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CASE REPORT

Advanced appendiceal goblet cell carcinoids with intestinal obstruction: two case reports

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Abstract

A goblet cell carcinoid is quite rare and has features, wherein, a carcinoid-like image and an adenocarcinoma-like image coexist. We encountered two cases of rare goblet cell carcinoid originating in the appendix. Case 1 is that of a 48-year-old man with a chief complaint of abdominal distension and case 2 is that of a 64-year-old woman with a chief complaint of constipation. At the time of diagnosis, both cases had already metastasized to the peritoneum and other organs, and no radical surgical treatment could be administered in either case. Chemotherapies were performed according to the regimen for colon cancer, and they were effective to a certain extent. During the course of treatment, however, both cases developed intestinal obstruction, presumably due to peritoneal dissemination, which led to worse condition and death several months afterwards. Chemotherapy for goblet cell carcinoids has not yet reached a consensus, and further studies and establishment of therapeutic strategy are desired in the future.

Keywords Appendiceal tumour · Goblet cell carcinoid · Intestinal obstruction

Abbreviations

FOLFIRI	5-Fluorouracil/leucovorin/irinotecan
FOLFOX	5-Fluorouracil/leucovorin/oxaliplatin
GCC	Goblet cell carcinoid
MiNEN	Mixed neuroendocrine-non-neuroendocrine neoplasms
PD	Progressive disease
PR	Partial response
SD	Stable disease

Introduction

Primary appendiceal cancer is extremely rare with less than 1% of all gastrointestinal malignancies. Neoplasms of the appendix are capable of developing into cancers with morphological diversity, which are classified into several groups, such as epithelial neoplasms and neuroendocrine neoplasms. The former include invasive adenocarcinomas; low-grade appendiceal mucinous neoplasm and high-grade appendiceal mucinous neoplasm. The latter include well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) [1, 2]. Among them, goblet cell carcinoid (GCC) is classified as MiNEN and is uncommon in the primary cancers of the appendix [2, 3]. Although there are no clinical trials or guidelines of treatment for advanced stage of GCC because of the rarity, chemotherapies based on the regimen for colorectal cancer is recommended and used in clinical practice [4].

We report two cases of appendiceal GCC with intestinal obstruction, inoperable due to the accompanying peritoneal dissemination.

Case presentation

Case 1 is that of a 48-year-old man who had visited our hospital with a chief complaint of abdominal distension since two months ago. Abdominal and pelvic CT examination showed wall thickening of the ascending colon from the cecum, elevated density of peripheral fat, ascites fluid retention, and diffuse nodules in the peritoneum (Fig. 1). The

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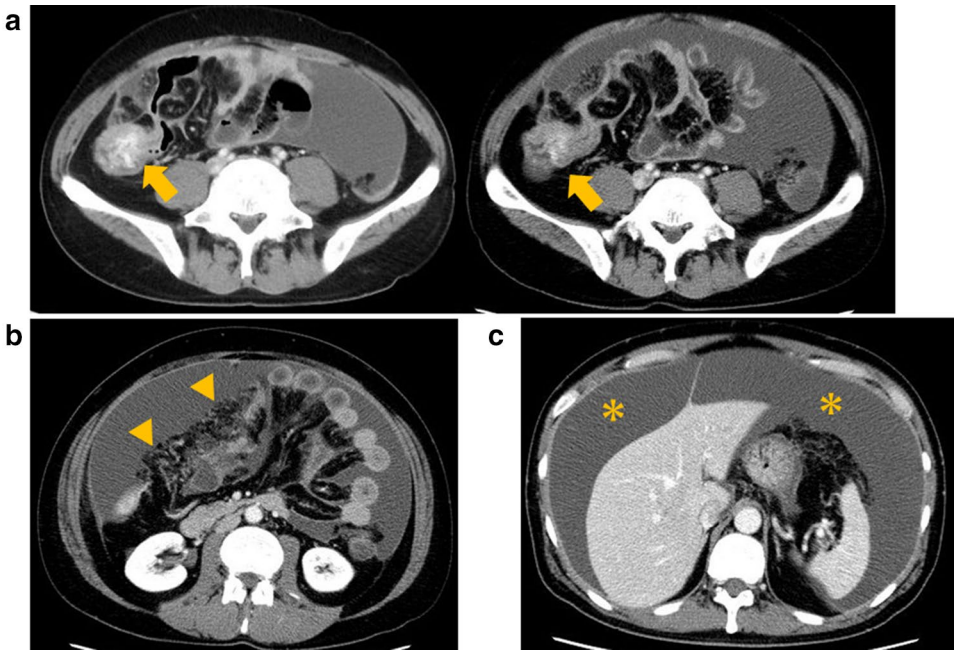

Fig. 1 Images of CT examination before the start of treatment (Case 1). **a** There was intestinal wall thickening with a contrast effect of about 2/3 around the ileocecal region (yellow arrow). In addition, **b** diffuse nodules in the peritoneum (yellow arrowhead) and **c** ascites fluid retention (yellow asterisk) were noted

presence of colorectal malignancies in the ileocecal region and associated peritoneal dissemination were suspected. Lower gastrointestinal endoscopy revealed an ulcerative type tumour in the ileocecal region. Due to the tumour, the intestinal lumen in the same area was narrowed, and passage of the scope was difficult. Therefore, the complete picture of the cecal wall, the appendix hole, and the Bauhin's valve could not be confirmed (Fig. 2). The tissue biopsy revealed that tumour cells had a signet ring appearance and were positive for several immunohistochemical markers for GCC (Fig. 3).

Due to peritoneal dissemination, it was adjudged that there was no indication for surgical treatment, and chemotherapy was to be performed. Although there are no clinical trials or guidelines of treatment for advanced stage of GCC, chemotherapies based on the regimen for colorectal cancer, including 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX) and 5-fluorouracil/leucovorin/irinotecan (FOLFIRI), have been recommended and used in clinical practice [4, 5]. In addition, other than FOLFOX/FOLFIRI, various types of treatment have been used and reported in scientific journals and case reports, including capecitabine, cisplatin, S-1, and anti-vascular endothelial growth factor (VEGF) therapy [6–9]. Moreover, it was suggested that anti-epidermal growth factor receptor (EGFR) directed therapy regimens might be eligible for GCC without KRAS mutations [10]. Since this tumour had wild-type KRAS, we decided to use FOLFOX therapy co-administered with panitumumab according to the chemotherapy for colon cancer. Developing peripheral neuropathy after 8 courses of FOLFOX therapy with panitumumab, the regimen was changed to FOLFIRI therapy with panitumumab. The side effect of peripheral nerve disorder appeared to be caused by oxaliplatin and the effect of the first-line chemotherapy was evaluated as

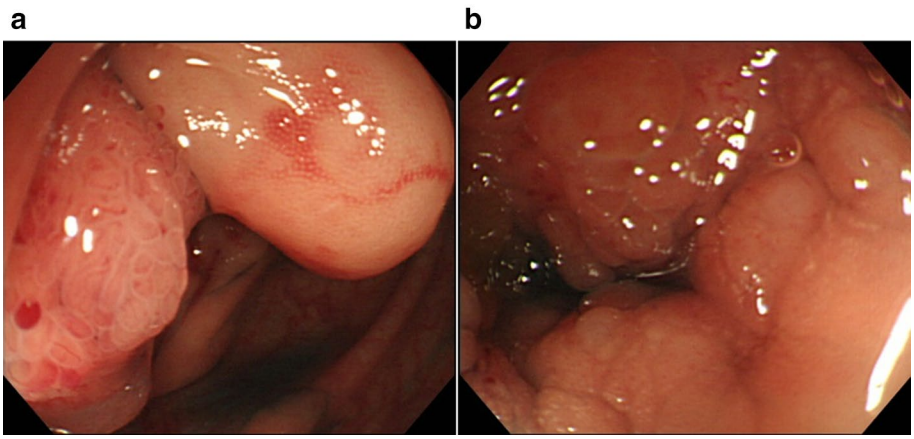

Fig. 2 Images of lower gastrointestinal endoscopy (Case 1). **a** An ulcerative type tumour with an ambiguous borderline and irregular margin was found at the ileocecal region. **b** Due to the tumour, the intestinal lumen was narrowed

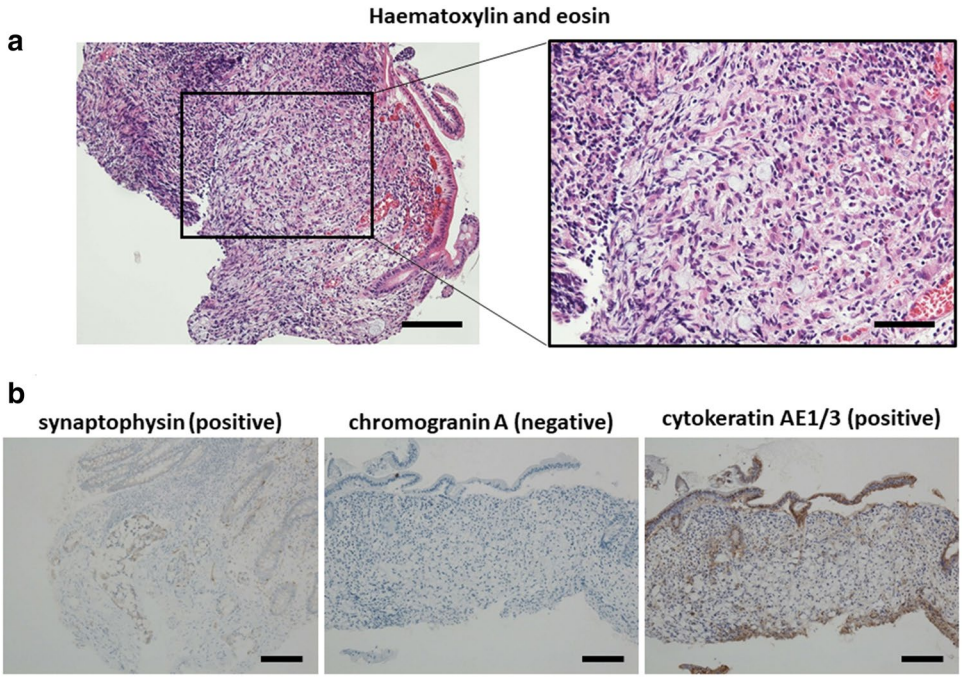

Fig. 3 Pathological evaluation of tumour biopsy specimens (Case 1). **a** In haematoxylin and eosin staining, the tumour cells had mucus vacuoles and a ubiquitous distribution of nuclei and exhibited a honeycomb-like structure. Scale bars, left 200 µm and right 500 µm. **b** Positive immunostaining for synaptophysin and cytokeratin AE 1/3 on the biopsy tissue of ileocecal tumour. Scale bars, 200 µm

stable disease (SD), therefore, panitumumab was continuously used with FOLFIRI treatment. After the first course of FOLFIRI therapy with panitumumab, the abdominal and pelvic CT examination showed that the primary tumour site could be classified as a partial response (PR) to SD, and ascites had almost disappeared (Fig. 4). However, 5 months after the initiation of chemotherapy, the patient developed small intestinal ileus. The treatment for the obstruction was started with ileus tube placement and continuous subcutaneous injection of octreotide acetate, after which, the condition became relatively stable. Three months later (8 months after diagnosis), he had pneumonia that was thought to be due to aspiration. The patient was poorly responsive to treatment with antibiotics, and finally died of respiratory failure.

Case 2 is that of a 64-year-old woman who had visited our hospital with a chief complaint of constipation since two months ago. Her abdomen was soft, but there was a palpable mass in right lower abdomen. Thoraco-abdominal and pelvic CT examination revealed ileocecal tumour, ovarian tumour, multiple lymph node enlargement of the mesentery, ascites fluid retention, and diffuse nodules in the lung (Fig. 5). The presence of colorectal malignancies in the ileocecal region and associated peritoneal dissemination, together with lung metastasis was suspected. Lower gastrointestinal endoscopy revealed an ulcerative type tumour in the ileocecal region. Similar to Case 1, the lumen narrowed (Fig. 6), and biopsy from the tumour revealed large irregular cluster formation by goblet cells or signet ring cells with several immunohistochemical markers for GCC, including synaptophysin and CD56 (Fig. 7). The ileocecal main lesion were negative on immunohistochemical staining for CA125, progesterone receptor, and oestrogen receptor, therefore, the association with primary ovarian tumour was contradictory.

We decided to use FOLFIRI therapy according to the chemotherapy for colon cancer, and the treatment could be continued without major side effects. After 17 courses of FOLFIRI therapy, however, thoraco-abdominal and pelvic CT examination displayed that the primary tumour site and metastatic ovarian tumour could be classified as progressive disease (PD). For the reasons, the regimen was changed to FOLFOX therapy. After 4 courses of FOLFOX therapy, CT examination showed that the primary tumour site and metastatic ovarian tumour could be classified as SD (Fig. 8). Thirteen months after the initiation of chemotherapy, the patient developed small intestinal ileus due to peritoneal dissemination. The treatment was started with ileus tube placement, but it was not effective. Although surgical treatment was tried, peritoneal dissemination occurred frequently, and bypass surgery was not feasible. Therefore, we decided to construct an artificial anus in the small intestine. Thereafter, the treatment policy was changed to best supportive care. After stable condition for about three months, the patient died of the underlying disease 18 months after diagnosis of GCC.

In case 2, intestinal obstruction was not apparent at diagnosis, but due to peritoneal dissemination, intestinal stricture was predicted in subsequent clinical course. Accordingly, FOLFOX was determined to use as the second-line therapy for the time when the disease showed no response to FOLFIRI treatment. Therefore, FOLFIRI was chosen as the first-line chemotherapy.

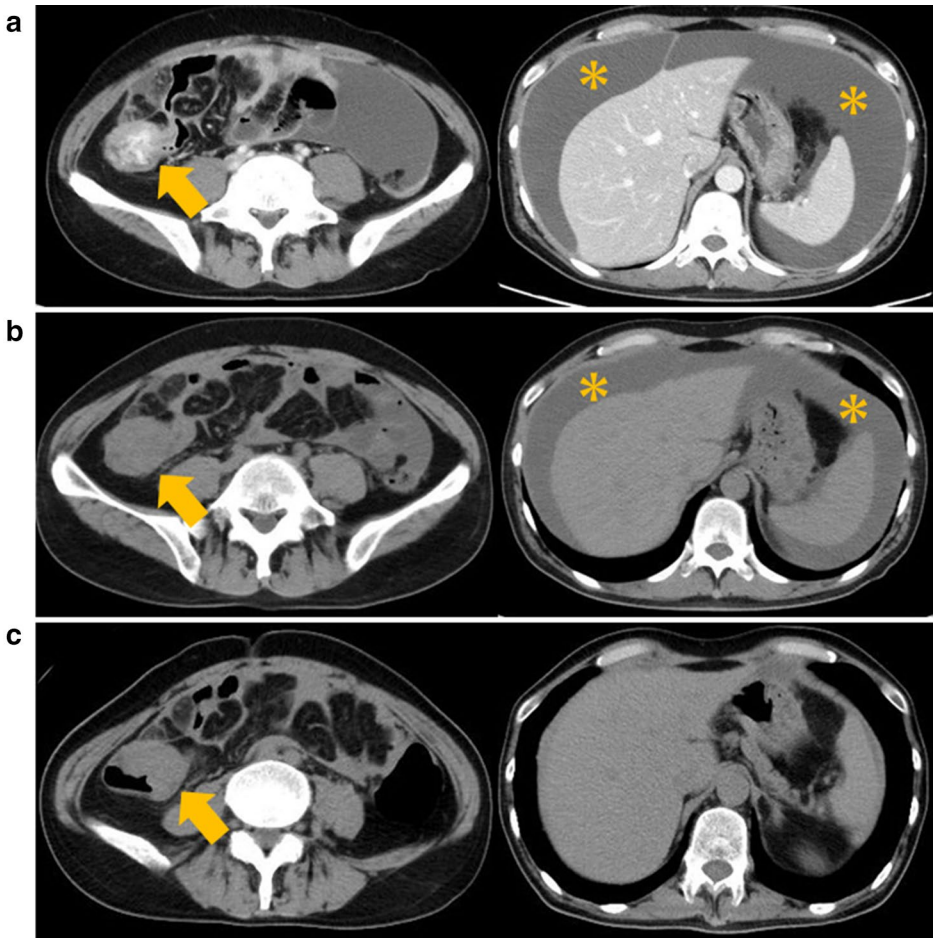

Fig. 4 The images of CT examination after chemotherapy (Case 1). CT images of the primary tumour site (yellow arrow) and ascites fluid (yellow asterisk) **a** before start of treatment, **b** after 6 courses of FOLFOX/panitumumab therapy, and **c** after 8 courses of FOLFOX/panitumumab therapy and 1 course of FOLFIRI/panitumumab therapy

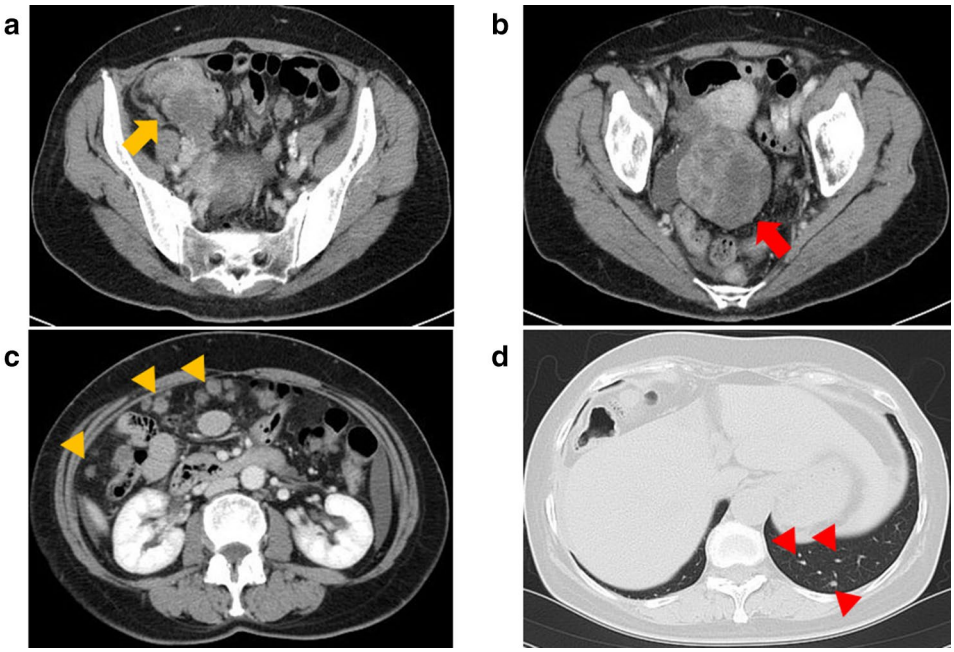

Fig. 5 Images of CT examination before the start of treatment (Case 2). **a** There were intestinal wall thickening with a contrast effect of the ileocecal region (yellow arrow). In addition, **b** ovarian tumour (red arrow), **c** multiple lymph node enlargement of the mesentery (yellow arrowhead), and **d** diffuse nodules in the lung (red arrowhead) were noted

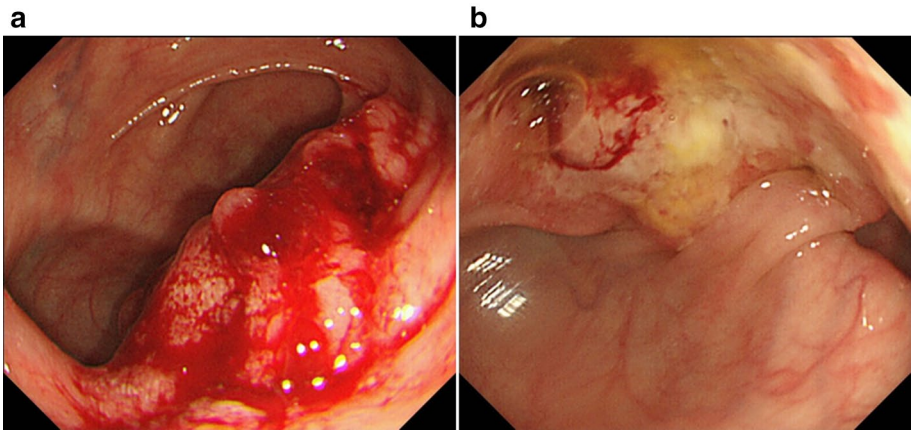

Fig. 6 Images of lower gastrointestinal endoscopy (Case 2). **a** An ulcerative type haemorrhagic tumour with an unclear borderline and irregular margin was found at the ileocecal region. **b** Due to the tumour, the intestinal lumen was narrowed

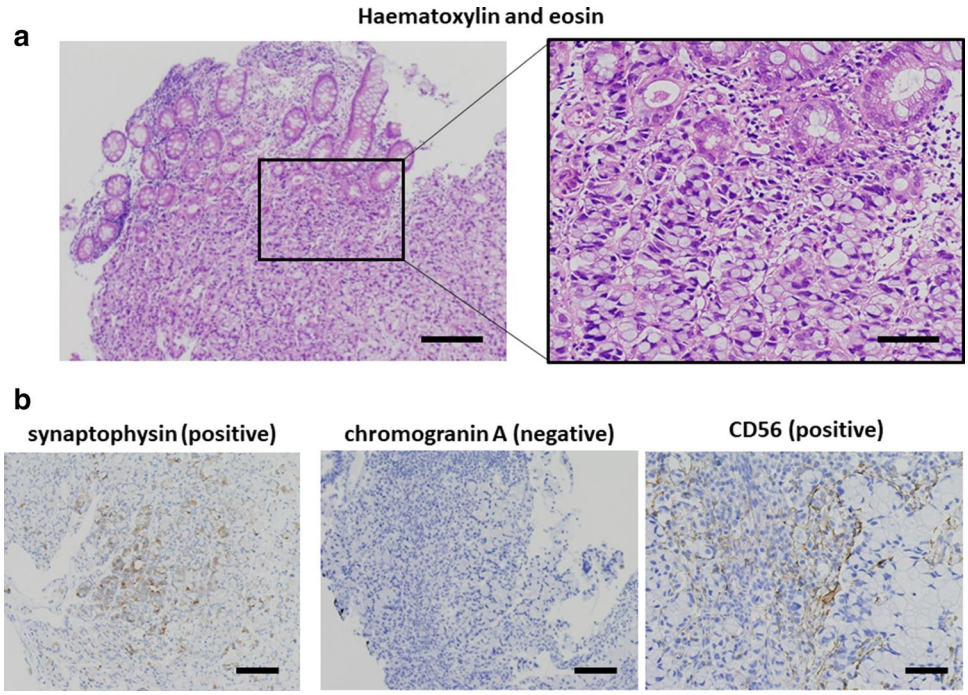

Fig. 7 Pathological evaluation of tumour biopsy specimens (Case 2). **a** In haematoxylin and eosin staining, the tumour cells had mucus vacuoles and a ubiquitous distribution of nuclei, and exhibited a honeycomb-like structure. Scale bars, left 200 µm and right 500 µm. **b** Positive immunostaining for synaptophysin and CD56 on the biopsy tissue of ileocecal tumour. Scale bars, left and middle 200 µm, right 500 µm

Discussion

GCC was first described as a special type of tumour in 1969 [11]. It is able to produce mucus and has both carcinoid-like and adenocarcinoma-like histopathological features, and later in 1974, was defined as GCC [12]. The tumour has been known by various names, including adenocarcinoid, mucinous carcinoid, crypt cell carcinoid, goblet cell adenocarcinoma, mixed carcinoid-adenocarcinoma, and mixed adenoneuroendocrine carcinoma [1, 13–15]. GCCs have been subclassified in several different ways. In the past, the Tang classification was often used. Tang et al. classified GCC and mixed GCC-adenocarcinoma into three groups based on histologic features; group A (typical GCC), group B (adenocarcinoma ex GCC, signet ring cell type), and group C (adenocarcinoma ex GCC, poorly differentiated type) [16]. Later, several researchers reported other methods for stratification of GCC according to the ratio of adenocarcinoma components, cytologic atypia, stromal desmoplasia, and solid growth pattern [17, 18]. It is, however, regarded that histologic judgement is still challenging to pathologists and a certain degree of subjectivity seems unavoidable [18]. In addition, although GCC belongs to neuroendocrine neoplasms [2], the WHO classification appears unclear whether adenocarcinomas ex-goblet cell carcinoids, which are goblet cell carcinoids of Tang B and C, can be considered as MiNEN [2, 19]. Indeed, recent papers still refer to the report by Tang et al. to evaluate GCCs instead of other classifications above [3, 8, 20].

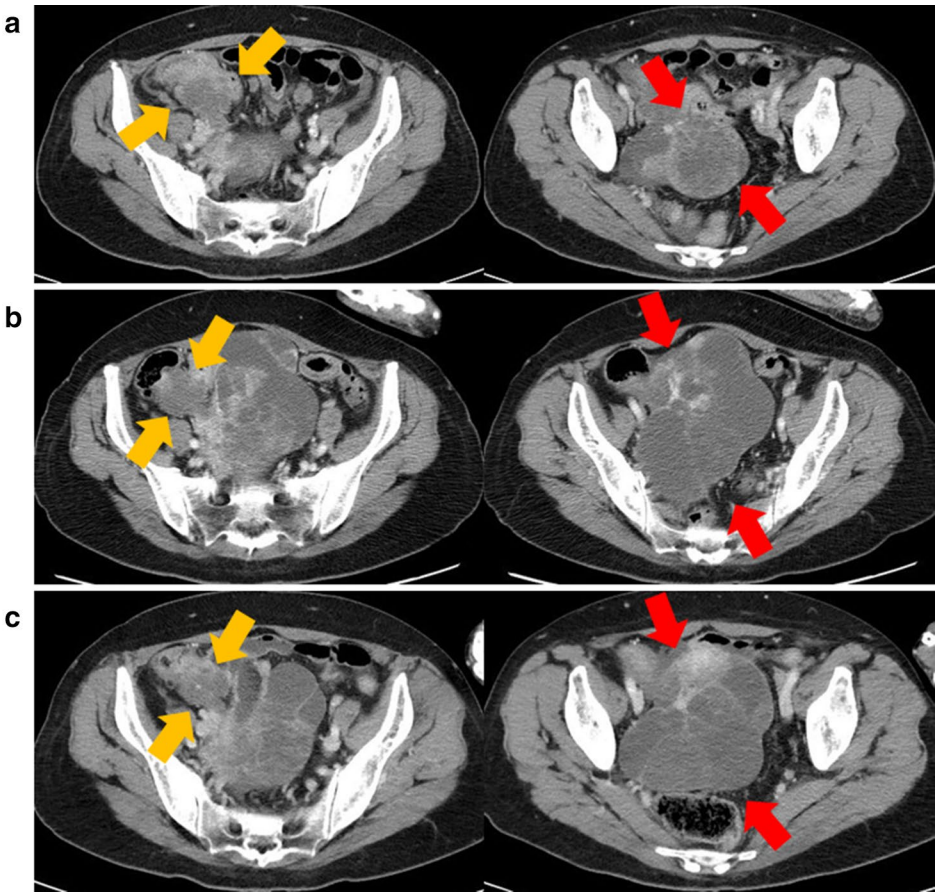

Fig. 8 Images of CT examination after chemotherapy (Case 2). CT images of the primary tumour site (yellow arrow) and metastatic ovarian tumour (red arrow) **a** before start of the treatment, **b** after 17 courses of FOLFIRI therapy, and **c** after 17 courses of FOLFIRI therapy and 4 courses of FOLFOX therapy

Appendiceal GCC is quite rare accounting for 5% of all primary tumours of the appendix [3]. The most typical clinical symptom by appendiceal GCC is acute appendicitis, which has been reported in about 40–50% of the cases [21, 22]. Other non-specific and rare symptoms are intestinal obstruction, gastrointestinal bleeding, lower abdominal pain, and iron deficiency anemia due to cecal ulcer [22, 23]. CT examination often shows swelling of the appendix and intestinal wall thickening of the ileocecal region. In lower gastrointestinal endoscopic examination, at the opening of the appendix, an ambiguous borderline tumour, greyish-white intestinal wall thickening, and an extension or deformation of the ileocecal region are observed. The ovaries and the peritoneum of the pelvis and peritoneal cavity are common sites of metastasis [24]. Histological findings exhibited that mucous producing goblet cells or signet ring-like cells with little nuclear atypia proliferate in alveolar, acinar and cord-like form. The cells also infiltrate into the submucosal layer beyond the mucosal plate with positive immunostaining for neuro-endocrine markers, including chromogranin A, synaptophysin, and CD56 [3].

Although the diagnoses of two cases were established by biopsy alone and it is not usually possible to evaluate and grade tumours accurately and confidently from biopsy specimens, both cases in the present report might be classified in Tang group C as well as high-grade by Lee stratification [18, 25]. According to the Tang classification, the 3-year disease-specific survival rates and the mean survival time were 100% and close to 10 years for group A, 85% and 43 ± 6 months for group B, and 17% and 31 ± 6 months for group C, respectively. Lee stratification also indicated that prognosis in patients with low-grade and high-grade histology showed median survivals of 51 months and 16.5 months, respectively. Since the present cases were considered as advanced stage with metastases or invasions at diagnosis, it was predicted that the prognoses of the two cases were poorer than those in the reports above. Indeed, the clinical course of case 1 was bad with dying 8 months after diagnosis.

The chemotherapies, however, appeared to have a certain therapeutic efficacy. In case 1, eight courses of FOLFOX/panitumumab and one course of FOLFORI/panitumumab therapies markedly reduced ascites, while more than 20 times of FOLFIRI or FOLFOX therapies could delay the progression of the disease in case 2. At present, a specific chemotherapy regimen for GCC has not been established, so a 5-fluorouracil-based chemotherapy regimen for colon cancer, mainly FOLFOX or FOLFIRI, has been used [5,

8]. In addition to FOLFOX/FOLFIRI, treatment effects of anti-VEGF and anti-EGFR have been suggested as described above [9, 10]. In case 1, panitumumab was used and the agent was thought to have a degree of anti-tumour action. The anti-VEGF agent bevacizumab was also considered in both cases. The therapy, however, was not employed, since gastrointestinal perforation was reported as a severe adverse event of anti-VEGF treatment and the risk factors include bowel obstruction, recent history of colonoscopy, and carcinomatous peritonitis [26, 27]. Recent papers also indicated that cytoreductive surgery and hyperthermic intraperitoneal chemotherapy exhibit anti-tumour effects and can be thought as optimal treatments for peritoneal involvement of the disease [28, 29]. Therefore, better prognosis may be expected with a combination of those therapies even in advanced stage of the disease. Since GCC is recognized histologically heterogeneous [3], further studies may be able to develop appropriate treatments by accurate evaluation of histological type and tumour grading.

In conclusion, we encountered two very rare cases of appendiceal GCC with poor prognosis. Both patients developed intestinal obstruction due to peritoneal dissemination and their quality of life significantly deteriorated. Careful histologic assessment can be considered critically important for predicting prognosis and guiding the clinical management. Further investigations are desired to establish more effective therapeutic strategy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights All human studies have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its subsequent amendments.

Informed consent Informed consent was obtained from the patients' relatives for being included in this report.

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