〈投稿論文〉

Appendicular goblet cell carcinoid presenting as acute appendicitis: A case series and literature review

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ABSTRACT

Appendicular goblet cell carcinoid (GCC) is a rare tumor, and often presents as acute appendicitis. Herein, we report 3 patients presenting to our department with acute appendicitis, in whom postoperative histopathologic examination revealed appendicular GCC. Case 1 was a 40-year-old man who underwent appendectomy for acute appendicitis. Ileocecal resection was performed 42 days after the appendectomy because histopathological examination showed GCC. Case 2 was a 45-year-old woman who underwent appendectomy for acute appendicitis. Ileocecal resection was performed 88 days after the appendectomy because histopathological examination showed GCC and positive resection margin. Case 3 was a 73-year-old woman who underwent appendectomy for acute appendicitis with periappendicular abscess. Ileocecal resection was planned because histopathological examination showed GCC. Subsequently, she developed aortic dissection, and the additional resection was abandoned. All three patients are alive to date without recurrence. Moreover, we reviewed appendicular GCC case reports in Japanese literature. Our analysis of the reported cases shows that the prognosis of patients with GCC associated with acute appendicitis is better than those with GCC without acute appendicitis. In addition, the incidence of lymph node metastasis increases with deeper invasion.

Key words：Goblet cell carcinoid, appendicitis, staged operation

Abbreviations:GCC: goblet cell carcinoid、
CT: computed tomography

BACKGROUND

Appendicular goblet cell carcinoid (GCC) is a rare tumor with neuroendocrine and mucinous differentiation [1)], which can metastasize to the ovaries and peritoneum; therefore, has a poor prognosis with 5-year overall survival of 45-75% [2, 3)]. However, the clinical features and management of appendicular GCC have not yet been elucidated because of its rarity. Herein, we reported three cases with appendicular GCC associated with acute appendicitis, and reviewed 105 cases reported in Japanese literature.

CASE PRESENTATION

Case 1

A 40-year-old man was referred to our department due to right lower abdominal pain and fever. Blood analysis showed leukocytosis (11900/μL) and elevated CRP (2.3 mg/dL). Contrast enhanced CT showed well enhanced dilated appendix with periappendicular fat stranding (Fig. 1). An appendectomy was performed with a preoperative diagnosis of acute appendicitis. Macroscopic examination of the resected specimen showed thickened wall, reddish ulcerated mucosa, and a perforation (Fig. 2). Histopathological examination revealed goblet cells forming small duct structures together with inflammatory cells, extending through the appendicular wall, and lymphatic invasion (Fig. 3a,b). Immunohistologically, chromogranin A and synaptophysin were positive (Fig. 3c,d), confirming appendicular GCC. An ileocecal resection with regional lymph node dissection was performed 42 days after the appendectomy. There were neither residual tumor nor lymph node metastasis; pT3N0M0, pStage II,

according to the UICC/TNM classification [4]. Adjuvant chemotherapy was not administered. The patient was alive without recurrence 101 months after the appendectomy.

Case 2
A 45-year-old woman was referred to our department due to right lower abdominal pain. Blood analysis showed leukocytosis (14200/μL) and elevated CRP (12.2 mg/dL). Contrast enhanced CT showed well enhanced appendix with periappendicular fat stranding (Fig. 4). An appendectomy was performed. Macroscopic examination showed thickened wall, multiple erosions and ulcers over the entire appendix (Fig. 5). Histopathological examination revealed goblet cells forming small duct structures between the lamina propria and subserosa throughout the appendix (Fig. 6). Immunohistologically, chromogranin A and synaptophysin were positive. Because tumor cells were detected in the proximal margin, an ileocecal resection with lymph node dissection was performed 88 days after the appendectomy. Residual tumor was detected in the cecum without lymph node metastasis; pT3N0M0, pStage II. Adjuvant chemotherapy was not administered. She has been alive without recurrence 47 months after the appendectomy.

Case 3
A 73-year-old woman was referred to our department with right lower abdominal pain. She had undergone a total aortic arch replacement for aortic dissection 7 years ago. Blood test showed elevated CRP (11.7 mg/dL) and normal WBC (8800/μL). Contrast enhanced CT showed a ring-enhanced fluid collection in the right lower abdomen, in which the appendix was present with wall disruption (Fig. 7). An appendectomy was performed with a diagnosis of acute perforated appendicitis with an abscess. Macroscopic examination of the resected specimen showed a ruptured appendix with localized wall thickening (Fig. 8). Histopathological examination revealed infiltration of the submucosa to the subserosal layer with goblet cells (Fig. 9). Immunohistologically, chromogranin A and synaptophysin were positive. No tumor cell was detected in the proximal margin. An additional ileocecal resection was planned, however, aortic dissection recurred 3 weeks after the appendectomy, and the additional surgery was abandoned. She was alive without recurrence 12 months after the appendectomy.

DISCUSSION

Appendicular GCC was firstly reported as a mucin-producing subtype of carcinoid tumors of the appendix by Gagne et al. in 1969, and Subbuswamy et al. named it as "Goblet cell carcinoid"[5, 6]. The incidence of appendicular GCC was reported to be around 0.05% of appendectomies [1, 7]. In our department, the incidence of GCC was 0.18% among the 1611 cases with appendectomies between 1995-2016.

Pathologically, appendicular GCC is composed of goblet-shaped epithelial cells and few neuroendocrine cells, arranged in discrete round or oval clusters arising from the deep lamina propria [8, 9]. The tumor cells show synaptophysin and chromogranin A slight positivity, in contrast to diffuse positivity in carcinoid tumors [8, 10]. The 3 cases reported here showed these histopathological features.

Appendicular GCC is frequently diagnosed by pathological examination after the appendectomy performed for acute appendicitis. Pham et al. reviewed 57 cases with appendicular GCC over a period of 20 years in Mayo Clinic and reported that 70% of appendicular GCC presented clinically as acute appendicitis [3]. Similarly, Byrn et al. reported that 50% (8/16 cases) of appendicular GCC presented clinically as appendicitis [11]. Nash et al. reviewed 32 cases with appendicular cancer and 38 cases with appendicular GCC, and reported that the frequency of appendicitis in GCC was larger than that in cancer (87% vs. 53%)[12]. As described above, all our three cases presented as acute appendicitis. Roy P et al. hypothesized the underlying mechanism for developing appendicitis: the tumor extends diffusely through the appendicular wall causing fibrosis, resulting in luminal narrowing or reduced wall flexibility, with consequent poor luminal drainage [13].

Lee et al. reviewed 27 cases with appendicular GCC, which were classified into 3 types: typical GCC, signet ring cell adenocarcinoma ex GCC, and poorly differentiated adenocarcinoma ex GCC (11, 14, and 2 cases, respectively). They reported that 64% of the cases showed contrast enhancement in CT, and the diagnosis of appendicitis on CT usually correlates with typical GCC on pathology [14]. Their results were in line with our case series.

Our extensive research of Japanese literature(1981-2016) on appendicular GCC revealed 105 resected cases. These cases were classified into GCC associated with appendicitis (n = 68) and GCC without appendicitis (n = 37) (Table 1). The mean age of patients with GCC without appendicitis was higher than those with appendicitis. The invasion was deeper in GCC without appendicitis than in GCC with appendicitis. Frequencies of lymph node metastasis and distant metastasis in GCC with appendicitis were lower than those in GCC without appendicitis. The metastatic organs in GCC without appendicitis were the peritoneum (n = 20) and the ovary (n = 9). Fifty patients with appendicitis were alive (other 22 patients were unknown) at a median follow-up of 12 months (interquartile range (IQR): 9-26 months). In contrast, 8 patients without appendicitis were dead (other 15 patients were unknown) with a median follow-up of 15 months (IQR: 10-26 months). Although our literature analysis has publication bias, these results suggest that GCC can be early diagnosed by the presentation as acute appendicitis.

The treatment of appendicular GCC diagnosed after an appendectomy is still not agreed upon. Several authors reported that tumor size (≥2.0 cm), vessel invasion, and the presence of an adenocarcinoma component were indications for additional colectomy [15, 16]. We investigated the relationship between the depth of invasion and lymph node metastasis in 74 cases that underwent regional lymph node dissection in Japanese literature. The incidence of lymph node metastasis increased with deeper invasion (Table 2). Pham et al.

reported that TNM classification well reflected the prognosis of patients with appendicular GCC, and recommended appendectomy for patients with stage I (T1 and T2), and right hemicolectomy for those with stage II/III [3]. Based on the results of 74 cases reported in Japanese literatures, patients with appendicular GCC in whom the invasion is beyond the proper muscle layer should be considered for colectomy with regional lymph node dissection.

Conclusion

Appendicular GCC often presents as appendicitis and the prognosis seems to be better than those without appendicitis. An additional lymph node dissection should be considered for patients with tumor invasion beyond the proper muscle layer.

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Disclosure Statement

The authors declare no conflicts of interest associated with this manuscript.

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Figure 1. Computed tomography showing a swollen and well enhanced appendix (arrowheads) and periappendicular fat stranding. (a) axial image; and (b) sagittal image.

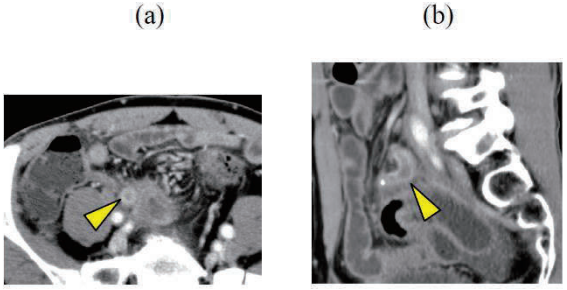

Figure 2. Macroscopic features of the resected specimen showing thickened wall, inflamed and ulcerated mucosa, and a perforation (arrowhead).

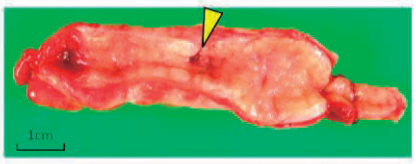

Figure 3. Light microgram showing small ducts with goblet cells and acidophil cells invading the full thickness of the appendicular wall, which were partly positive for chromogranin A and synaptophysin. (a) Hematoxylin and eosin (HE)×40; (b) HE×200; (c) chromogranin A staining ×100; and (d) synaptophysin staining ×100.

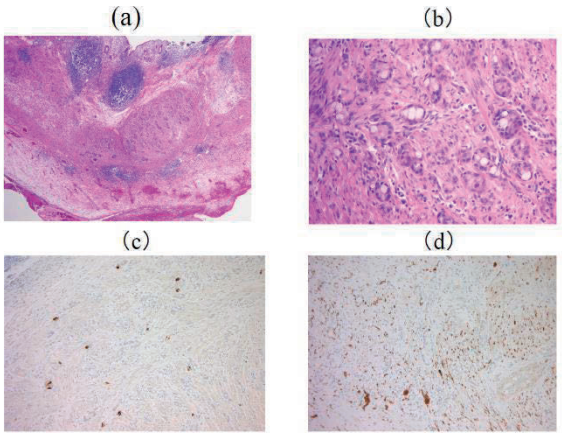

Figure 4. Computed tomography showing a swollen and well enhanced appendix (arrowheads) and periappendicular fat stranding. (a) axial image; and (b) coronal image

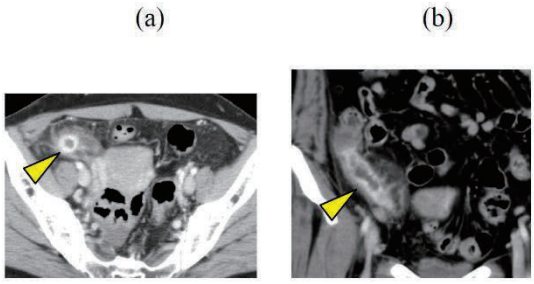

Figure 5. Macroscopic features of the resected specimen showing thickened wall, multiple erosions and ulcers over the entire appendix.

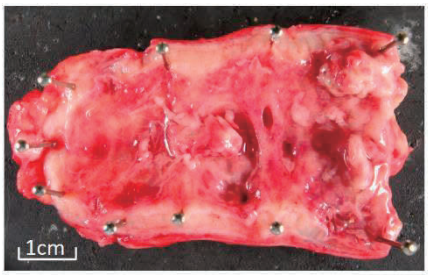

Figure 6. Light microgram showing small ducts with goblet cells and acidophil cells invading the full thickness of the appendicular wall. (a) loupe image (b) HE×40; (c) HE×200

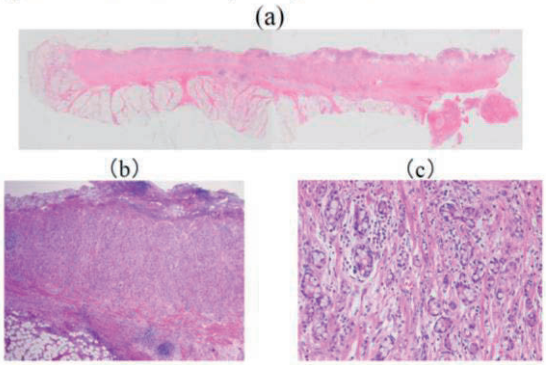

Figure 7. Computed tomography showing irregular tubular structure suggesting the appendix (arrowhead) in a ring-enhanced fluid collection in the right lower abdomen (arrow). (a) axial image; and (b) coronal image.

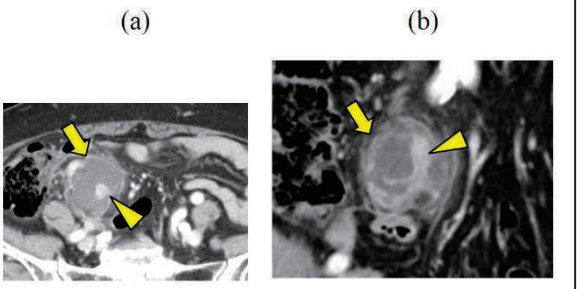

Figure 8. Macroscopic features of the resected specimen showing localized wall thickening (bracket) and a defect (arrowhead) of the appendix.

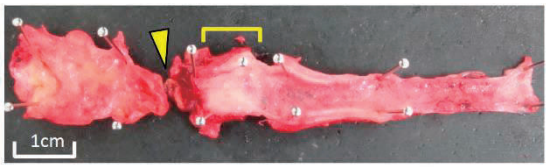

Figure 9. Light microgram showing small ducts with goblet cells and acidophil cells invading the full thickness of the appendicular wall. (a) HE×40; (b) HE×200

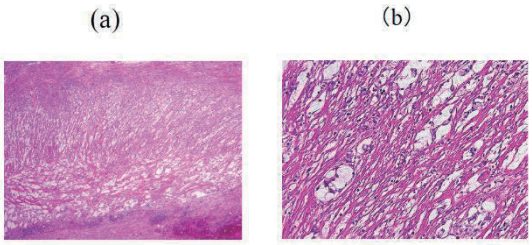

Table 1. Clinicopathological features of goblet cell carcinoid(GCC) with or without appendicitis in Japanese literature

		GCC with appendicitis (n=68)		GCC without appendicitis (n=37)		p value
Age mean±SD (range)		56.3±13.0 (26-80)		61.4±14.0 (30-90)		0.0700 *1
Sex	Male	43	(63%)	18	(49%)	0.1554 *2
	Female	25	(37%)	19	(51%)	
Depth of invasion	T1	2	(3%)	1	(3%)	
	T2	9	(13%)	4	(11%)	
	T3	44	(65%)	10	(27%)	**0.0008** *2
	T4	8	(12%)	16	(43%)	
	Unknown	5	(7%)	6	(16%)	
Lymph node metastasis	+	7	(10%)	14	(38%)	
	-	48	(71%)	7	(19%)	**<0.0001** *2
	Unknown	13	(19%)	16	(43%)	
Distant metastasis	+	1	(1%)	21	(57%)	
	-	65	(96%)	12	(32%)	**<0.0001** *2
	Unknown	2	(3%)	4	(11%)	

*1: Student t-test, *2: chi-square test

Table 2. Relationship between depth of invasion and lymph node metastasis in 74 cases with lymph node dissection for appendiceal GCC in Japanese literature

Depth of invasion	Lymph node metastasis	
	+	-
T1	0 (0%)	3 (100%)
T2	0 (0%)	10 (100%)
T3	8 (19%)	35 (81%)
T4	12 (67%)	6 (33%)