86]**
Macroscopic types	
Flat, depressed	**85**
Sessile, protruded	**45**
Mean size of lesions (mm [range])	**17.0 [5-80]**
Locations	
Right colon	**49**
Left colon, rectum	**81**
Histopathology	
Adenoma	**15**
pM*, pSM-superficial (pSM1)**	**82**
pSM-deep(pSM2-3)#	**33**

*** intramucosal cancer, ** SM superficial invasion (<1000μm), # SM deep invasion (≥1000μm)**

Table 2 - Sensitivity, specificity and diagnostic accuracy of the CP Type III

	Histological diagnosis	
	M*, SM-superficial (SM1)**	**SM-deep(SM2-3)[#]**
CP type IIIA	**86**	**5**
CP type IIIB	**11**	**28**

Sensitivity: 84.8%, Specificity: 88.7%, Accuracy: 87.7%,
NPV (negative predictive value): 94.5%, PPV (positive predictive value): 71.8%

*** intramucosal cancer, ** SM superficial invasion (<1000μm), [#] SM deep invasion (≥1000μm)**