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Case report

Goblet cell carcinoid of the appendix endoscopically diagnosed and examined with *p53* immunostaining

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Abstract: We report a case of a 62-year-old woman with goblet cell carcinoid of the appendix. She was admitted to our hospital in September 1994 after the discovery of liver tumors. After admission, a tumor in the right kidney and multiple tumors in the liver were found. She was diagnosed with renal cell cancer and metastasis to the liver and underwent excision of the kidney and enucleation of the largest liver tumor. Histological examination revealed that the liver tumor was a metastatic carcinoid tumor. As carcinoid tumors have frequently been found in the appendix, endoscopic examination was performed and a lesion was found in the appendix by colonoscopy. As predicted, the biopsy specimen was a carcinoid tumor, and she underwent an appendectomy. Histologically, the tumor was a goblet cell carcinoid. Goblet cell carcinoid is a rather rare neoplasm that has the histologic features of both carcinoids and adenocarcinoma. Forty-two cases of goblet cell carcinoid of the appendix have been reported thus far in Japan. However, few were diagnosed via endoscopic examination before surgical operation. We also carried out an immunohistochemical study with anti *p53* antibody on the goblet cell carcinoid tumor of the appendix. Most tumor cells were strongly positive, while in three benign carcinoid tumors investigated simultaneously they were negative. These findings suggest that goblet cell carcinoid has an aggressive phenotype compared with benign carcinoid tumors.

Key words: goblet cell carcinoid, *p53*-immuno staining

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Introduction

Tumors of the appendix are relatively rare neoplasms in the gastrointestinal tract. Among appendiceal tumors, carcinoids are most common. The incidence is approximately 1 in every 300 appendectomies.[1]

Appendiceal carcinoids are divided into three distinct histological patterns according to the World Health Organization (WHO) classification: typical argentaffin carcinoid, non-argentaffin carcinoid, and the more recently described mucinous, goblet cell carcinoid or adenocarcinoid. The first two variants are reported to be benign and are effectively treated by appendectomy.[1] The third variety is far more rare and behaves in a different clinical fashion. As the nomenclature implies, goblet cell carcinoid tumors possess morphologic features suggestive of both carcinoid and glandular differentiation. They have a more aggressive natural history than classic appendiceal carcinoids, and their clinical management is not sufficiently defined.[1]

In a search of the Japanese literature, we found 43 reports of appendiceal goblet cell carcinoids in Japan, including our case, up to 1996.[2] Few cases were diagnosed endoscopically before surgery.

We also investigated the *p53*-immuno staining to indicate the malignant potential of the tumor.

Case report

A 62-year-old woman was admitted in September 1994 after a liver tumor was discovered in July of the same year during a routine examination. On admission, she had no particular complaints. Physical examination revealed no abnormalities. Laboratory data showed normocytic anemia (Hb, 9.4 g/dl), mild hypoproteinemia (albumin, 3.5 g/dl), and slight elevation of C-reactive protein (CRP). Her past medical history included; pulmonary abscess at age 3 years and

subdiaphragmatic abscess at age 17 years, with splanchnectopia.

After admission, a tumor in the right kidney and liver tumors were found. Abdominal computed tomography (CT) revealed low-density areas in S2, S4, S5 and S6 of the liver, and they were enhanced with contrast medium (Fig. 1a,b). The masses were hypoechoic on ultrasonographic examination of the abdomen (Fig. 1c). Angiography of the superior mesenteric artery demonstrated two tumor stains at the peripheral end of the right hepatic artery. Angiography of the right kidney disclosed a circular tumor in its dorsal part. We diagnosed the liver masses as metastatic tumors from the right kidney, because the staining patterns of the renal and hepatic tumors were similar.

In November 1994, she underwent excision of the right kidney and enucleation of the liver tumor in S6 (first operation). The histological findings of the renal and hepatic tumors were different; the renal tumor was a typical "clear-cell type" renal cell carcinoma. The liver tumor was diagnosed as metastatic liver carcinoid with small uniform cuboidal cells, growing in a ribbon-shape. These findings prompted us to look for the origin of the metastatic liver carcinoid.

It is widely accepted that most gastrointestinal carcinoid tumors are found in the appendix. Although we performed a barium enema study, no significant result was obtained because of unclear visualization of the appendix. Colonoscopic examination revealed that the orifice of the appendix was swollen, as if a submucosal tumor existed, and closer observation showed tumor vegetation, with surface redness (Fig. 2). A biopsy specimen revealed a carcinoid tumor. With the diagnosis that the appendiceal tumor was the primary lesion of the metastatic liver carcinoid tumors, we attempted resection of the primary appendiceal tumor. However, several other metastatic lesions were found in the peritoneum, and as a result, only resection of the appendix was possible. After this second operation, the metastatic liver tumors were successfully treated by chemoembolization.

The resected appendix was about 3.5 cm in length. The wall was diffusely thickened along the full length. The wall thickness was approximately 5–7 mm. The surface of the mucosa was smooth, but with some erosions (Fig. 3).

Hematoxylin and eosin staining revealed infiltration of the appendiceal tumor cells through the mucosal layer to the serosa (Fig. 4a). The tumor consisted of small ovoid cells with nuclei of uniform size and shape. Ribbon-like arrangements were seen in some parts of the tumor with some chromogranin A-positive cells in these parts of the tumor (Fig. 4b). Grimelius staining was performed and there were a few positive cells in the tumor. Many goblet cell-like cells which infiltrated the nerve showed positive periodic acid-Schiff (PAS)-Alcian blue staining (Fig. 4c,d).

Prominent venous and lymphatic infiltration was observed. The histochemical studies strongly suggested the resected tumor was a goblet cell carcinoid, while

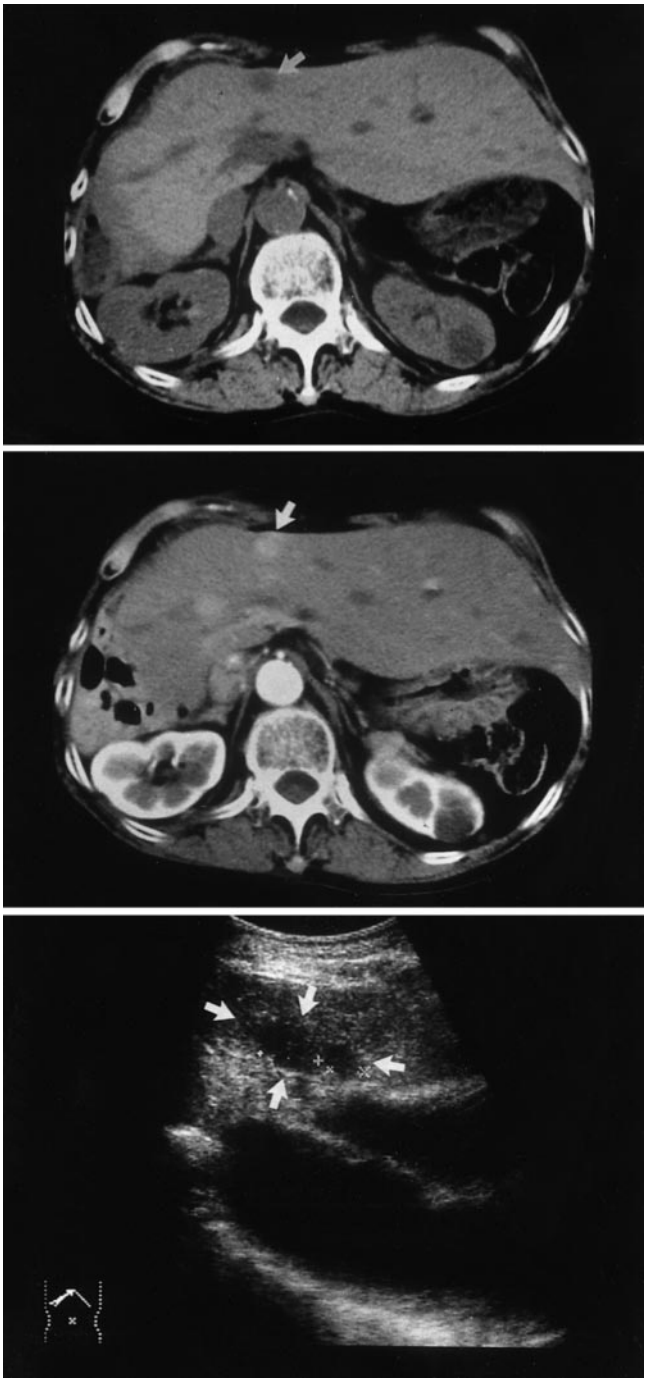

Fig. 1a,b. Abdominal computed tomography (CT) images showing a low-density area in S4 of the liver (*arrow*) enhanced with contrast medium; **c** Ultrasound sonogram of the liver, showing a hypoechoic mass (*arrows*) in S4

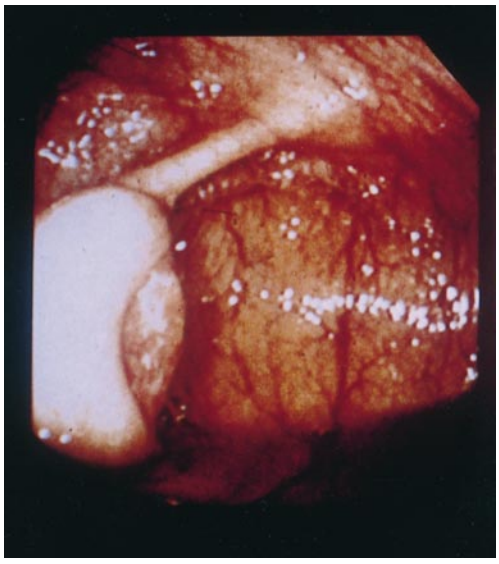

Fig. 2. Endoscopic appearance of the orifice of the appendix

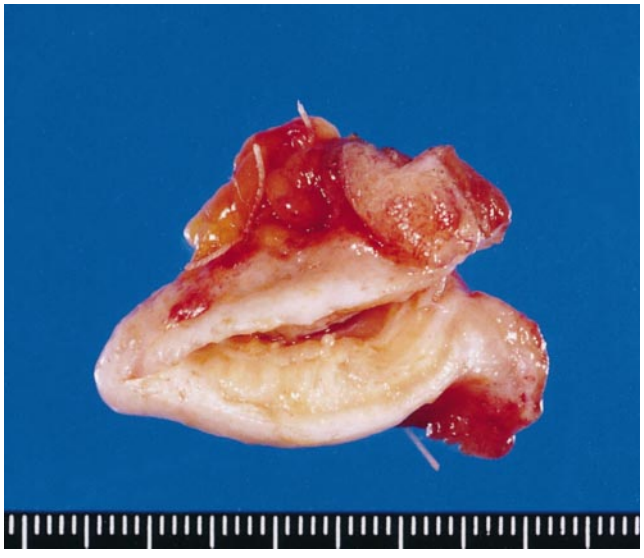

Fig. 3. Resected appendix

the metastatic liver tumor showed a typical carcinoid pattern without goblet cells.

To indicate the malignant potential of the tumor, we also investigated immunohistochemical detection of the *p53* protein. Immunostaining of *p53* protein was performed with a monoclonal antibody, DO-7 (Dako) which recognizes both mutant and wild type *p53* proteins. The antigen retrieval procedure was performed by boiling in 10 mM citrate buffer. Most of the tumor cells in specimens of both the primary and metastatic lesions were strongly positive, while three control benign carcinoid tumors (stomach, duodenum, and rectum) were negative for *p53* immunostaining (Fig. 5).

Discussion

In 1969 Gagne et al.[5] first noted extremely uncommon neoplasms arising in the appendix that had both classical carcinoid-like and adenocarcinoma-like features. Subbuswamy et al.[6] described 12 similar cases and named them goblet cell carcinoids. Various names have since been given to this tumor; "mucinous carcinoid,"[7] "signet-ring cell (microglandular) adenocarcinoma,"[8] "adenocarcinoid,"[9] crypt cell carcinoma,"[10] and "mixed crypt cell carcinoma."[11]

The origin of the goblet cell carcinoid remains unclear. Goddard and Lonsdale[12] concluded that ordinary carcinoids and goblet cell carcinoids are histogenetically distinct, with goblet cell carcinoids derived from epithelial crypt stem cells, and ordinary carcinoids derived from sub-epithelial neuroendocrine cells. Other theories have been proposed for the cell origin of goblet cell carcinoid; the amine precursor uptake and decarboxylation (APUD) cell system,[13] two independent cell origins for mucin-producing cells and carcinoid cells,[14–16] subepithelial neurosecretory cells (SNC),[13,15] bidirectional differentiation of a common cell origin,[15,17,18] and amphicrine cell origin.[15,19]

Goblet cell carcinoids are composed mainly of endocrine cells and goblet cell-like cells, that is, mucin-producing cells. The former are positive for Grimerlius, Fontana-Masson, serotonin, and chromogranin A staining and the latter are positive for PAS, mucicarmine, and Alcian-blue staining. The specimens from our patient showed histologic features consistent with goblet cell carcinoids of the appendix, reacting positively with PAS, Alcian-blue, and chromogranin A.

We also found numerous cells in the appendiceal tumor that were strongly positive for *p53* immunostaining, suggesting that they had a malignant potential. Contrary to this finding, three cases of ordinary carcinoids in other organs reacted negatively. Unfortunately, dual staining of *p53* protein and chromogranin A was not studied, and it was impossible to identify whether *p53*-positive cells were also chromogranin A-positive. However, the fact that our patient had many metastatic lesions in the liver and peritoneum supports the biological aggressiveness of the tumor.

Anderson et al.[20] emphasized the difficulty of detecting appendiceal goblet cell carcinoids on macroscopic inspection in 11 patients in their hospital. In the 43 cases reported in Japan to date (including ours),[2–4] the tumors in only 2 patients were diagnosed by endoscopy before surgical operation. Most of the patients were diagnosed with acute appendicitis and carcinoid tumors were

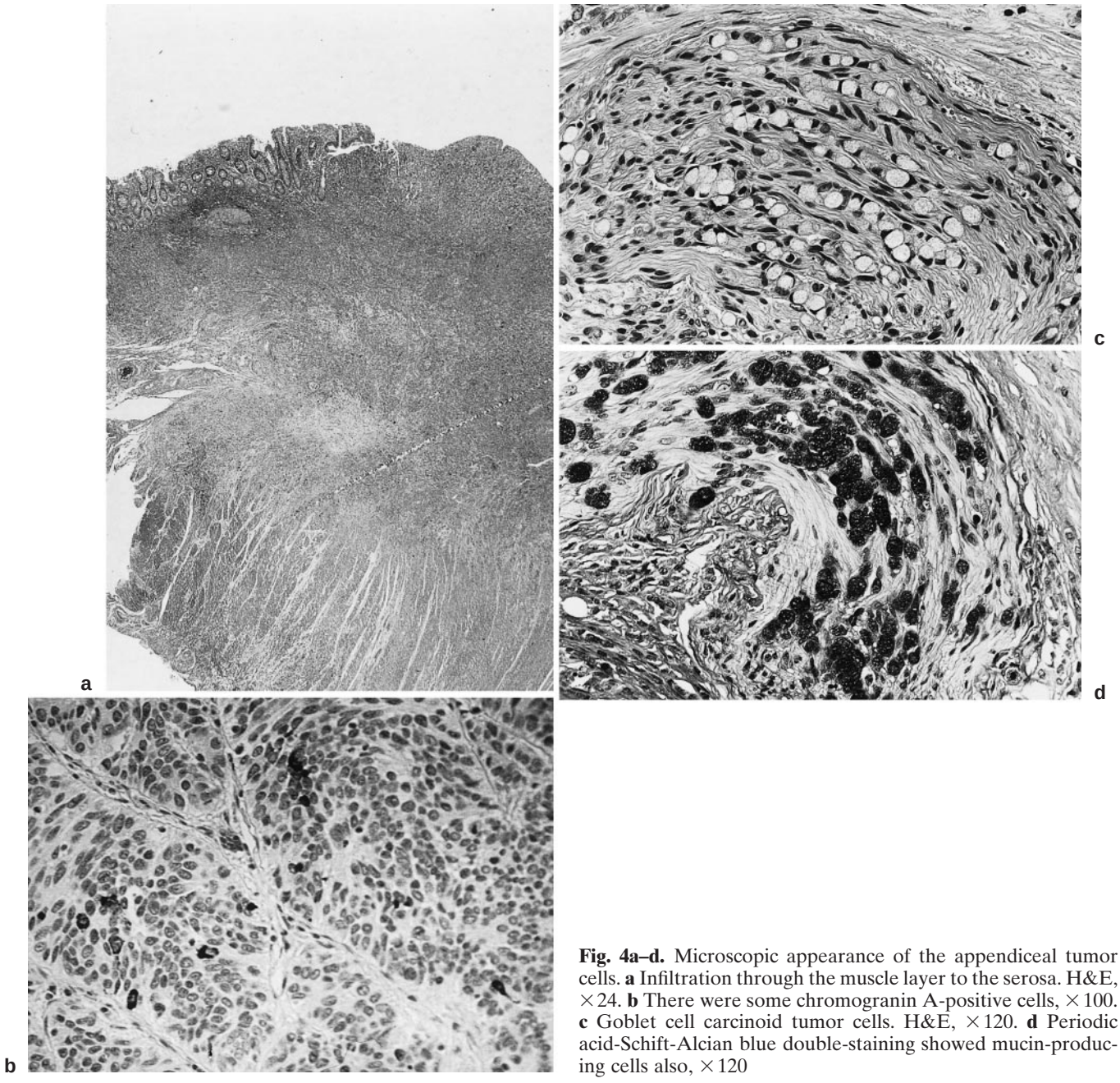

Fig. 4a–d. Microscopic appearance of the appendiceal tumor cells. **a** Infiltration through the muscle layer to the serosa. H&E, ×24. **b** There were some chromogranin A-positive cells, ×100. **c** Goblet cell carcinoid tumor cells. H&E, ×120. **d** Periodic acid-Schift-Alcian blue double-staining showed mucin-producing cells also, ×120

subsequently found in the resected specimens. Fortunately we observed the goblet cell carcinoid tumor endoscopically in our patient and found that it looked like a submucosal tumor, with a well-preserved smooth surface that was red colored and swollen. These findings are distinct from those of ordinary carcinomas, which show endoscopically.

Having studied all these results, we diagnosed the appendiceal tumor as a goblet cell carcinoid and as the primary lesion.

Because of the variable clinical behavior of goblet cell carcinoids, no general agreement has yet been reached on the appropriate treatment.[21] Earlier studies[6,7] showing that goblet cell carcinoid was prognostically equivalent to ordinary carcinoid recommended only appendectomy as adequate treatment. More recently, the aggressive clinical behavior of these tumors has been recognized.[11,12] In the study by Warkel et al.,[9] 20% of the goblet cell carcinoid tumors showed metastasis, resulting in death. As other studies confirmed their metastatic

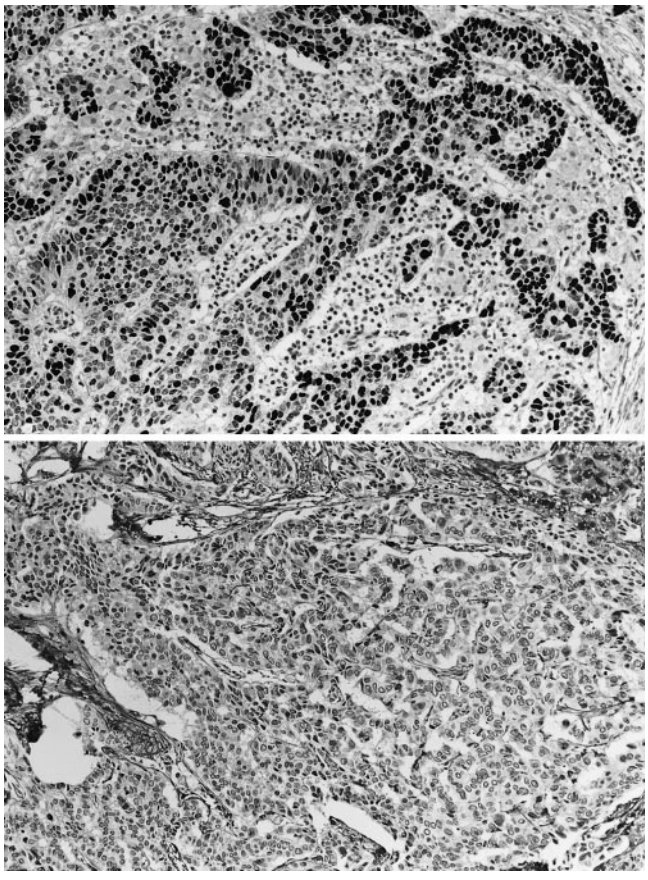

Fig. 5. **a** Most of the appendiceal tumor cells showed a positive immunoreaction for *p53*. **b** There were no *p53*-positive cells in an ordinary carcinoid tumor in the rectum (control)

potential, the prognosis for these tumors was felt to be somewhat between that of carcinoids and that of well differentiated adenocarcinomas.[11,23]

Therefore, under certain conditions (cellular nondifferentiation, increased mitotic activity, involvement of the base of the appendix with cecal wall infiltration, lymph node metastasis, and tumor size), a right hemicolectomy is currently recommended.[10,24,25] As the ovaries are a frequent site of metastases, Butler et al.[1] have recommended bilateral oophorectomy in addition to right hemicolectomy for patients with diffuse involvement of the appendix. They also stated that an appendectomy should be performed in women with Krukenberg tumors who have no known gastrointestinal primary tumor. In deed, 2 of the 43 goblet cell carcinoids reported in Japan were found after preoperative diagnoses of ovarian tumors had been made.[2]

In the present patient it was possible to perform only an appendectomy, because of metastasis. She underwent transarterial embolization for the residual liver tumor and is now under close observation in the outpatient clinic of our department.

More case studies are required to establish the biological character of goblet cell carcinoids; however, considering the case under discussion, we would like to emphasize the malignant aspect of the tumor.

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