

CASE REPORT

Signet-Ring Cell Carcinoma Co-Existing with Adenocarcinoma of the Ampulla of Vater. A Case Report

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ABSTRACT

Context We report a case of signet-ring cell carcinoma admixed with adenocarcinoma of the ampulla of Vater. Signet-ring cell carcinoma of the ampulla of Vater is rarely encountered in clinical practice. **Case report** A 78-year-old man was admitted to our hospital with jaundice. Computed tomography demonstrated dilatation of the biliary tract and an enhanced mass lesion measuring 1.5 cm in the pancreatic head. Endoscopic examination showed a reddish swollen papilla of Vater, and the pathological findings on a biopsy from the papilla suggested signet-ring cell carcinoma. A pancreaticoduodenectomy was performed with a diagnosis of carcinoma of the ampulla of Vater. Postoperative pathological examination showed that the tumor was composed of signet-ring cell carcinoma and tubular adenocarcinoma. The signet-ring cell carcinoma had infiltrated to the duodenal wall and pancreatic parenchyma. Both the signet-ring cell carcinoma and the adenocarcinoma were positive on immunohistochemical staining with 45M1. **Conclusion** Several cases of signet-ring cell carcinoma of the ampulla of Vater have previously been reported. In our case, the histological origin of both signet-ring cell and adenocarcinoma was hypothesized to have been pancreaticobiliary epithelial cells.

INTRODUCTION

Carcinoma of the ampulla of Vater represents about 5% of all carcinomas in the gastrointestinal tract [1]. Signet-ring cell carcinoma is more commonly found in the stomach while signet-ring cell carcinoma of the ampulla of Vater is rarely encountered clinically. We report a case of signet-ring cell carcinoma of the ampulla of Vater admixed with adenocarcinoma.

CASE REPORT

A 72-year-old man was admitted to our hospital with jaundice. He had a 15-year history of diabetes mellitus. There were no palpable masses or lymph nodes at physical examination. Full blood count and renal values were normal, but liver biochemistry showed total bilirubin of 11.7 mg/dL (reference range: 0.2-1.0 mg/dL), direct bilirubin of 8.8 mg/dL (reference range: 0.1-0.4 mg/dL), AST of 88 IU/L (reference range: 0-40 IU/L), ALT of 184 IU/L (reference range: 0-40 IU/L), alkaline phosphatase of 3,414 IU/L (reference range: 115-360 IU/L) and GGT of 1,356 IU/L (reference range: 10-60 IU/L). The serum level of CA 19-9 was

elevated to 69 U/mL (reference range: 0-37 U/mL), that of DUPAN-2 was 1,320 U/mL (reference range: 0-150 U/mL) and that of SPAN-1 was 63 U/mL (reference range: 0-150 U/mL). Computed tomography showed dilatation of both the biliary tract and the main pancreatic ducts as well as an enhanced mass lesion measuring 1.5 cm in the pancreatic head (Figure 1). These findings suggested the existence of a tumor involving the ampulla of Vater. Endoscopic examination showed a reddish swollen papilla of Vater (Figure 2). Pathological findings on biopsy from the papilla suggested tubular adenocarcinoma and signet-ring cell carcinoma. Endoscopic examination of the stomach and the colon did not disclose any other foci of signet-ring cell carcinoma. Having diagnosed carcinoma of the ampulla of Vater, a pancreaticoduodenectomy was performed.

Macroscopically, the tumor measured 1.5x1.5x2 cm and the tumor surface was exposed at the papilla, showing that its surface was nodular, but there was no ulceration. Histologically, signet-ring cell carcinoma was predominant, but partially well- to poorly-differentiated tubular adenocarcinoma also existed in the lesion (Figure 3a). Signet-ring cell carcinoma arose from the ampulla of Vater, slightly involving the muscularis propria of the duodenum and infiltrating the pancreatic parenchyma. The cytoplasm of the signet-ring cell carcinoma was positive for periodic acid Schiff staining (Figure 3b). Lymphatic and vascular involvement was seen in parts, but resected lymph

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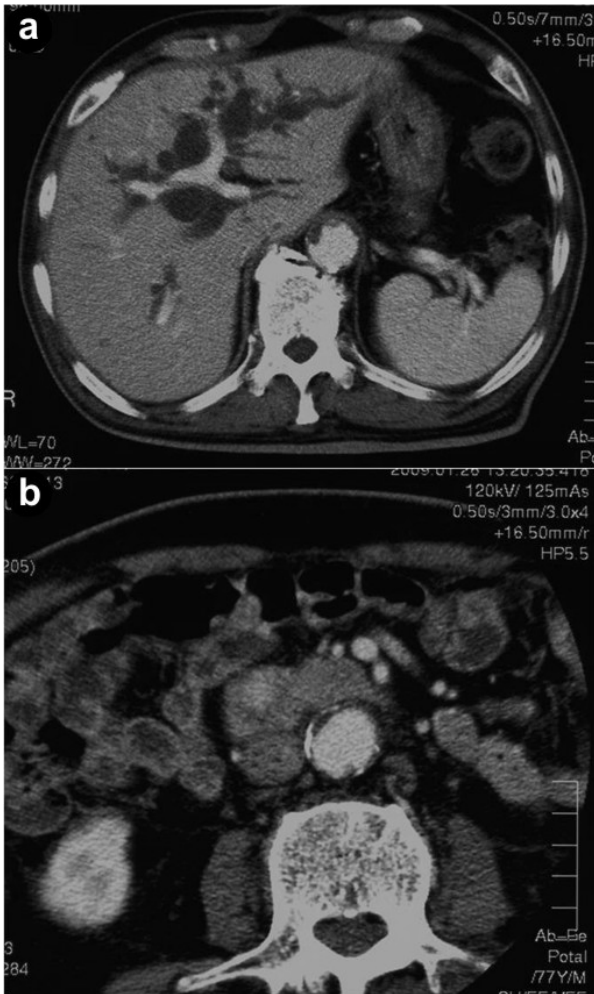


Figure 1. Abdominal axial computed tomography images. **a.** Computed tomography showed dilatation of the intrahepatic biliary tract. **b.** An enhanced mass lesion measuring 1.5 cm was detected in the pancreatic head.

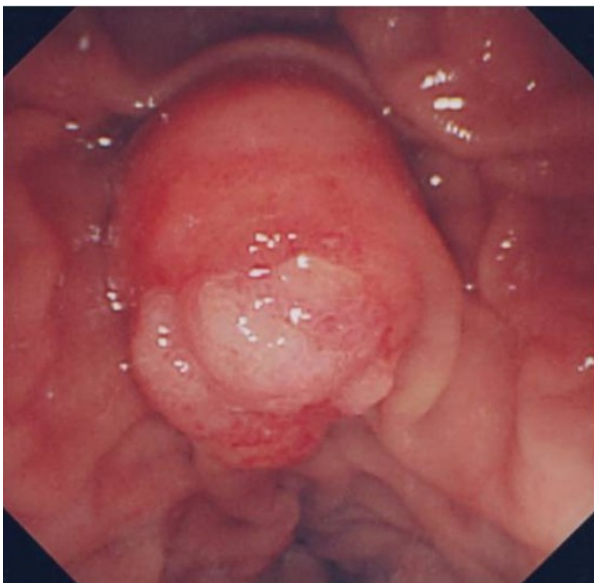


Figure 2. Endoscopic findings of the papilla of Vater. Endoscopic examination showed a reddish swollen papilla.

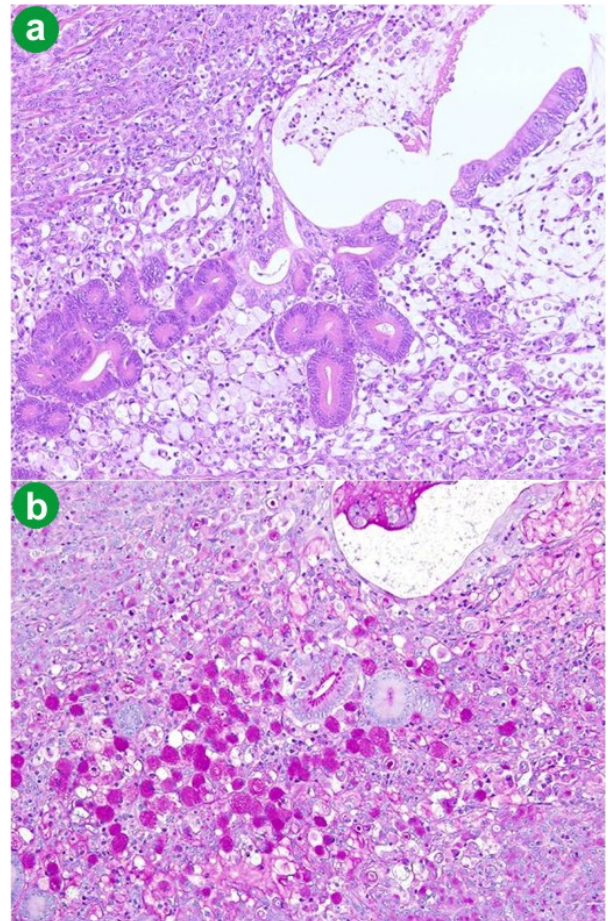


Figure 3. Histopathological findings of the carcinoma. **a.** Signet-ring cell carcinoma co-existing with tubular adenocarcinoma (H&E x50). **b.** The signet-ring cell carcinoma was positive for periodic acid Schiff staining (H&E x50).

nodes were free from metastasis. Immunohistochemical staining was performed and both the signet-ring cells and the adenocarcinoma cells were positive for human gastric mucin (45M1) (Figure 4). Both types of tumor cells were positive for CK7, MUC1 and MUC6, but negative for CK20, MUC2 and CD10

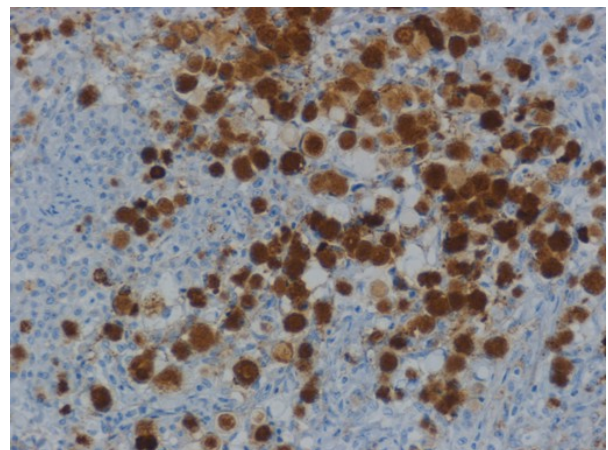


Figure 4. Immunohistochemical findings for human gastric mucin (45M1). Signet-ring cells and adenocarcinoma cells were both positively stained. (original magnification x100).

(Figure 5). The signet-ring cell carcinoma was partially positive for CDX2 (Figure 6). The carcinoma of the ampulla of Vater was diagnosed as T3N0M0 stage IIA according to the International Union Against Cancer TNM classification. The patient did not receive chemotherapy. Six months after surgery, the patient developed pneumonia. Subsequently, the pneumonia worsened and the diabetes mellitus also deteriorated. The patient finally died from multiple organ failure due to sepsis. However, no recurrence of the signet-ring cell carcinoma was detected on repeated imaging studies.

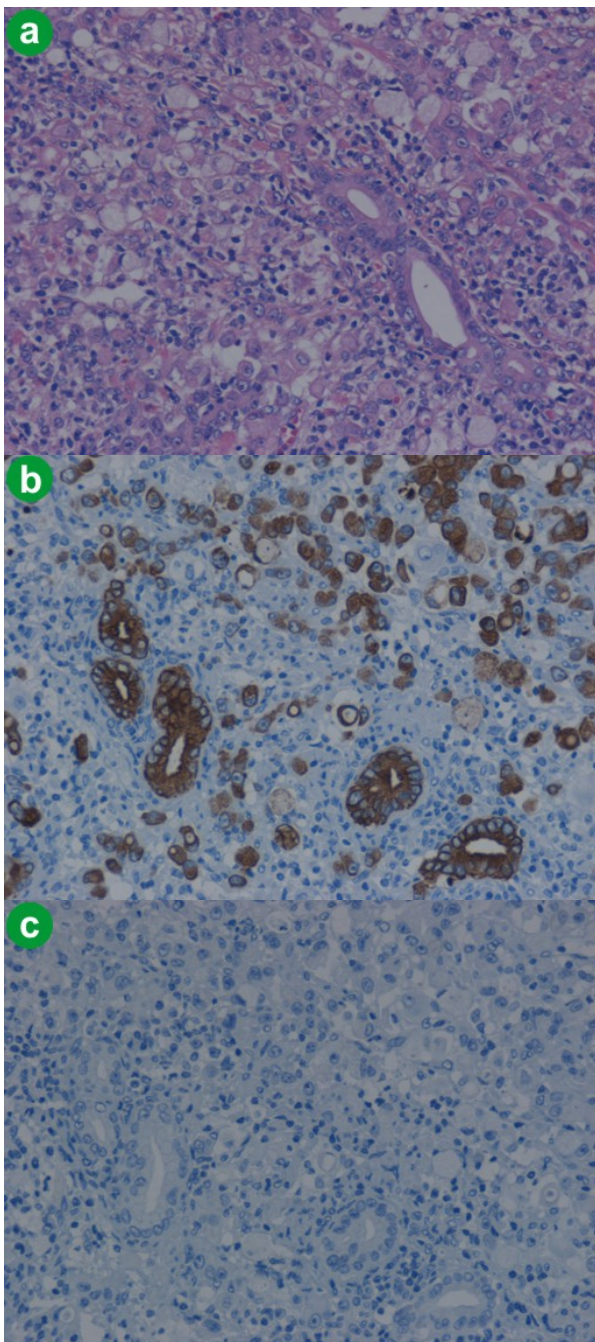


Figure 5. Both signet-ring cells and adenocarcinoma cells stained positively for CK7, but negatively for CD20 (a. H&E, x100; b. Immunohistochemical findings for CK7, x100; c. CK20, x100).

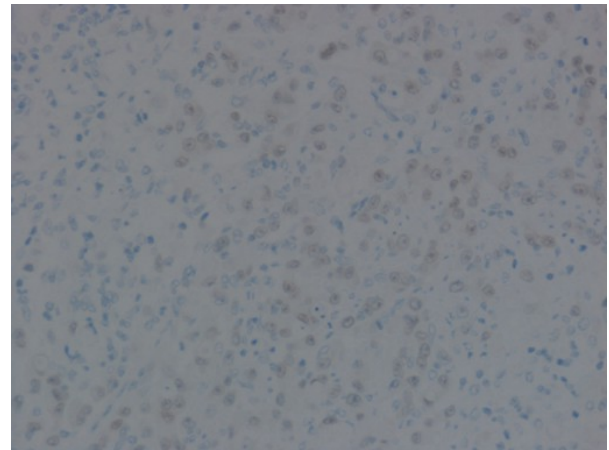


Figure 6. Immunohistochemical findings for CDX2. Signet-ring cells were partially positive for CDX2 (x100).

DISCUSSION

Signet-ring cell carcinoma was first described by Sekoguchi *et al.* in 1979 [2]. Since then there have been 23 cases previously reported [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. Histologically, the origin of signet-ring cells remains unknown, but the following hypotheses have been proposed by various investigators. One is that signet-ring cell carcinoma arises from ectopic gastric mucosa found in the duodenum. Gardner *et al.* and Ramia *et al.* observed ectopic gastric mucosa peritumorally [3, 10]. Another theory is that signet-ring cell carcinoma arises from areas of gastric-type metaplastic epithelia. These metaplastic changes are considered to be a protective response to elevated acidity and have usually been seen at the duodenal bulb in peptic ulcer patients [21]. In this theory, signet-ring cell carcinoma originates from periampullary duodenal heterotopias of an ulcerative etiology and expands to the ampulla of Vater. In our case, there was no ectopic gastric mucosa found in the peritumoral mucosa, and the patient had no history of peptic ulcer disease.

The histopathological findings of three previously reported cases of signet-ring cell carcinoma of the ampulla of Vater showed that signet-ring cell carcinoma co-existed with adenocarcinoma, as in our case (Table 1). We hypothesized that the signet-ring cell carcinoma in our case might have differentiated from common adenocarcinoma, which means that signet-ring cell differentiation from the common type of adenocarcinoma could be another theory explaining the histogenesis of signet-ring cell carcinoma. However, this hypothesis fails to explain why most previously reported cases of signet-ring cell carcinoma of the ampulla of Vater did not demonstrate coexisting adenocarcinoma. A tumor microdissection technique should have been used but this technique was not available in our hospital. So this hypothesis could not be proven.

Kimura *et al.* histologically subdivided carcinoma of the ampulla of Vater into the intestinal-type and pancreaticobiliary-type [22]. Fischer and Zhou

demonstrated differences between these groups on staining for immunohistochemical markers. The intestinal type expressed the immunohistochemical marker profile of intestinal mucosa, that is, negative for CK 7 and positive for CK 20 and MUC2. However, the pancreaticobiliary type shows the immunohistochemical profiles of pancreaticobiliary mucosa, that is, positive for CK 7 and negative for CK 20 and MUC 2 [23]. Fischer and Zhou described the immunohistochemical profiles of three signet-ring cell carcinomas of the ampulla of Vater as follows: all the specimens of signet-ring cell carcinoma were negative for CK 7 and positive for CK 20 and MUC 2 [23]. In our case, the tumor cells were positive for CK7 and negative for CK20 and MUC 2. We suspected that there may be several patterns of immunohistochemical staining for apomucin in signet-ring cell carcinoma of the ampulla of Vater. Our case was thought to be similar to the pancreaticobiliary type because of the positive findings for CK7 and the negative finding for MUC2 staining. But we think it is difficult to conclude that our case was a real pancreaticobiliary type using only these immunohistochemical findings. The positive finding for human gastric mucin (45M1) staining also suggested that both the signet-ring cell carcinoma and the adenocarcinoma in our case were similar to the pancreaticobiliary type. Sonoue *et al.* suggested that the pancreatobiliary mucosa of the ampulla of Vater demonstrates regenerative hyperplasia in response to some stimuli, representing a functional modification

Table1. Reported cases of signet ring cell carcinoma of the ampulla of Vater.

| Case | Histopathology |
|--|---|
| Sekoguchi <i>et al.</i> , 1979 [2] | Co-existence of SRCC and ADSC |
| Gardner <i>et al.</i> , 1990 [3] | Pure SRCC |
| Arnal Monreal <i>et al.</i> , 1994 [4] | Co-existence of SRCC and endocrine cells |
| Casella <i>et al.</i> , 1994 [5] | Pure SRCC |
| Tseng <i>et al.</i> , 2002 [6] | Pure SRCC |
| Hara <i>et al.</i> , 2002 [7] | Pure SRCC |
| Nabeshima <i>et al.</i> , 2003 [8] | Pure SRCC |
| Eriguchi <i>et al.</i> , 2003 [9] | Pure SRCC |
| Ramia <i>et al.</i> , 2004 [10] | Pure SRCC |
| Fang <i>et al.</i> , 2004[11] | Pure SRCC |
| Li <i>et al.</i> , 2004 [12] | Co-existence of SRCC and ADC |
| Zhou <i>et al.</i> , 2004 [13] | Four cases reported but unknown in detail |
| Prohit <i>et al.</i> , 2005 [14] | Pure SRCC (biopsy specimen) |
| Valeri <i>et al.</i> , 2005 [15] | Pure SRCC |
| Bloomston <i>et al.</i> , 2006 [16] | Pure SRCC |
| Akatsu <i>et al.</i> , 2007 [17] | Pure SRCC |
| Gao <i>et al.</i> , 2009 [18] | Pure SRCC |
| Ishibashi <i>et al.</i> , 2009 [19] | Pure SRCC |
| Tas <i>et al.</i> , 2011 [20] | Pure SRCC (bioptic specimen) |
| Present study | Co-existence of SRCC and ADC |

ADC: adenocarcinoma; ADSC: adenosquamous cell carcinoma; SRCC: signet ring cell carcinoma

and expressing some features of a gastric surface marker for immunohistochemical staining [24].

In conclusion, we encountered a case of signet-ring cell carcinoma of the ampulla of Vater. Our case was thought to be a pancreaticobiliary type from the results of the immunohistochemical staining. However, the histogenesis of signet-ring cell carcinoma remains unknown and additional investigation is required to confirm its histological origin.

Conflicts of interest The authors have no potential conflicts of interest

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