Primary minute mucinous adenocarcinoma of vermiform appendix arising from appendiceal diverticulosis☆

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Abstract Primary mucinous adenocarcinoma (MA) of vermiform appendix is extremely rare; only three cases have been reported in the English literature. A 77-year-old man presented with abdominal pain, and was diagnosed with acute appendicitis. Appendectomy was performed. The resected appendix showed submucosal swelling measuring 0.7×0.6×0.6 cm in the tip of appendix. The appendix showed inflammation and numerous diverticuloses. Microscopically, the submucosal swelling was a mucin lake in which adenocarcinoma cells were floating. The adenocarcinoma cells were MA in 80% and signet-ring cell carcinoma in 20%. The carcinoma cells were located in the submucosa, muscular layer and subserosa, sparing the mucosa. No apparent lymphovascular permeation was seen. The surgical margins were negative for tumor cells. The non-tumorous appendix shows numerous diverticulosis, diverticulitis, and appendicitis. Immunohistochemically, the tumor cells were positive for CK CAM5.2, CK AE1/3, CK8, CK18, CK19, CK20, EMA, CEA, CA19-9, MUC1, MUC2, MUC5AC, MUC6, NCAM, p53 and Ki-67 (labeling index = 23%). The tumor cells were negative for CK34BE12, CD5, CK6, CK7, NSE, chromogranin, synaptophysin, CA125, KIT, and PDGFRA. No metastasis has been seen 2.5 years after the operation.

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1. Introduction

Appendiceal cancer is 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 case per 1,000,000 people per year [1]. Primary appendiceal cancer is diagnosed in only 0.9%–1.4% of appendectomy specimens [2]. Further, mucinous adenocarcinoma (MA) and signet-ring cell carcinoma (SRCC) of vermiform appendix are extremely rare, accounting only for 0.21% and 0.43% of all appendiceal malignancies, respectively [2]. To the best of the author’s knowledge, there have been only three case reports of appendiceal primary MA [3–5] and also only three cases of primary SRCC [6–9].

2. Case report

A 77-year-old man presented with lower abdominal pain, and was admitted to a hospital. The blood data showed leukocytosis (12,000/μl) and increased C-reactive protein...
(6.2 mg/dl). Lanz’s, and Kummel’s, McBurney’s tenderness, and Blunberg’s sign were present. The CT imaging demonstrated a swelling of the appendix. The patient was diagnosed with acute appendicitis and appendectomy was performed.

The resected appendix showed submucosal swelling measuring 0.7×0.6×0.6 cm in the tip of appendix. The appendix also showed severe inflammation and numerous diverticuloses. Microscopically, the submucosa swelling was a mucin lake in which adenocarcinoma cells were floating (Fig. 1A). The adenocarcinoma cells were MA in 80% (Fig. 1B) and signet-ring cell carcinoma (Sig) in 20% (Fig. 1C). The carcinoma cells were located in the submucosa, muscular layer and subserosa, sparing mucosa. No apparent lymphovascular permeation was seen. The surgical margins were negative for tumor cells. The non-tumorous appendix shows numerous diverticulosis (Fig. 1D), diverticulitis, and acute appendicitis.

Histological examination was done as previously reported [10]. It showed neutral, carboxylated and sulfated mucins in the mucin pool and carcinoma cells (Fig. 2A and B).

An immunohistochemical study was performed with the use of Dako Envision method as previously reported [11,12]. Immunohistochemically, the tumor cells were positive for cytokeratin (CK) CAM5.2 (Fig. 3A), CK AE1/3, CK8, CK18, CK19, CK20 (Fig. 3B), EMA, CEA, CA19-9, MUC1, MUC2 (Fig. 3C), MUC5AC (Fig. 3D), MUC6, NCAM (Fig. 3E), p53, CDX-2 (Fig. 3F), and Ki-67 (labeling index (LI) = 23%). The tumor cells were negative for CK34BE12, CD5, CK6, CK7, NSE, chromogranin, synaptophysin, CA125, KIT, and PDGFRA. Since no carcinoma was seen in the mucosa and numerous diverticuloses were seen, the carcinoma seemed to arise from the diverticuloses. The location of the tumor is appendiceal tip, no lymphovascular permeation and the surgical margins were negative.

Post-pathological diagnosis whole body examinations including CT, MRI, PET, and endoscope revealed no tumors. The patient was not treated by chemotherapy, but strictly followed up. No metastasis has been seen 2.5 years after the operation. No pseudomyxoma peritonei was seen.

3. Discussion

The current case is the fourth case report of primary MA of the appendix [3–5], and the first report of primary MA clinically and pathologically manifesting as acute appendicitis. In the present study, the adenocarcinoma cells were composed of MA in 80% and signet-ring cell carcinoma (SRCC) in 20%. According to WHO, the only appendiceal adenocarcinoma containing more than 50% of SRCC elements is called appendiceal SRCC [9]. Therefore, the present case is not SRCC but MA. The primary SRCC of the current case was very small (0.7×0.6×0.6 cm) and the

![Fig. 1](image)  
**Fig. 1** Histologic findings of the appendix. A: A small mucinous tumor is seen. B: The most of carcinoma cells are tubular adenocarcinoma. HE, ×200. C: A minority is signet ring cell carcinoma. HE, ×100.
incidental finding of the appendectomy. This suggests that pathologists should perform meticulous examination of the appendectomies.

The present MA 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 MA cells of the present tumor were immuno-histochemically positive for CDX2, a colonic type epithelium-specific antigen.

Interestingly, the present primary MA of the appendix clinically manifested as acute appendicitis. The physical findings, blood test, and CT findings were typical for acute phlegmonous appendicitis. However, small MA was pathologically found in the distal appendix. The remnants of the appendix showed typical severe acute phlegmonous appendicitis. The MA narrowed the appendiceal lumen; thus the author speculates that this narrowing caused by MA 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 adjacent to the tip. Curiously the appendiceal mucosa was free from tumor, despite multiple sections. The MA was located in the submucosa, muscle layer and subserosa, indicating that the present MA is not derived from mucosa. Therefore, the present MA is likely derived from metastasis or from misplaced epithelium, i.e. appendiceal diverticulosis. As mentioned above, metastasis is unlikely. Therefore, the author thinks that the present tumor arose from diverticulosis.

The present study performed a histochemical and immunohistochemical study of primary appendiceal MA. This is the first case of this kind of study. The immunohistochemistry showed neutral, carboxylated and...
sulfated mucins in the tumor cells and in the mucin lake. The findings imply that the tumor is authentic MA, and mucin glycoprotein moiety contains these neutral, carboxylated and sulfated side chains. Mucins are very high molecular weight glycoproteins, in which numerous carbohydrate side chains are attached to the protein back borne called MUC apomucins. At present at least 20 kinds of MUC apomucins are known to exist and their genetics are vigorously debated. Thus, the evaluation of mucins should be composed of those of MUC apomucins (proteins) and those of carbohydrate side chains (carbohydrates). In practical pathology, the proteins of mucins were evaluated by MUC apomucins, and carbohydrate moieties by immunohistochemistry and histochemistry. In the present study, four MUC apomucins were investigated. MUC1 (transmembranous non-secretory mucins, polymorphic epithelial mucins), MUC2 (secreted mucins, goblet cell mucins), MUC5AC (secreted mucins, gastric foveolar mucins) and MUC6 (secreted mucins, gastric pyloric gland mucins) were expressed, suggesting that the present appendiceal MA contains these four apomucins. The expression of MUC5AC and MUC6 suggests the gastric metaplastic phenotype of the present MA. In histology, the MA and SRCC were of gastric type.

The present study have for the first time revealed the CK profile in appendiceal MA. In the present MA, the CK profile was as follows; CAM5.2+, CK AE1/3+, CK8+, CK18+, CK19+, CK20+, CK34BE12−, CD5−, CK6−, and CK7−. Thus, the present tumor contained low molecular weight CK. CK7−/CK20+ pattern is compatible with appendiceal origin. EMA was positive, suggesting the epithelial nature. NCAM was positive, suggesting that the tumor has neuroendocrine or stem cell features. NSE, chromogranin, and synaptophysin were negative, suggesting that the neuroendocrine features are not broad. CEA and CA19-9 were positive, suggesting that the present tumor is an adenocarcinoma. CA125 was negative, suggesting no association with female genital organs. p53 was positive, suggesting p53 mutations and malignant potential of the present tumor. Ki-67 labeling was high (LI = 23%), suggesting high cell proliferation and malignant potential. KIT and PDGFRA were negative, suggesting that these tyrosine kinase receptor oncoproteins were not expressed in the tumor cell membranes. CDX-2 was positive, indicating that the present tumor is gastrointestinal malignancy.

References


