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【 CASE REPORT 】

Fistula Formation Secondary to Mucinous Appendiceal Adenocarcinoma May Be Related to a Favorable Prognosis: A Case Report and Literature Review

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Abstract:
A 90-year-old man was referred to our hospital because of a positive fecal occult blood test. Colonoscopy revealed a lesion with multiple nodules covered with abundant mucus at the hepatic flexure. Computed tomography showed a dilated appendix attached distally to the hepatic flexure. Right hemicolectomy was performed, and the pathological examination revealed a mucinous appendiceal adenocarcinoma infiltrating the hepatic flexure without pseudomyxoma peritonei. The patient is doing well without recurrence 12 months postoperatively. Extraperitoneal drainage of the malignant ascites caused by the fistula may allow for an early diagnosis, while also making it possible to successfully resect the lesion, thus resulting in a favorable outcome.

Key words: mucinous appendiceal adenocarcinoma, pseudomyxoma peritonei, fistula formation, prognosis

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Introduction

Appendiceal adenocarcinoma is a rare malignancy, accounting for only 0.5% of all gastrointestinal malignancies (1). A mucinous type of appendiceal adenocarcinoma (MAA) is frequently accompanied by mucocele (2). The tumor itself is not aggressive; however, the disease has an unfavorable prognosis due to the absence of specific symptoms and the potential of tumor rupture, resulting in difficulty achieving an early diagnosis (3-5). Mucocele rupture leads to pseudomyxoma peritonei (PMP), which is the dissemination of malignant cells in the intraperitoneal cavity (6). Fistula formation into adjacent organs is an unusual presentation of MAA. Although some authors have reported that fistula formation might improve the patient outcome by preventing the development of PMP (7, 8), the prognosis of such cases remains unclear.

We herein report a case of MAA with fistula formation and review the pertinent literature to discuss the clinical features and prognostic impact of this rare manifestation.

Case Report

A 90-year-old man with no significant medical history was referred to our hospital for a positive fecal occult blood test (FOBT). No remarkable findings were noted in a physical examination. A laboratory analysis revealed a slightly decreased level of hemoglobin (12.7 g/dL; normal range 13.4-17.6 g/dL). Tumor markers (carcinoembryonic antigen and carbohydrate antigen 19-9) were normal. Colonoscopy revealed multiple nodules forming a mass-like lesion 35 mm in diameter and covered with a large amount of mucus at the hepatic flexure of the colon (Fig. 1). Mucinous colon carcinoma was suspected, but biopsies from the lesion showed only mucus products and granulation tissue. Other colonoscopy findings included an elevated lesion with multiple small granular protrusions covered with intact epithelium

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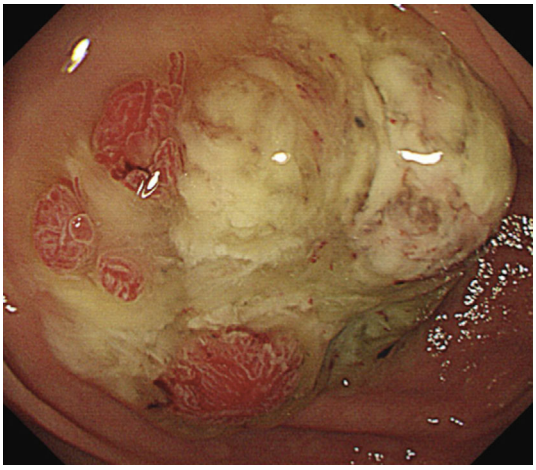

Figure 1. Colonoscopy revealed multiple nodules forming a mass-like lesion covered with a large amount of mucus, 35 mm in diameter, at the hepatic flexure.

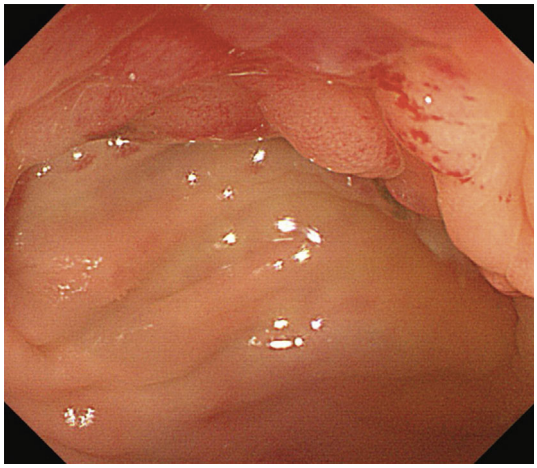

Figure 2. Other colonoscopy findings included an elevated lesion with multiple small granular protrusions covered with intact epithelium at the appendiceal orifice.

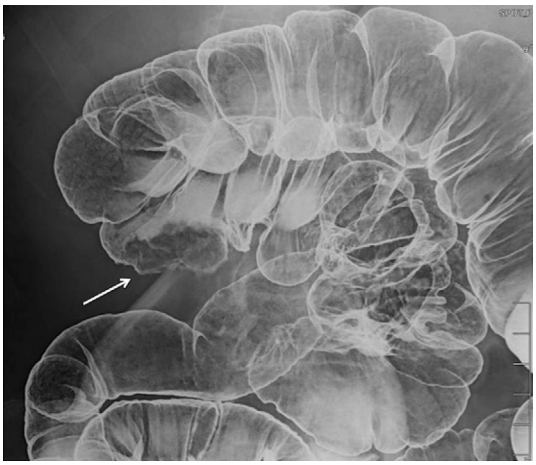

Figure 3. A barium enema showed extrinsic compression at the ileocecum and a filling defect at the hepatic flexure of colon (arrow), but the appendix could not be visualized.

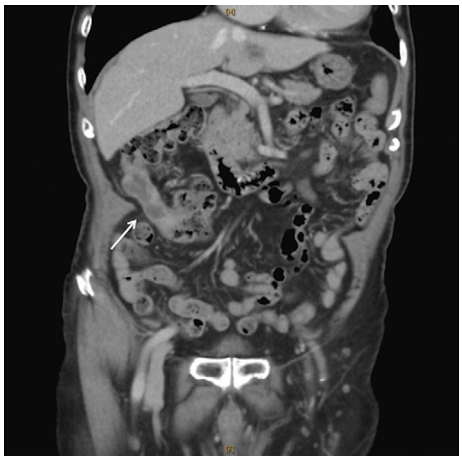

Figure 4. Abdominal contrast-enhanced computed tomography (coronal image) revealed a dilated appendix adherent to the hepatic flexure (arrow).

at the appendiceal orifice (Fig. 2). The biopsy from the appendiceal orifice was negative for cancer cells.

A barium enema (BE) showed extrinsic compression at the ileocecum and a filling defect at the hepatic flexure of colon, but the appendix could not be visualized (Fig. 3). Thus, abdominal computed tomography (CT) was performed and revealed a dilated appendix adhering to the hepatic flexure (Fig. 4). A second colonoscopy was then performed. A repeat biopsy from the lesion at the hepatic flexure was positive for mucinous adenocarcinoma. The biopsy from the appendiceal orifice was also positive for adenocarcinoma, which infiltrated the submucosal layer. Based on these findings, a diagnosis of appendiceal carcinoma with fistula to the hepatic flexure was established. He had neither distant metastasis nor peritoneal dissemination.

En bloc right hemicolectomy with extended lymph node dissection was performed for curative resection. A pathological examination revealed a well-differentiated mucinous adenocarcinoma originating from the appendiceal tip, which infiltrated the hepatic flexure with histological negative margins (Fig. 5). One of the 27 resected lymph nodes was positive. The final pathological stage was T4bN1M0. No adjuvant chemotherapy was performed because of his advanced age. The postoperative course was good with no signs of recurrence at the time of writing (follow-up period: 12 months).

Discussion

Appendiceal carcinoma is a rare malignancy that comprises less than 0.5% of all gastrointestinal malignancies (1). This disease is classified into five histological subtypes: colonic-type adenocarcinoma, mucinous type (MAA), signet ring cell type, goblet cell carcinoid, and malignant carcinoid. The 5-year disease-specific survival rate depends on the histologic subtypes, ranging from 93% for carcinoid to 27%

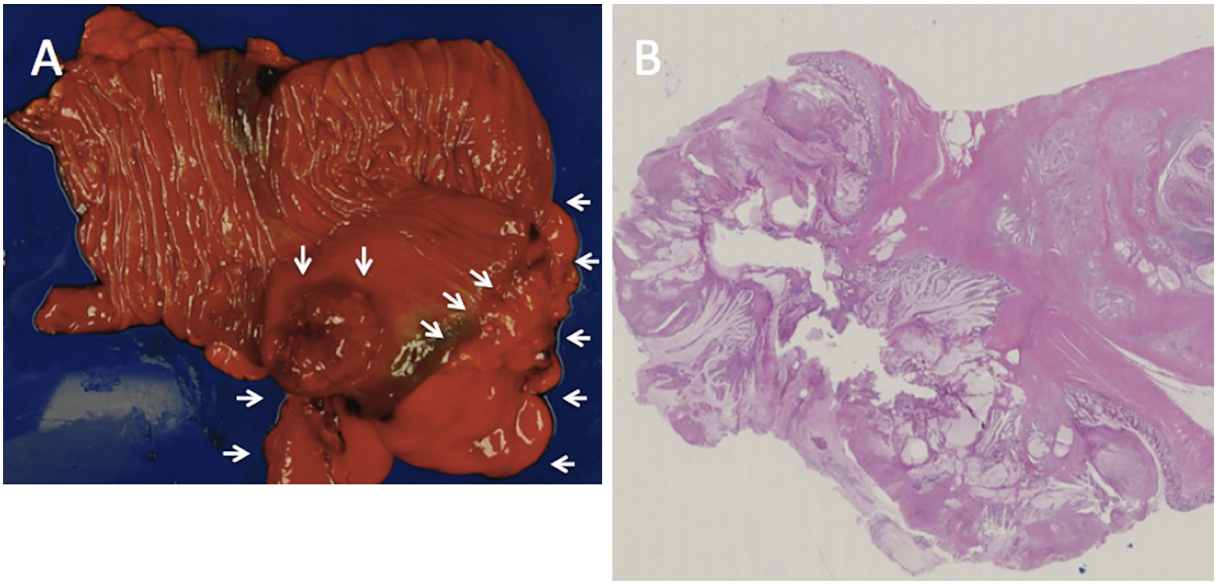

Figure 5. **A: Macroscopically, the appendiceal tumor had invaded the hepatic flexure with fistula formation (arrows). B: Histological findings showed a well-differentiated mucinous adenocarcinoma (Hematoxylin and Eosin staining; magnification, ×20).**

for signet ring cell type (3). Although the tumor itself is well-differentiated and not typically aggressive, the disease-specific survival rate of MAA is only 58%. This unfavorable outcome can be explained by the potential for mucocele rupture as well as a delayed or inaccurate diagnosis as a result of nonspecific symptoms (4, 5).

A ruptured mucocele can result in the peritoneal spread of mucus material followed by mucinous ascites, known as PMP. Smeenk et al. reported that 20% of patients with appendiceal mucinous tumor (73% benign, 27% malignant) develop PMP (6). The most common symptoms included appendicitis-like events, increasing abdominal distention, and new onset hernia (9). The 3- and 5-year overall survival rates were 51% and 38%, respectively, for patients with PMP from MAA (10). This suggests that malignant ascites is associated with a worse prognosis than overall MAA. The treatment of patients with PMP depends on the resectability of the tumor. The recommended treatment for invasive MAA is right hemicolectomy with lymph node dissection for complete resection (11). Taken together, these data indicate that obtaining a diagnosis during the resectable stage of MAA is crucial to ensuring a good prognosis.

In the present case, the positive result of FOBT caused by the fistula formation led to further investigations, such as colonoscopy, BE, and CT. Thus, an early and accurate preoperative diagnosis was made before progression to PMP. Our search of a medical literature database showed that only 29 cases of MAA with fistula formation have been reported in the English literature. The clinical characteristics of these previous patients and our own are summarized in Table (7, 8, 12-36). The patients were 19 women and 11 men with a median age of 65.5 years (range, 38 to 90). The organs involved in the fistula were the bladder (n=16), skin (n=9), colon (n=4), vagina (n=2), and ileum (n=1). Chief complaints were associated with blood or mucus discharge from the involved organs in almost all of the patients. Appendiceal tumor was diagnosed in 14 (70%) of the 20 patients, while PMP was observed in only 3 (12.5%) of the 24 patients. Surgery was performed as primary treatment in all cases but two. The median follow-up period was 12 months (range, 3 days to 120 months), and follow-up information was available for all 24 cases. Twenty patients (83.3%) were alive at the end of the follow-up period; of them, only 1 had cancer recurrence. However, 4 patients (16.7%) died, but among them, 2 died of other diseases.

Our literature review suggests that, as in our case, the symptoms caused by the fistula led to a further investigation and an early accurate diagnosis, which resulted in the potential for curative resectability. PMP is less frequently observed than typical appendiceal mucinous tumors in patients with MAA with a fistula. Nakao et al. and Hakim et al. reported that fistula formation might improve the prognosis by preventing PMP (7, 8). Fistula formation secondary to MAA may confine the disease to a resectable state by causing drainage of the malignant ascites into the involved organs. The operability itself may explain the good outcome of MAA with fistula formation; indeed, surgery was performed in almost all of the reported cases. However, a publication bias cannot be excluded, so further studies are required to determine the influence of fistula formation on the prognosis of patients with MAA.

We herein report the case of a 90-year-old man with MAA with fistula to the hepatic flexure. Our case shows that fistula formation secondary to MAA may allow for the early diagnosis and resectability, which results in a better prognosis.

Table. **Summary of Cases of MAA with Fistula Formation.**

Reference	Age/ sex	Fistula location	Chief complaints	Presumed diagnosis	Therapy	PMP	Follow-up	Cause of death
12	82/F	Bladder	Hematuria, fecaluria	Large bowel tumor invading urinary bladder	Anterior pelvic exenteration	No	Alive (84Mo)	-
13	57/M	Skin	Weight loss, skin fistula in the old appendectomy scar	-	RHC, SE	-	Died (3days)	Acute cardiac failure
14	50/M	Bladder	Pyuria, dysuria	Appendiceal adenocarcinoma	Radical cystoprostatectomy, RHC, RT	-	Alive (24Mo)	-
15	58/M	Bladder	Pollakiuria, urinary urgency	Bladder cancer	RHC, PC, RT	-	-	-
16	82/F	Bladder	Urinary tract infections, lethargy, nausea, increasing obtundation	-	RHC, PC	No	-	-
17	85/F	Vagina	Vaginal discharge, rectal bleeding, constipation, urinary incontinence	MAA	ICR, partial vaginal resection	-	Alive (9Mo)	-
18	60/F	Skin	Mucinous discharge from a skin fistula in the old appendectomy scar	MAA	RT	No	Died (6Mo)	Gastric cancer
19	70/F	Bladder	Hematuria	-	PC, ICR, RT	-	Alive (120Mo)	-
19	67/F	Bladder	Hematuria	-	PC, RHC	-	Died (72Mo)	Appendiceal carcinoma
20	67/M	Bladder	Dysuria, pollakiuria	Appendiceal neoplasm	RHC, PC, AC	No	-	-
21	80/F	Bladder	Hematuria	-	RHC, PC	No	Alive (9Mo)	-
22	56/M	Skin	Right iliac fossa pain, pyrexia, leukocytosis	MAA	RT	Yes	Died (39Mo)	Appendiceal carcinoma
23	46/M	Skin	Skin ulcers	Scrofuloderma, tuberculosis, pseudomyxoma, malignant tumor of the ascending colon, cecum, appendix, or retroperitoneum	RHC	No	Recurrence (3Mo)	-
24	78/F	Bladder	Pollakiuria, micturition pain	Cecal or appendiceal tumor	RHC, PC	No	Alive (12Mo)	-
7	75/F	Skin	Skin ulcer with mucus discharge	Appendiceal carcinoma, colonic adenocarcinoma, ovarian adenocarcinoma	RHC, SE	No	Alive (84Mo)	-
25	60/F	Skin	Skin swelling	Myxoid variant of liposarcoma or desmoid tumor	RHC, SE	No	Alive (2Mo)	-
26	48/F	Vagina	Lower abdominal pain, vomiting, anorexia, pyrexia	Diverticulitis	Ap, rectosigmoid resection, oophorectomy	No	-	-
27	67/F	Bladder	Urinary tract infections, hematuria, pollakiuria, urinary urgency	Colonic cancer	RHC, PC	No	Alive (3Mo)	-
28	59/F	Ascending colon	Right lower quadrant abdominal pain	MAA	RHC	No	Alive (6Mo)	-
29	44/F	Bladder	Right lower quadrant abdominal pain, hematuria	MAA	RHC, PC, right salpingo-oophorectomy, AC	Yes	-	-
30	51/F	Skin	Skin ulcer with mucus discharge	-	Ap including a portion of the iliac bone, AC	No	Alive (36Mo)	-
31	38/M	Small bowel, sigmoid colon, bladder	Abdominal pain, rectal bleeding, hematuria	Crohn's disease, sigmoid malignancy small bowel malignancy or lymphoma	RHC, Sx, PC, AC	No	Alive (10Mo)	-
32	68/F	Skin	Skin swelling	Acute appendicitis, appendiceal carcinoma	RHC, SE, AC	No	-	-
33	64/F	Bladder	Abdominal discomfort, pollakiuria	-	RHC, PC, AC	No	Alive (2Mo)	-
34	68/M	Skin	Mucinous discharge from a skin fistula in the old appendectomy scar	-	RHC, SE, HIPEC	No	Alive (12Mo)	-
35	63/M	Bladder	Dysuria, mucusuria	Appendiceal pseudomyxoma	ICR, PC, electrovaporization of gelatinous nodules, HIPEC	Yes	Alive (15Mo)	-
36	45/F	Bladder	Pyuria, mucusuria	-	RHC, PC	No	Alive (60Mo)	-
36	78/F	Bladder	Mucusuria	Appendiceal carcinoma	RHC, PC	No	Alive (36Mo)	-
8	68/M	Sigmoid colon	Right lower quadrant abdominal pain, tenderness, constipation	-	Ap, Sx, ICR, resection of right vas deferens, testicular vessels, anterior abdominal wall	No	Alive (12Mo)	-
Our case	90/M	Hepatic flexure	Positive fecal occult blood test	Appendiceal carcinoma	RHC	No	Alive (12Mo)	-

AC: adjuvant chemotherapy, Ap: appendectomy, F: female, HIPEC: hyperthermic intraperitoneal chemotherapy, ICR: ileocecal resection, M: male, MAA: mucinous appendiceal adenocarcinoma, Mo: months, PC: partial cystectomy, PMP: pseudomyxoma peritonei, RHC: right hemicolectomy, RT: radiotherapy, SE: skin excision, Sx: sigmoidectomy

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The authors state that they have no Conflict of Interest (COI).

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