Primary signet-ring cell carcinoma of vermiform appendix clinically and pathologically presenting as acute appendicitis

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Abstract Primary signet-ring cell carcinoma (SRCC) of vermiform appendix is extremely rare; only three cases have been reported in the English literature. An 89-year-old man suddenly presented right lower abdominal pain, and transferred to a hospital, where he was diagnosed with acute appendicitis by physical data, blood data, and CT. He was further transferred to our hospital for emergency operation. Physical examination showed positive abdominal pain, Blumberg sign, and Rosenstein sign. Blood test showed leukocytosis and increased C-reactive protein. An appendectomy was performed. Gross examination during operation showed inflamed appendix, appendiceal adhesion, and acute peritonitis. Gross pathological examination showed no apparent tumor, but the proximal appendix showed wall thickening and luminal occlusion. The appendix was cut into three sections, and was observed under microscopically. Nests of carcinoma cells were seen in the proximal appendix. The carcinoma was composed of SRCC (70%) and mucinous carcinoma (30%). The size of carcinoma was 6 × 7 mm. The carcinoma cells invaded into muscular layer. No lymphovascular permeation was seen. The cut margins were negative for carcinoma cells. Immunohistochemically, SRCC cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK8, CK18, CK19, CK20, EMA, CEA, CA19-9, p53, Ki-67 (labeling = 30%), CDX2, MUC2, and MUC5AC. They were negative for CK34PE1, CK5/6, CK7, CK14, p63, vimentin, TTF-1, MUC1, MUC 5AC, NSE, synaptophysin, chromogranin, and CD56. No further treatments were performed, because the appendiceal carcinoma was small, the surgical margins were negative and the patient was very old. He was followed up by various imaging modalities. No recurrence or metastasis is found 17 months after the operation.

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1. Introduction

Appendiceal cancer is very rare; it accounts for only 0.5% of all gastrointestinal neoplasms [1]. According to a nationwide cancer database (SEER), the age-adjusted incidence of appendiceal malignancies was 0.12 cases per 1,000,000 people per year [1]. Primary appendiceal cancer is diagnosed in only 0.9%–1.4% of appendectomy specimens [2]. Further, signet-ring cell carcinoma (SRCC) of vermiform appendix is extremely rare, accounting for 0.43% of all appendiceal malignancies [2]. To the best of the author’s knowledge, there have been only three case reports of appendiceal SRCC [3–5]. Herein, reported is a
very rare case of primary appendiceal SRCC clinically and pathologically presenting as typical acute appendicitis.

2. Case report

An 89-year-old Japanese man suddenly presented with right lower abdominal pain, and transferred to a hospital, where he was diagnosed with acute appendicitis by physical test, blood data, and CT. CT demonstrated appendiceal swelling. He was further transferred to our hospital for emergency operation. Physical examination showed positive abdominal pain, Blumberg sign, and Rosenstein sing. Blood test showed leukocytosis (13,200/µl: normal 3500–9000) of predominant segmented neutrophils (94%, normal 43%–59%), and increased C-reactive protein (2.24 mg/dl: normal 0–0.3). An appendectomy using laparoscopy was performed. Gross examination during the operation showed inflamed appendix, appendiceal adhesion, and acute peritonitis. Gross pathological examination showed no apparent tumor, but the proximal appendix showed wall thickening and luminal narrowing (Fig. 1). After fixation in formalin, the appendix was cut into three sections, and was observed under microscopically. Nests of carcinoma cells were seen in the proximal appendix (Fig. 2A). The carcinoma was composed of SRCC element (70%) (Fig. 2B) and mucinous carcinoma element (30%). The size of carcinoma was 0.6 × 0.7 cm. The carcinoma cells invaded into the muscular layer (pT1). No lymphovascular permeation was seen. The cut margins were negative for carcinoma cells. No distant metastasis, lymph node metastasis or peritoneal dissemination was found by imaging techniques as well as by clinical findings. The TNM classification and stage of the appendiceal carcinoma were rated pT2N0M0P0H0 and Stage I or Dukes A.

An immunohistochemical study was performed by the use of Dako Envision system and its variation methods (Dako, Glostrup, Denmark), as previously described [6–14]. Immunohistochemically, the SRCC cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK8, CK18 (Fig. 3A), CK19, CK20, EMA, CEA, CA19-9, p53, Ki-67 (labeling = 30%), CDX2 (Fig. 3B), MUC2 (Fig. 3C), and MUC5AC. They were negative for CK34PE1, CK5/6, CK7, CK14, p63, vimentin, TTF-1, MUC1, MUC 5AC, neuron specific enolase (NSE), synaptophysin, chromogranin, and CD56.

The other parts of the appendix showed typical severe acute phlegmonous appendicitis (Fig. 4). No further therapeutic treatments were performed, because the appendiceal carcinoma is small, the surgical margins were negative, and the patient was very old. He was followed up by various imaging modalities. No recurrence or metastasis is found 17 months after the operation.

Fig. 1  Gross findings of the appendix. The lumen is open, but the walls of the proximal appendix (right) are thickened (arrows). The appendix distal appendix (left) shows severe appendicitis.

Fig. 2  Histological findings of the appendix. A: The proximal appendix shows proliferation of signet ring cell carcinoma and mucinous adenocarcinoma. HE, ×40. B: Higher power view of the signet ring cell carcinoma element. Features of signet ring cell carcinoma are apparent. HE, × 200.
3. Discussion

The current case is the fourth case report of primary SRCC of the appendix [3–5], and the first report of primary SRCC clinically and pathologically manifesting as acute appendicitis. According to WHO book, only appendiceal adenocarcinoma containing more than 50% of SRCC elements is called appendiceal SRCC [15]. The present case was composed of SRCC element (70%) and mucinous carcinoma element (30%); thus the current case fulfills the criteria of primary appendiceal SRCC. The primary SRCC of the current case was very small and the incidental finding of the appendectomy. This suggests that pathologist should perform meticulous examination of the appendectomies.

The present SRCC of the appendix seems to be the primary site since no tumors other than the appendiceal tumor were found in the body by various imaging modalities, and also because the SRCC cells of the present tumor were immunohistochemically positive for CDX2, a colonic type epithelium-specific antigen.

Interestingly, the present primary SRCC of appendix clinically manifested as acute appendicitis. The physical findings, blood test, and CT findings were typical for acute phlegmonous appendicitis. However, small SRCC was pathologically found in the proximal appendix. The remnants of the appendix showed typical severe acute phlegmonous appendicitis. The SRCC narrowed the appendiceal lumen; thus the author speculates that this narrowing caused by SRCC is the soil and cause of the severe appendicitis in the present case. In the present case, the SRCC is located in the proximal appendix, and the cecum-side margin was negative. Furthermore, the depth of invasion of the current SRCC is muscular layer (pT2), and no lymphovascular permeation was seen. The TNM classification was pT2N0M0P0H0. The stage was Stage I or Dukes A. Therefore, the author considered that the prognosis of this patient was not so bad, although histological type (SRCC) seems to reflect poor prognosis. In fact, the patient is free from recurrence and metastasis 17 months after the operation.

The present study performed an extensive immunohistochemical study of primary appendiceal SRCC. This is the second case of this kind of study after Suzuki et al [3]. The CK profile indicates that the SRCC cells have a wide range of CK. CK7−/CK20+ pattern is compatible with appendiceal origin. EMA was expressed and vimentin was not expressed, suggesting that the present tumor is epithelial origin. P53 was expressed, suggesting p53 gene mutations. Ki-67 labeling was high (30%), suggesting a high cell proliferative activity. The present SRCC expressed CEA and CA19-9, indicating that the present tumor is a kind of adenocarcinoma. The present SRCC did not express TTF-1, indicating no association with pulmonary phenotypes. The MUC profiles suggest that product of MUC2 and MUC5AC genes is operative, while MUC1 and MUC genes not. The negative reaction for NSE, chromogranin, synaptophysin, and CD56 indicates that the present tumor is not goblet cell carcinoid. Although there were slight differences of the antigenic

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expression, the immunoprofile of the current case is similar to that of SRCC of other organs [3].

Finally, the present tumor is definitely different from appendiceal signet ring carcinoma, because the present tumor showed apparent malignant morphological features and because the tumor is negative for neuroendocrine antigens (NCAM, NSE, chromogranin and synaptophysin).

In summary, the author reported the forth case of primary appendiceal SRCC, and the first case of this tumor manifesting as acute appendicitis clinically and pathologically. An extensive immunohistochemical study was also performed.

The author has no conflict of interest.

References


