A 71-year-old woman presented with hematochezia and narrowing of the stool. She suffered from progressive systemic sclerosis for 12 years and underwent home oxygen therapy due to pulmonary fibrosis and moderate pulmonary hypertension. Colonoscopy revealed a pedunculated, cauliflower-like polyp with a depressed surface in the sigmoid colon. The polyp was regarded as early colon cancer with possible submucosal invasion, and subsequent computed tomographic (CT) scans showed no evidence of lymph node involvement or distant metastases. Because of perioperative risks due to moderate pulmonary hypertension, she underwent an endoscopic resection of the early colon cancer. Pathological examination of the resected specimen of 20 mm diameter revealed the peculiar morphology of an adenocarcinoma with moderate lymphatic invasion. Immunohistochemical analysis for epithelial membrane antigen showed the specific ‘inside-out growth pattern’ indicative of invasive micropapillary carcinoma (IMPC). Taking the perioperative risks into consideration, she opted to undergo close follow-ups without an additional sigmoidectomy. At 6 months after the resection, the follow-up colonoscopy revealed a local recurrence of the colon cancer, and subsequent CT scans revealed multiple distant metastases including the lung, liver, lymph nodes and spleen. This is a rare case of a pure, submucosal IMPC of the colon. Furthermore, pure IMPC of the colon may represent a reliable predictor of lymphogenous and/or hematogenous metastases. Therefore, one should recommend an additional colectomy after endoscopic mucosal resection treatment when pathological findings confirmed IMPC of the colon and should continue a close follow-up for IMPC patients even when curative resections were performed at an early stage.

Key words: invasive micropapillary carcinoma – submucosal colon cancer – endoscopic mucosal resection – progressive systemic sclerosis

INTRODUCTION

Invasive micropapillary carcinoma (IMPC), originally described as a distinctive type of invasive carcinoma of the breast, is now being increasingly recognized as a separate entity in many other organs including the urinary bladder, ovary, lung and parotid gland (1,2,14,18,21). Pathologically, IMPC is characterized by small neoplastic cell clusters surrounded by peculiar stromal spaces, and clinically it is associated with a poor prognosis and extensive lymph node metastases. Almost all primary IMPCs of the colon reported thus far were advanced cancers, and showed the pathological features of a conventional adenocarcinoma mixed with IMPC (8,11,23). To the best of our knowledge, there are no reports describing a pure, submucosal IMPC of the colon.

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The association between an increased incidence of malignancy and the development of connective tissue disease is well established in polymyositis/dermatomyositis (25). The increased risk of malignancy in progressive systemic sclerosis (PSS) is not as clear, although an association with lung, esophageal and skin cancers has been noted (4,26). The mechanisms responsible for the development of malignancy secondary to long-standing PSS remain elusive, although the immunological abnormalities characteristic of PSS may play a role in carcinogenesis.

Here, we present a case of pure, submucosal IMPC of the colon in a long-suffering PSS patient who deteriorated rapidly over a short follow-up period due to distant metastases after an endoscopic resection of the lesion.

CASE REPORT

A 71-year-old woman was seen at the Kyoto University Hospital because of occasional melena and narrowing of her stools. She had a 12-year history of PSS and underwent home oxygen therapy for the last year because of a deterioration of her dyspnea due to lung fibrosis and consequent pulmonary hypertension. She had taken oral low-dose steroids for 8 years since the onset of PSS, but for the last 4 years, she had no steroids or immunosuppressive drugs. Marked sclerosis of all digits of the hands was noted, and she complained of Raynaud’s symptoms. Fine crackles were audible bilaterally on chest auscultation. The laboratory data were unremarkable, except for high titers of antinuclear antibody.

Echocardiography revealed moderate pulmonary hypertension of 80/17 mmHg (mean: 38 mmHg). Pulmonary function testing showed mild obstructive changes and a decrease in diffusing capacity: %VC 81.6%, FEV1.0% 69.8% and %DLco 29.4%. Blood oxygenation was satisfactory under the nasal administration of 2 l/min of oxygen. A total colonoscopy (CS) revealed a pedunculated, cauliflower-like polyp with a depressed surface in the sigmoid colon (Fig. 1A and B). The polyp was regarded as an early colon cancer with possible submucosal invasion. Computed tomographic (CT) examination of the whole body showed neither lymph node involvement nor distant metastases.

Although a radical operation along with regional lymph node dissection was proposed in terms of the possibility of deeper local invasion than anticipated, she underwent an endoscopic mucosal resection (EMR) because of possible severe perioperative complications resulting from moderate pulmonary hypertension. The polypoid lesion was successfully resected endoscopically without any complications. The resected specimen was 20 mm x 15 mm x 15 mm in size and was pathologically diagnosed as an adenocarcinoma with a negative surgical margin (Fig. 1C), although submucosal invasion of the tumor and moderate lymphatic vessel invasion were noted. Because of the peculiar histological appearance (Fig. 1D), additional immunohistochemical staining for epithelial membrane antigen (EMA) using the specific primary antibody (Dako, Glostrup, Denmark, clone E-29, dilution 1:500) was performed. This revealed a characteristic ‘inside-out’ staining pattern in almost all tumor clusters, except for the coexisting adenomatous portions, thus leading to the final diagnosis of a pure IMPC of the colon (Fig. 1E and F). Following a careful discussion about successive treatment options, she chose to undergo a close follow-up without additional sigmoidectomy because of a high incidence of perioperative morbidity events due to pulmonary arterial hypertension and the poor prognosis anticipated by her PSS.

At 6 months after the EMR treatment, however, a follow-up CS showed a suspicious lesion, possibly local recurrence (Fig. 2A). A histological examination of the biopsy samples confirmed the recurrence of IMPC (Fig. 2B). Subsequent CT scans of the whole body revealed multiple distant metastases including the lung, liver, pelvic lymph nodes and spleen (Fig. 2C–F). She refused systemic chemotherapy and decided to take the best supportive care. Because of the rapid progression of the metastatic lesions, she died of respiratory failure at 12 months after the EMR treatment.

In order to clarify the pathological features of this distinctive type of the tumor, we performed immunohistochemical staining for podoplanin, a specific marker of the lymphendothelium, and for cell adhesion molecules including E-cadherin and CD44, using the specific primary antibodies (Nichirei, Tokyo, Japan, clone D2-40, dilution 1:3; Novocastra, Newcastle upon Tyne, UK, clone 36B5, dilution 1:100; and Novocastra, clone F10-44-2, dilution 1:100), respectively. Although several clusters of tumor cells were surrounded by podoplanin immunopositive endothelial cells, which indicated lymphatic invasion by the tumor cells, the cells surrounding most of the tumor clusters were immunonegative for podoplanin (Fig. 3A). Therefore, the peculiar morphological appearance did not reflect excessive lymphatic invasion but the intrinsic, histological properties of the tumor. The expression of E-cadherin was markedly reduced in the majority of tumor clusters, although several clusters retained membranous expression at the cell-to-cell interface but not at the interface between the cytoplasmic membrane of the tumor cells and the stroma, which may reflect the characteristic property of ‘inversion of cell polarization’ (Fig. 3C and D). In contrast, there was no detectable immunoreactivity for CD44 in any tumor clusters (Fig. 3B). These findings suggested a global down-regulation of cell-to-cell and cell-to-matrix adhesions in the IMPC of the colon, which seemed to result in highly invasive and metastatic biological potentials.

DISCUSSION

There are several reports describing IMPC in the breast, lung and urinary bladder cancers (12,15,20). Regardless of the organs affected, IMPC is associated with more frequent...
Figure 1. Colonoscopic findings and pathological features of invasive micropapillary carcinoma (IMPC) of the colon. (A and B) A total colonoscopy revealed a pedunculated, cauliflower-like polyp with a depressed surface in the sigmoid colon, which was regarded as colon cancer with possible submucosal invasion. (C) A low magnification view of the whole, resected specimen showed a negative surgical margin of the tumor stalk (HE ×4). An open arrow shows the surgical margin of the tumor. (D) A high magnification view revealed a peculiar histological appearance, suggestive of an IMPC (HE ×200). (E and F) Immunohistochemical staining for epithelial membrane antigen (EMA) showed a characteristic ‘inside-out’ staining pattern in the whole specimen, except for the coexisting adenomatous portions, which in contrast showed strong immunostaining of the luminal side of the cytoplasm (F) (×200). The solid arrows show the ‘inside-out’ immunostaining pattern of EMA in this tumor.
involvement of the lymph nodes and a poorer clinical outcome, when compared with conventional adenocarcinomas, possibly because of its much more aggressive biological properties. The pathological and diagnostic feature of IMPC is its characteristic ‘inside-out’ immunostaining pattern for EMA or MUC1, indicative of the inversion of cell polarization; the outer surface of the tumor cell clusters is immunopositive for EMA or MUC1.

In order to differentiate IMPC from pseudo-IMPC, which is conventional adenocarcinoma but shows an IMPC-like pattern due to artefacts in the preparation of the paraffin sections, immunohistochemical staining for EMA or MUC1 is recommended for the precise diagnosis of IMPC (13,14,19,20). In IMPC cases, EMA expression was found at the reversed apical membrane of the tumor cell clusters, whereas pseudo-IMPC cells showed EMA expression along the cytoplasmic membrane and/or in the cytoplasm of the tumor cells. In addition, immunostaining of the lymphatic endothelia with the specific antibody, D2-40, was useful to exclude the possibility of conventional adenocarcinomas.

Figure 2. Local recurrence and multiple metastases after the EMR treatment. (A) A local recurrence at the resection site was suspicious on a follow-up colonoscopy at 6 months after the treatment. (B) Biopsy samples confirmed the recurrence of invasive micropapillary carcinoma (arrowheads) (HE ×100). (C–F) Computed tomographic scans of the whole body revealed multiple, distant metastases including the liver (C), spleen (D), pelvic lymph nodes (E) and lung (F). The arrows indicate metastatic lesions in multiple organs.
with extensive lymphatic invasion (13,23). In this case, nearly all tumor clusters showed a typical 'inside-out' EMA immunostaining pattern, and podoplanin immunostaining revealed infrequent lymphatic invasion by the tumor cells. Therefore, we considered the lesion as a pure, submucosal IMPC of the colon.

It is noteworthy that the proportion of the micropapillary component, which varies among IMPC cases, has a prognostic impact in breast cancer. The disease-free and overall survival rates were lower in pure IMPC cases when compared with mixed-IMPC of the breast (13). With respect to IMPC of the colon, the presence of a micropapillary component was regarded as an aggressive variant of the adenocarcinoma, although there was no definite association between the proportion of the micropapillary component and the prognosis (8,11). Since there are few reports describing pure IMPCs of the colon as shown in this case, further analysis is required to recognize pure IMPC as a separate disease entity in colon cancers.

The relationship between the peculiar histological appearance of IMPC and its biological malignant properties is another intriguing, but unresolved issue. Gong et al. (6) examined the expression patterns of cell adhesion molecules in IMPC of the breast and concluded that the markedly reduced expression of CD44, but not E-cadherin, whose expression was retained at the cell-to-cell interface, may play a significant role in the high incidences of invasion and metastasis (3). Immunohistochemical staining in this case showed a loss of CD44 expression along with a marked reduction of E-cadherin expression in the tumor clusters. Thus, this global down-regulation of the major cell adhesion molecules may induce detachment of the tumor cells from the primary lesions due to a weakening of cell-to-cell and cell-to-matrix adhesion and facilitate the subsequent penetration into the lymph-vascular spaces in IMPC of the colon. Recent comprehensive analysis using high-resolution microarray-based comparative genomic hybridization and expression profiling using tissue microarray in IMPC of the breast (16) revealed that the genomic profiles of IMPC were significantly different from those of invasive ductal carcinomas of no special type, and that...
high cyclin D1 expression, high proliferation rates and MYC amplification were significantly associated with IMPC. From these findings, they hypothesized that IMPC of the breast was a distinct disease entity, not only at the histological, but also at the molecular genomic level.

Although PSS patients have a predisposition for bronchial and esophageal cancers due to long-standing pulmonary fibrosis, decreased esophageal motility and refractory reflux esophagitis, there are no reports demonstrating an increased incidence of colon cancer in PSS patients. It is well documented that PSS patients show several immunological abnormalities, including the enhanced production of TNFα, TGFβ, IL2, IL4 and IL6, and a dysfunction of T helper cells, T suppressor cells and natural killer cells (7,9,10,24). Therefore, in this case, there is a possibility that the hematogenous and lymphogenous progression of IMPC may accelerate due to the immunological dysfunction inherent in PSS patients, in addition to the intrinsically aggressive nature of IMPC. In addition, PSS might give an advantage to the pathogenesis of pure IMPC in the colon, although a mechanism responsible for the development of IMPC in the colon, instead of the more prevalent breast IMPC, remains unclear.

In this case, there is a possibility that surgical intervention may have improved the prognosis despite the aggressive properties of pure IMPC, since the colon lesion was detected without any radiographic evidence of distant metastases, although, in contrast, operation per se may accelerate the progression of the disease due to mechanical spread of cancer cells during the manipulations. According to the study by Mukerjee et al. (17), the 3-year survival rate of PSS patients with moderate pulmonary hypertension of 32–44 mmHg mean pulmonary artery pressure (mPAP) was estimated to be 61%, which was much worse than that of early-stage colon cancers. In addition, 60 of the 145 patients (42%) with mPAP >25 mmHg at rest experienced at least one short-term morbid event, and 10 patients (7%) suffered early surgery-related deaths when they underwent non-cardiac surgery with general anesthesia (22). Since our patient refused additional surgical resection because of possible post-operative complications, we decided to follow-up her condition closely without any additional treatment.

To our knowledge, this is a rare case of pure, submucosal IMPC of the colon. Although further studies are required to determine the clinicopathological and biological features of IMPC of the colon, pure IMPC of the colon may represent a reliable predictor of lymphogenous and/or hematogenous metastases. Therefore, one should recommend an additional colectomy after EMR treatment when pathological findings confirmed IMPC of the colon and should continue a close follow-up for IMPC patients even when curative resections were performed at an early stage.

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**Conflict of interest statement**

None declared.

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