Single Case

Signet Ring Cell Carcinoma of the Ampulla of Vater: A Rare Histopathological Variant

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Keywords
Periampullary carcinoma · Signet ring cell carcinoma · Jaundice

Abstract
Signet ring cell carcinoma (SRCC) of the ampulla of Vater is an extremely rare tumor. Our case describes a 45-year-old female presenting with jaundice and pruritus. Computed tomography, endoscopy, and endoscopic retrograde cholangiopancreatography showed a tumor of the ampulla of Vater without distant metastasis. Histological biopsy confirmed a malignant tumor with SRCC characteristics and immunohistochemical staining revealed a mixed type profile (both intestinal and pancreatobiliary characteristics). A pylorus-preserving pancreatoduodenectomy was performed and the patient recovered without complications. Pathology results concluded a pT2N0 ampullary SRCC. SRCC of the ampulla of Vater is known to be highly malignant. After 13 months of follow-up, our patient showed no signs of recurrence.

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Introduction

The ampulla of Vater, also known as the hepatopancreatic duct, is formed by the union of the main pancreatic duct and the common bile duct. At this confluence, the epithelium of the biliary, pancreatic and intestinal system merges. Therefore, the ampulla of Vater is considered an interesting area regarding histopathology. Tumors in the region of the ampulla, or periampullary tumors, represent only a small portion of all gastrointestinal tumors. Especially true ampullary cancers are rare, with a reported population incidence of 2–6 per million \[1\]. True ampullary tumors have better prognoses than other periampullary tumors in general, as well as a higher resectability rate \[2\]. Most ampullary tumors are adenocarcinomas with intestinal or pancreatobiliary origin, although several histopathologic variants have been described. One of those variants is the highly malignant signet ring cell carcinoma (SRCC).

SRCC is predominantly found in gastric tumors \[3\], but it is also found in various tumors including tumors of the gastrointestinal tract, hepatopancreatobiliary system, and urogenital system. This adenocarcinoma subtype is thought to be associated with poor prognosis in advanced cancer, and is thought to be less chemosensitive than non-SRCC \[4\]. Very few cases of SRCC of the ampulla of Vater are described. Less is known about the pathogenesis, treatment, and outcome of this infrequent histologic subtype. Immunohistochemical staining might be used for further investigation of origin and characteristics of the tumor \[5\]. This report adds a case of ampullary SRCC to the few known cases.

Case Report

A 45-year-old female presented at the emergency department with jaundice and pruritus. Apart from a hepatitis B infection in the past, the patient was healthy and her history and physical examination gave no further clues. Laboratory results showed high levels of total bilirubin (83 µmol/L at first presentation, increasing to levels above 500 µmol/L within 2 weeks). Computed tomography showed a double duct sign (Fig. 1). Endoscopic retrograde cholangiopancreatography was performed, which showed a swollen ampulla of Vater suspicious for malignancy. A histological biopsy showed an adenocarcinoma with the characteristics of signet ring cells (Fig. 2). Immunohistochemical staining showed that the signet ring cells were positive for CK20, CK19, MUC-1 (weak), MUC-2, CDX-2, and DPC-4, and negative for CK7, ER, GCDFP, and MUC-5ac (Fig. 3).

In the absence of metastatic disease, a pylorus-preserving pancreatoduodenectomy (PPPD) was performed. Histopathological findings showed an SRCC of 1.2 cm, poorly differentiated, without peripancreatic invasion, lymph node involvement, angioinvasion, or perineural invasion (Fig. 2, 3). The resection margins were clear of tumor cells, minimal margin to the tumor was 1.0 cm. Fourteen lymph nodes were identified without metastasis. The TNM classification according to the International Union Against Cancer (7th edition) was pT2N0M0.

Our patient recovered well from surgery, and no adjuvant treatment was given. After 13 months of follow-up, there was no evidence of recurrence.
Discussion

This report presents a patient with an early-stage SRCC of the ampulla of Vater, with no signs of recurrence after a PPPD and 13 months of follow-up.

Less is known about the pathogenesis of SRCC. Signet ring cells are round-shaped and contain large vacuoles. They form highly malignant and invasive tumors, with dedifferentiated cells without cell-cell interaction. Fukui [6] described a mechanism of mutations in cells with a preexistent malignant phenotype, resulting in the formation of signet ring cells. SRCC is defined as the occurrence of more than 50% signet ring cells.

Carcinoma of the ampulla of Vater accounts for 0.2% of all gastrointestinal malignancies and <6% of all periampullary cancers [7]. Only 37 cases of SRCC of the ampulla have been described so far, of which 27 in the English literature [8–11] (Table 1). The patient in the presented case is relatively young, and only 5 studies reported younger patients than our patient. The median age described in the literature is 60 years. The disease is described in male and female patients, although there is a slight predominance in male patients.

Ampullary SRCC may be further divided into intestinal type (I), pancreatobiliary type (PB), gastric type, and mixed type [5, 12]. This classification is based on immunohistochemical staining. Expression of CK7, CK19, and MUC-1 is associated with PB-type, expression of CK20, MUC-2, and CDX-2 is associated with I-type, whereas co-expression of MUC-5ac and MUC-6 is associated with gastric type. Our case showed an immunohistochemical profile compatible with I-type SRCC, but it also shows the PB-type (CK19 expression and weak expression of MUC-2). This is a mixed type of SRCC, which has only been previously described once [5].

Like all periampullary tumors, surgery remains the cornerstone of treatment. In our case, PPPD was performed. The Dutch guideline does not recommend adjuvant chemotherapy for ampullary tumors in general [13]. Different case reports of adding 5-fluorouracil or gemcitabine/cisplatin have been described, with variable results [5, 10].

For metastatic ampullary tumors, chemotherapy is given and the subtype of the tumor determines the regime (PB-type vs. I-type). However, in the case of SRCC of the ampulla of Vater the response is unknown. The response to chemotherapy of SRCC, which is mostly studied in gastric, esophageal, and colorectal cancer, is thought to be less [4].

Median overall survival rates of 24.9 months are described with a range of 6–132 months [8]. This compared to 37 months, which is reported for resected ampullary carcinoma in general [14]. Only a handful of cases report a survival of more than 5 years, although follow-up time is often limited at the time of publication. Lymph node invasion appears to be the most important prognostic factor [12, 15]. Also an I-type SRCC might have a better prognosis than a PB-type SRCC [5]. Mixed type SRCC is associated with poorer prognosis, although follow-up is too short in our case.

In conclusion, SRCC of the ampulla of Vater is an extremely rare gastrointestinal tumor; this report adds a 38th case.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no potential conflicts of interest.

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Fig. 1. CT image with adjusted plane showing a double duct sign (a) and a dilated common bile duct (b).
Fig. 2. **a** Low-power view of the ampullary tumor, infiltrating in the mucosa, submucosa, and inner muscularis propria of the duodenum. HE. ×20. **b** High-power magnification, showing preexisting duodenal crypts (right) and submucosa (right) infiltrated by signet ring cells. HE. ×200.
Fig. 3. Immunohistochemical staining of the ampullary tumor, with benign tissue on the left border of each image. Positive staining for CK-19 (a), CK-20 (b), MUC-1 (c), MUC-2 (d), CDX-2 (e), DPC-4 (f), and negative for MUC-5ac (g).
Table 1. Case reports of signet ring cell carcinoma of the papilla of Vater in the English literature sorted chronologically

| First author       | Year | Age, years | Sex | Size, mm | TNM       | Treatment                     | Follow-up, months | Outcome |
|--------------------|------|------------|-----|----------|-----------|-------------------------------|-------------------|---------|
| Gardner [16]       | 1990 | 69         | F   | 20       | T3N0M0    | PD                            | 0                 | –       |
| Hara [15]          | 2002 | 68         | M   | 15       | T2N0M0    | PPPD                          | 10                | Alive   |
| Tseng [17]         | 2002 | 47         | M   | 20       | T3N0M0    | PD                            | 6                 | Alive   |
| Eriguchi [18]      | 2003 | 83         | M   | 15       | T3N0M0    | PD                            | 18                | Alive   |
| Li [19]            | 2004 | 56         | F   | 15       | T2N1M0    | PD                            | 12                | Alive   |
| Ramia [20]         | 2004 | 67         | F   | 18       | T2N0M0    | PD                            | 12                | Alive   |
| Fang [21]          | 2004 | 53         | M   | 26       | T2N0M0    | PD                            | 25                | Alive   |
| Bloomston [22]     | 2005 | 58         | F   | 10       | T2N0M0    | PD                            | 134               | Alive   |
| Akasu [23]         | 2007 | 43         | F   | 20       | T2N0M0    | PD                            | 90                | Alive   |
| Gao [24]           | 2009 | 38         | F   | 20       | T3N0M0    | PD                            | 6                 | Alive   |
| Ishibashi [25]     | 2009 | 59         | M   | 30       | T3N0M0    | PD                            | 18                | Died    |
| Gheza [26]         | 2011 | 66         | M   | –        | –         | PD                            | 8                 | Alive   |
| Paplomata [27]     | 2011 | 45         | F   | 30       | T4N1Mx    | PPPD adjuvant chemotherapy     | 12                | Died    |
| Maekawa [28]       | 2011 | 75         | M   | 20       | T3N0M0    | PD                            | 6                 | Died    |
| Lesquerreux-Martínez [29] | 2012 | 78     | F   | 11       | TxN1M0    | PD adjuvant chemotherapy       | 14                | Alive   |
| Daoudi [30]        | 2012 | 55         | M   | –        | T3N0M0    | PD adjuvant chemotherapy       | 8                 | Alive   |
| Acharya [31]       | 2013 | 78         | F   | 30       | T3N0M0    | PD                            | 6                 | Alive   |
| Wen [5]            | 2014 | 40         | F   | 30       | T3N0M0    | PD                            | 8                 | Alive   |
| Wen [5]            | 2014 | 64         | F   | 65       | T4NxM0    | PD                            | 76                | Alive   |
| Wen [5]            | 2014 | 75         | F   | 35       | T4NxM0    | PD                            | 16                | Died    |
| Wen [5]            | 2014 | 62         | M   | 24       | TxN1M0    | PD                            | 27                | Died    |
| Wen [5]            | 2014 | 62         | M   | 30       | TxN1M0    | PD                            | 9                 | Died    |
| Wen [5]            | 2014 | 53         | M   | 12       | T3N0M0    | PD                            | 45                | Alive   |
| Wen [5]            | 2014 | 66         | F   | 15       | T3N0M0    | PD                            | 54                | Alive   |
| Wen [5]            | 2014 | 68         | M   | 95       | T4NxM0    | PD                            | 72                | Alive   |
| Wakasugi [10]      | 2015 | 59         | F   | 20       | T3N1M1    | PD adjuvant chemotherapy       | 7                 | Alive   |
| Ushida [9]         | 2017 | 82         | F   | 22       | T3N0M0    | PD                            | 60                | Alive   |
| Our case           | 2017 | 45         | F   | 12       | T2N0M0    | PPPD                          | 12                | Alive   |

F, female; M, male; PD, pancreatoduodenectomy; PPPD, pylorus-preserving pancreatoduodenectomy.