Primary micropapillary carcinoma of the colon with submucosal invasion: A case report

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Background and study aims: We present a case of invasive micropapillary carcinoma (IMPC) of the colon treated by endoscopic resection following magnifying endoscopy. A 47-year-old woman visited our hospital for follow-up of a positive fecal occult blood test. Colonoscopy revealed a semipedunculated reddish polyp, the surface of which showed gentle irregularity, and mild tension in the sigmoid colon. Magnifying colonoscopy with narrow band imaging revealed an irregular surface pattern with heterogeneity in vascular diameter and distribution. Magnifying endoscopic findings using crystal violet staining showed an irregular pit pattern with an expansion of stromal areas. Endoscopic resection of the sigmoid colon tumor was performed, and the histology of the resected specimen primarily revealed a micropapillary component with a small moderately differentiated adenocarcinoma component that massively invaded into the submucosal layer, accompanied by lymphatic invasion, although the tumor was very small (7 mm in diameter, smaller than any in previous reports). Laparoscopy-assisted sigmoidectomy and regional lymph node resection were performed; neither cancer nor lymph node metastases were present. This is the first report of a case with early-stage colonic IMPC observed with magnifying colonoscopy.

Introduction

Invasive micropapillary carcinoma (IMPC) was first identified as a variant of invasive breast cancer by Siriaunkgul and Tavassoli [1]. Recently, IMPC has been reported in association with other tissues, including the urinary bladder, lung, ovary, salivary gland, stomach and colon [2]. IMPC has clinical characteristic carcinoma findings, with a high incidence of lymphatic involvement, lymph node metastases, and a poor clinical outcome, and has histological features consisting of round-to-oval micropapillary clusters surrounded by clear spaces and a lack of fibrovascular cores. IMPC has an inside-outside growth pattern with reversed polarity, where the stromal-facing surfaces of the tumor cells acquire apical secretory properties, as demonstrated by MUC1 or EMA immunohistochemical staining on the surface.

In the case of colorectal IMPC, few descriptions of endoscopic observation via magnifying colonoscopy and endoscopic mucosal resection exist in the literature. Magnifying endoscopy was developed for the diagnosis of colorectal tumors. Pit pattern classification of colorectal lesions determined by magnifying endoscopy has been reported to be related to the histologic characteristics of the lesions [3]; therefore, this modality is effective for invasion depth diagnosis and treatment selection. Additionally, given that the irregular microvessels of the lesion are analyzed with respect to the heterogeneity of their diameter and/or distribution using narrow band imaging (NBI) magnification, it is possible to discriminate between adenoma versus carcinoma, and to determine the depth of invasion [4]. Herein we report a case of colon IMPC that underwent colonoscopic observation and endoscopic mucosal resection.

Case report

A 47-year-old woman visited our hospital as follow-up for a positive fecal occult blood test. She did not have any symptoms or any remarkable medical or family history. Blood tests only revealed the existence of mild anemia (hemoglobin, 10.7 g/dL); serum levels of carcinoembryonic antigen (CEA) and CA19-9 were normal.

Colonoscopy was performed using a magnifying colonoscope (PCF-Q260AZI, Olympus, Tokyo, Japan). White light colonoscopy revealed a semipedunculated reddish polyp < 10 mm in diameter with a gently irregular surface, but without ulceration or erosion, as well as mild tension in the sigmoid colon (**Fig.1**).

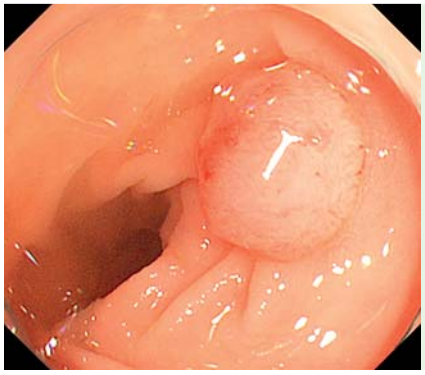

Fig. 1 A white light colonoscopic examination of the sigmoid colon revealed a semi-pedunculated reddish polyp < 10 mm in diameter with a gently irregular surface, but without ulceration or erosions. The tumor was associated with mild tension, suggestive of submucosal invasion.

Magnifying NBI colonoscopy showed an irregular surface pattern with heterogeneity in the vascular diameter and a sparse vascular distribution, suggestive of stromal invasion of tumor cells (**Fig. 2**). Magnifying endoscopy using crystal violet staining revealed pits with irregular margins, unclear contours, and narrowed lumens, and decreased/disappearing stainability in the stromal area. These findings were considered to indicate a highly irregular type V_I pit pattern [3]. In addition, the stromal area between each duct was dilated (**Fig. 3**). The preoperative diagnosis was early-stage sigmoid colon cancer with submucosal invasion, and diagnostic endoscopic resection of the sigmoid colon tumor was performed because the patient strongly hoped for endoscopic resection due to the small size of the lesion.

Macroscopically, the tumor was a 7-mm semi-pedunculated polyp. Microscopically, massive submucosal invasion to a depth up to 3.6 mm with extensive lymphatic invasions was observed (**Fig. 4a**). The lesion was predominantly (~80%) composed of polygonal cells arranged in clusters surrounded by lacunar-like clear spaces (**Fig. 4b**), and the remaining 20% was moderately differentiated tubular adenocarcinoma. Immunohistochemically, MUC1 expression was observed at the stromal edges of tumor clusters in the micropapillary structures, thus appearing as an 'inside-out' staining pattern [2] (**Fig. 4c**). In addition, the tumors cells were positive for cytokeratin 20 (**Fig. 4d**) and negative for cytokeratin 7 (**Fig. 4e**), indicative of primary IMPC of the colon.

Although the vertical margin of the resected specimen was negative and no regional lymph node swelling or metastasis by chest and abdominal computed tomography (CT) were apparent, laparoscopy-assisted sigmoidectomy and regional lymph node resection were performed. No residual cancer cells or lymph node metastases were observed. This patient remains alive 15 months after surgery, with no recurrence.

Discussion

IMPC was first reported as a variant type of invasive breast cancer by Siriaunkgul and Tavassoli in 1993 [1]. IMPCs of the colon are being increasingly recognized since Sakamoto et al. reported 3 colon IMPC cases in 2005 [2]. However, the endoscopic features of and optimal therapeutic management strategies for colon IMPC have not yet been elucidated. We recently encountered a case of early-stage colon IMPC, and performed a minute magnifying colonoscopic observation, including NBI endoscopy and crystal violet chromoendoscopy. In the current report, we have discussed the endoscopic diagnosis and the therapeutic strategy for this case of colon IPMC.

Most colon IMPC cases are identified at an advanced stage; therefore, surgery and chemotherapy are the primary clinical management strategies. Only 5 cases of colon IMPC (including the current case) have been categorized as T1 (TNM classification) tumors (**Table 1**) [5–8]. In 4 cases including the current one, endoscopic resection was performed [5, 6, 8]. However, in all of these cases, submucosal invasion and lymphatic vessel invasion were observed. Additional surgeries were performed in 3 cases, and conservative treatment was selected in the fourth case due to severely complicated disease. In the latter case, unfortunately, colonoscopy and CT scans revealed local recurrence and multiple distant metastases in the lung, liver, lymph node, and spleen 6 months after endoscopic resection [6]. Thus, sufficient attention should be paid to colon IMPC even if the disease is diagnosed at an early clinical stage, because these patients have been reported to experience a worse prognosis than those with non-IMPC early-stage colon cancer [9, 10].

In the current case, white light and magnifying colonoscopy using NBI and crystal violet staining were performed. First, white light colonoscopy revealed a semi-pedunculated reddish polyp with a gently irregular surface and producing mild tension despite its small size, suggestive of submucosal invasion. Magnifying NBI colonoscopy showed an irregular surface pattern with heterogeneity in vascular diameter and distribution, and magnifying endoscopy using crystal violet staining revealed a highly irregular type V_I pit pattern [3]. In addition, the vascular contribution was sparse, and the stromal area between each duct was dilated. Based on these endoscopic findings, the current case was not considered to be a typical mucosal adenoma or carcinoma, and distinction from an unusual type of carcinoma, such as mucinous or undifferentiated carcinoma with submucosal deep invasion, was required. An endoscopically resected specimen revealed massive submucosal invasion and was composed of micropapillary cells. IMPC consists of neoplastic cells without fibro-

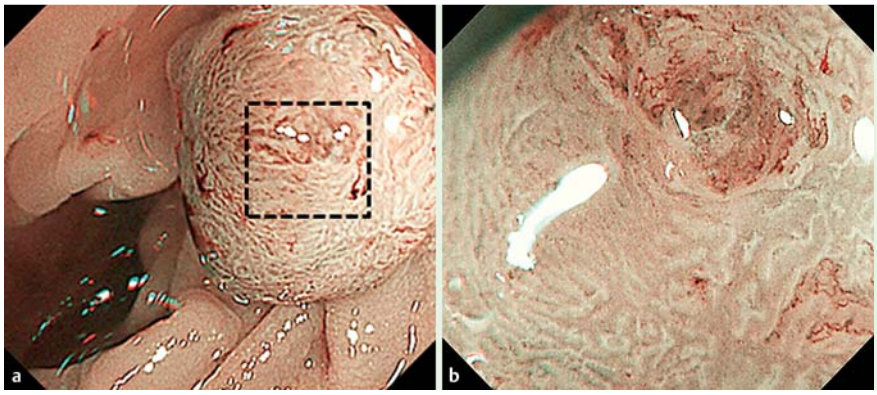

Fig. 2 Magnifying NBI colonoscopy findings. A global image is shown in **a**, and an extended image of the area in the box is shown in **b**. This polypoid lesion had an irregular surface pattern and heterogeneity in both vascular diameter and distribution. The vascular distribution was also sparse.

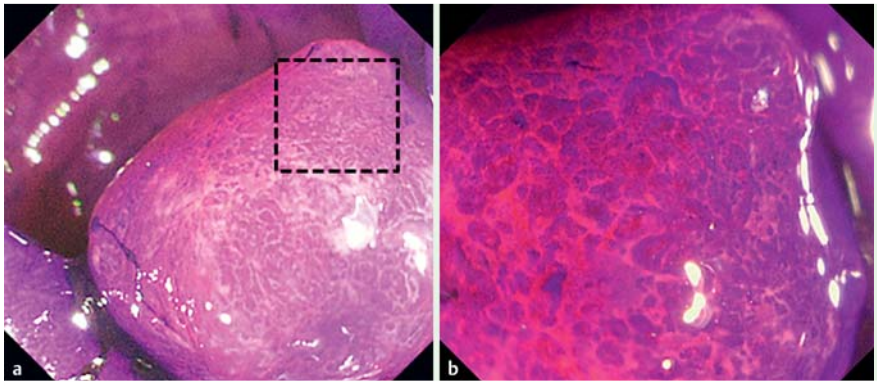

Fig. 3 Magnifying colonoscopic findings using crystal violet staining. A global image is shown in **a**, and an extended image of the area in the box is shown in **b**. The polypoid lesion had irregular margins, unclear contours, and narrow pit lumens, and the crystal violet stainability in the stromal area was diminished and partially disappeared.

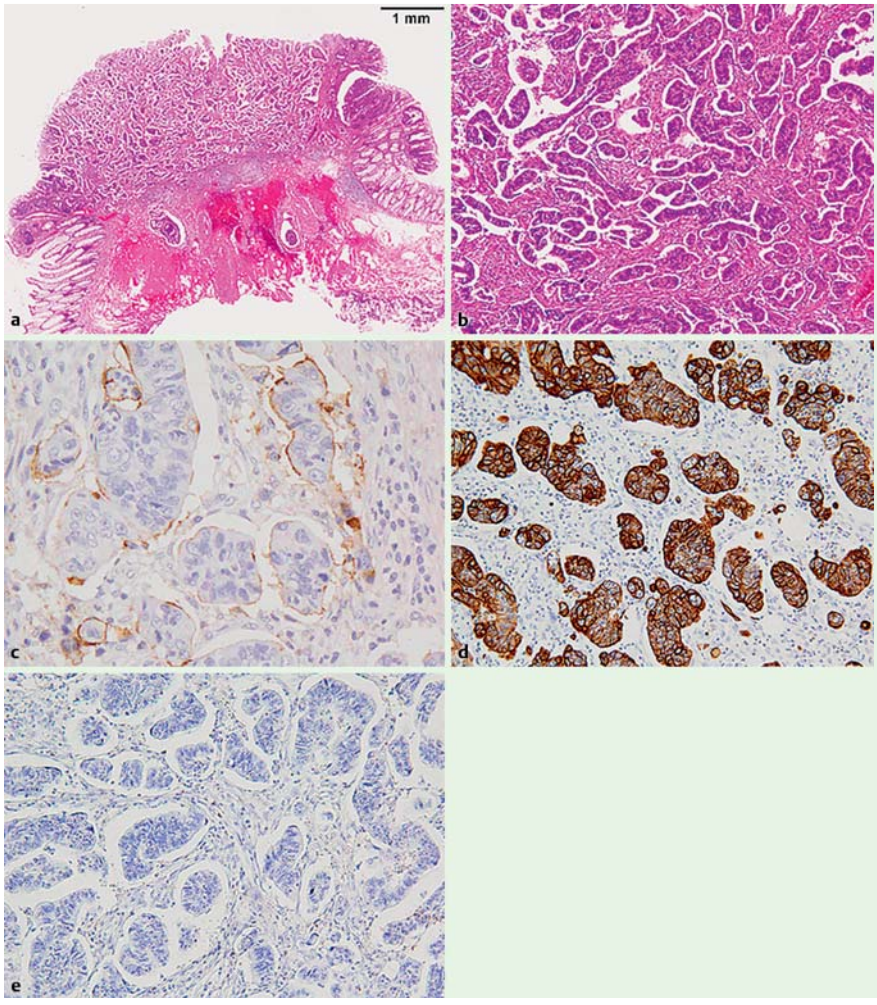

Fig. 4 **a** Histological analysis of the resected specimen showed a massive submucosal invasion to 3.6 mm, with extensive lymphatic invasion. **b** This lesion was predominantly composed of polygonal cells arranged in clusters surrounded by lacunar-like clear spaces. **c** MUC1 expression of tumor cells was found at the stromal edges of tumor clusters in the micropapillary structures, a characteristic 'inside-out' staining pattern. **d** Cytokeratin 20 expression was positive in tumor cells. **e** Cytokeratin 7 expression was negative in tumor cells. These immunohistochemical findings suggested IMPC of the colon.

vascular cores that proliferate into the stroma, and the tumor clusters are surrounded by clear spaces. The present case was 7 mm, which is the smallest colonic IMPC thus far reported. We suggest that IMPC should be considered in the differential diagnosis if colonoscopy suggests a submucosal deep invasion, an irregular pit pattern with a wide stromal area, and an invisible vascular pattern despite a small size. These may be characteristic features of early-stage colon IMPC identifiable with magnifying colonoscopy. However, a future study with a larger number of cases is required to confirm these findings.

The clinical characteristic findings of colon IMPC include a high incidence of lymphatic involvement and lymph node metastases, as well as a poor clinical outcome. Extensive lymphatic involvement was observed in the current case, despite the very small size of the lesion. Kim et al. showed that metastases to local lymph nodes were observed in 2 out of 3 patients with IMPC tumors that infiltrated into the submucosal membrane (pT1) [9]. Xu et al. reported that stage I and II IMPC patients experience shorter survival compared to non-IMPC patients [10]. In conclusion, we suggest that cases of colon IMPC should be diagnosed at the earliest stage possible and should be appropriately treated. We have found that submucosal deep invasion, an irregular pit pattern with a wide stromal area, and invisible vascular patterns despite a small tumor size are key endoscopic features of colon IMPC.

Table 1 Five cases of colon IMPC categorized as T1 (TNM classification) tumors.

Case	Author	Age	Sex	Location	Tumor size (mm)	Macroscopic findings	Histology	ly	v	Therapy	Lymph node metastasis	Prognosis
1	Kondo	70	M	S	11	ND	IMPC (< 5 %) with mostly tubulovillous adenoma	+	ND	ER + surgery	None	Alive
2	Sonoo	64	M	S	30 × 25 × 20	Pedunculated polyp	IMPC (80 %) with moderately adenocarcinoma	+	+	Surgery + chemotherapy	Existent	Alive (25 months)
3	Hisamori	71	F	S	20 × 15	Pedunculated, cauliflower-like polyp with a depressed surface	IMPC (100 %)	+	–	ER	None by CT	Dead 12 months after ER due to a local recurrence and multiple distant metastases
4	Mukai	82	M	S	20	Pedunculated polyp	IMPC (70 %) with poorly adenocarcinoma	+	ND	ER + surgery + chemotherapy	Existent	Alive (12 months)
5	Present case	47	F	S	7	Semi-pedunculated polyp	IMPC (80 %) with moderately differentiated tubular adenocarcinoma	+	–	ER + surgery	None	Alive (15 months)

ly, lymphatic invasion; v, venous invasion; S, sigmoid colon; ND, not described; ER, endoscopic resection; CT, computed tomography

Competing interests: None

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