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Adenocarcinoid of the Appendix: Report of Two Cases

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Abstract
Adenocarcinoid of the appendix is a rare tumor with the histological features of both adenocarcinoma and carcinoid tumor. However, its biological behavior and malignant potential are still unclear. We treated two patients with this unusual tumor; a 60-year-old man and a 79-year-old woman. Both patients were initially diagnosed with acute appendicitis followed by an appendectomy. At surgery, the appendix was seen to be acutely inflamed without any macroscopic signs of tumor. Postoperative histological analysis revealed an adenocarcinoid tumor in the appendix, which had spread diffusely into its wall without forming a mass. Immunohistochemical staining with p53, MIB-1, bcl-2, and carcinoembryonic antigen suggested that neither of these tumors were particularly aggressive. Adenocarcinoid of the appendix is a rare tumor, which is very difficult to diagnose preoperatively and even macroscopically, making histological examination essential.

Key words Adenocarcinoid · Carcinoid · Carcinoma of appendix vermiformis

Introduction

The biological behavior and malignant potential of adenocarcinoid of the appendix, which has the histological features of both adenocarcinoma and carcinoid tumor,[1] are still not well understood. This report presents two cases of adenocarcinoid of the appendix. We investigated the characteristics of these tumors immunohistochemically using molecular markers.

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Case Reports

Case 1

A 60-year-old man was referred to our hospital with severe abdominal pain in the lower right quadrant. Physical examination revealed muscular defense and rebound tenderness over McBurney's point. Preoperative blood examination showed leukocytosis (14800/mm^3), and an ultrasonogram revealed a swollen appendix suggestive of acute appendicitis. An appendectomy was performed, revealing a severely inflamed and perforated body of the appendix. Macroscopically, the mucosa of the appendix was acutely inflamed, but no neoplastic changes were seen. Microscopically, there was infiltration by inflammatory cells, as well as atypical cells diffusely infiltrating from the submucosal layer to the subserosal layer, and forming a microlumen structure. There was a large amount of mucin in the lumen and surrounding tissue, which was stained by alcian blue. The growth pattern of these tumors was unique in that they arose within the lower lamina propria and extended through the muscularis propria into the subserosa without destroying the appendiceal wall structure (Fig. 1a,b). No mitotic cells were found. The tumor cells were positive for carcinoembryonic antigen (CEA) and chromogranin A (Fig. 1c), which led to a diagnosis of adenocarcinoid with glandular differentiation accompanied by gangrenous appendicitis. Staining for neuron-specific enolase (NSE) was weakly positive, CEA was positive, MIB-1 was weakly positive (less than 50% of the nuclei were stained), bcl-2 was negative, and p53 was negative (Table 1). Due to the positive surgical margin, ileocecal resection was performed with dissection of the lymph nodes. Histologically, there was no residual tumor and no regional lymph node metastasis. The patient is alive and disease-free 18 months after surgery.

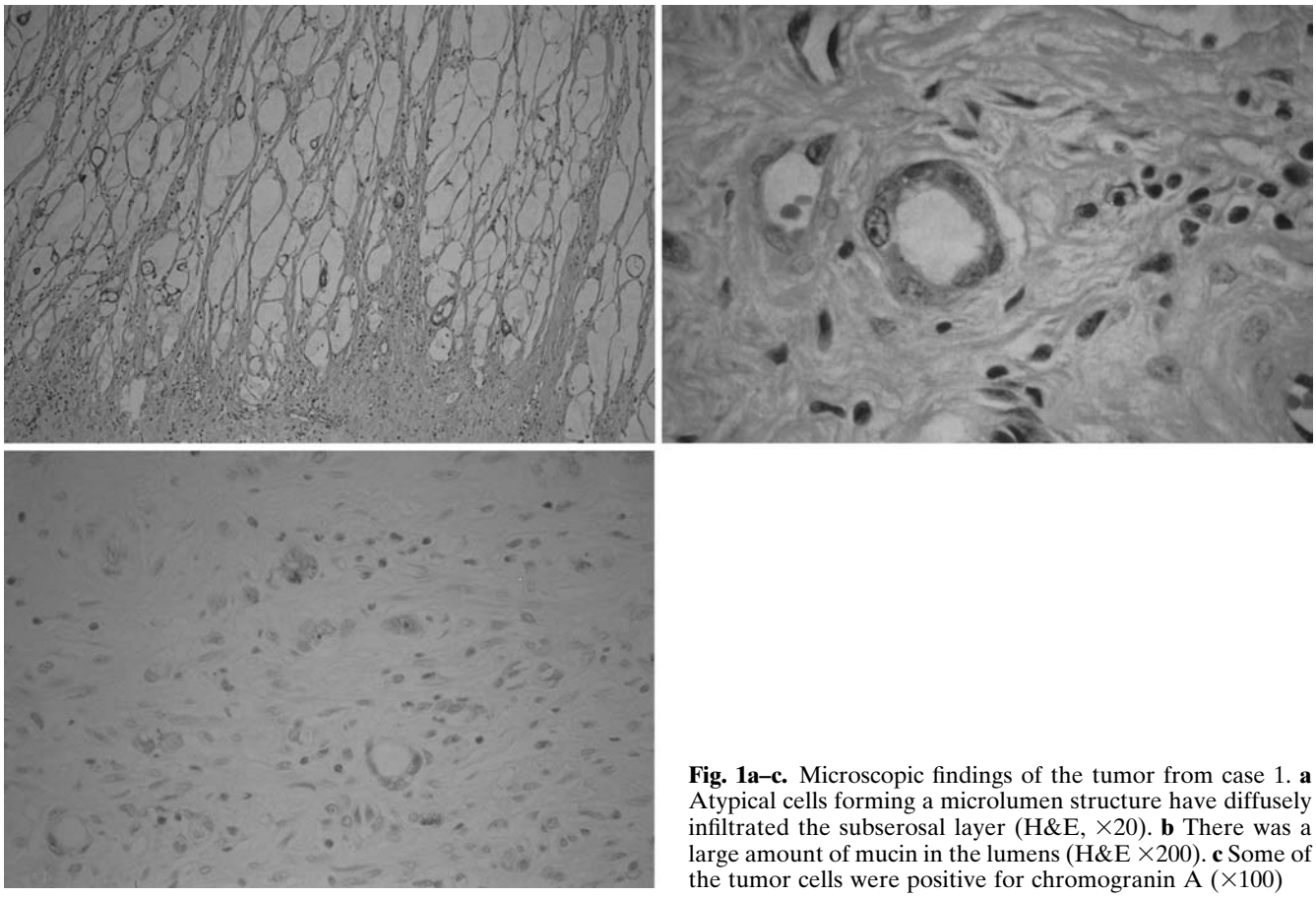

Fig. 1a–c. Microscopic findings of the tumor from case 1. **a** Atypical cells forming a microlumen structure have diffusely infiltrated the subserosal layer (H&E, ×20). **b** There was a large amount of mucin in the lumens (H&E ×200). **c** Some of the tumor cells were positive for chromogranin A (×100)

Table 1. Results of immunohistochemical staining of the tumors

	Case 1	Case 2
CEA	+	++
Chromogranin A	+	+
NSE	+	++
MIB-1	+	+
bcl-2	−	−
p53	−	−

+ indicates weak staining with less than 50% of the nuclei stained; ++ indicates strong staining with more than 50% of the nuclei stained
CEA, carcinoembryonic antigen; NSE, neuron-specific enolase

Case 2

A 79-year-old woman was admitted to our hospital with abdominal pain in the lower right quadrant. Physical examination revealed muscular defense and rebound tenderness over McBurney's point. Preoperative blood examination showed leukocytosis (15400/mm^3), and an emergency computed tomography (CT) scan demonstrated luminal enhancement of the appendix and a thickened wall of the terminal ileum (Fig. 2), suggesting that she had acute appendicitis with terminal ileitis. Under this diagnosis, an appendectomy was performed. At laparotomy, the appendix was severely inflamed and perforated at its tip, accompanied by suppurative ascites. Macroscopically, the mucosa of the appendix was acutely inflamed, but no signs of neoplastic change were seen. The microscopic findings were essentially the same as those seen in case 1. The tumor cells comprised glands with acini and small lumen. The cell cytoplasms were clear, homogeneous, and coarsely vacuolated with nuclei localized in the rim of the cell due to the abundant cytoplasmic mucin. Thus, the cells resembled goblet cells. No mitotic cells were found. Staining for NSE was partially positive, MIB-1 was weakly positive, bcl-2 was negative, p53 was negative, and CEA was strongly positive (Table 1). The pathological diagnosis was adenocarcinoid, goblet cell type, with gangrenous appendicitis. The surgical margin was free of tumor. The patient is alive and disease-free 1 year after surgery.

Discussion

Adenocarcinoid is a tumor with the histological features of both carcinoid tumor and adenocarcinoma.[1] This

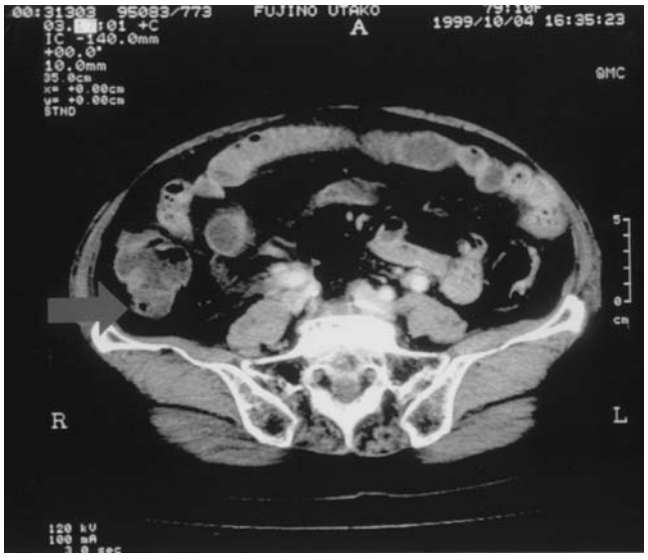

Fig. 2. Computed tomography of case 2 showing the luminal enhancement of the appendix and a thickened mesoappendix

means that an adenocarcinoid has cytoplasmic neurosecretory granules and a glandular structure, thereby producing large amounts of mucin. The nomenclature for this tumor is confusing. Gagne et al. first reported this tumor in 1969,[2] and Klein[3] named it "mucinous carcinoid" in 1974. Subbuswamy et al.[4] subsequently described 12 similar cases and named it "goblet cell carcinoid." In 1978, Warkel et al.[1] reported a series of 39 cases and renamed the tumor "adenocarcinoid." It has also been termed "crypt cell carcinoid"[5] and "composite tumor."[6]

Adenocarcinoid tumors are rare. In fact, only 52 cases have been reported in Japan[7] and just over 130 cases have been reported worldwide. In 1988, Martin and Pia found that the mean age for adenocarcinoid was higher than that for conventional carcinoid tumor.[8] Their analysis of 20 cases revealed a mean age for adenocarcinoid of 58.8 years, whereas that for carcinoid tumor was 35.9 years. The sites of occurrence include the gastrointestinal, biliary, and urinary tracts, but the appendix is the most common site.[9] Clinical symptoms frequently include acute appendicitis, intra-abdominal mass, and ovarian swelling.[10] Carcinoid symptoms do not appear with adenocarcinoid,[1] which is said to be more malignant than carcinoid tumors, but less malignant than adenocarcinomas.[1] Martin and Pia also reported in their analysis of 98 cases from the literature that 22.4% of the tumors spread beyond the appendix to the cecum, to the peritoneum directly, or metastasized to the lymph nodes and ovaries.[8]

Histologically, adenocarcinoid is composed of tumor cells with abundant cytoplasmic mucin. These cells form nests or have a microglandular lumen structure. Neuron-specific granules in the cytoplasm are reactive for NSE, chromogranin A, synaptophysin, Grimelius stain, Fontana-Masson stain, serotonin, substance P, peptide YY, glucagon, and S-100 protein. The tumor cells proliferate sparsely and do not form nodules. The appendiceal wall thickens diffusely and fibrously, leading to contraction of the appendiceal lumen, which is assumed to be the cause of appendicitis. It is therefore difficult to diagnose this tumor preoperatively or macroscopically.[11] Mitotic cells are not frequently observed. In most cases, mitotic cells are seen at less than 1 per 10 high-powered magnification fields. If more than 2 or 3 were to be found per 10 high-powered magnification fields, then the prognosis would be very poor.[8] In the two cases presented, no mitotic cells were found.

In colorectal cancers, p53 protein, bcl-2 protein, and MIB-1 have been explored by immunohistochemical staining, and can be an important prognostic factor.[12,13] The results of immunohistochemical staining of the tumors in our patients indicate that these two tumors were similar. Given that no mitotic cells were detected in either tumor, and that both were weakly positive for MIB-1, and negative for bcl-2 and p53, it seems likely that the two tumors had low potential for malignancy. In contrast, Horiuti et al. reported a case of adenocarcinoid accompanied by multiple liver metastases, where most of the tumor cells were positive for p53.[14]

It is thought that appendectomy is sufficient in cases of low malignancy.[1] However, if adenocarcinoid extends beyond the appendix or if postoperative histological analysis reveals high malignant potential, then secondary colectomy with lymph node dissection is recommended.[1] In our case 1, ileocecal resection was performed because the tumor was positive at the resected margin, even though the malignant potential of the tumor was low.

In conclusion, adenocarcinoma of the appendix is a rare tumor that is very difficult to diagnose preoperatively and even macroscopically, making histological examination essential. The tumors in our two patients were confined to the appendix and showed low-grade malignancy.

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