

CASE REPORT

Rare carcinoma of the ampulla of Vater with mixed histologies: A case report

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Abstract

The current case is about a 62-year-old female presented with persistent fever for 10 days and yellowing of the skin for 5 days at our outpatient clinic. Laboratory tests revealed elevated levels of total bilirubin, direct bilirubin, indirect bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ -glutamyl transpeptidase. Abdominal computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography revealed a mass in the ampulla of Vater, as well as dilatation of the intra- and extra-hepatic bile and pancreatic ducts. The patient underwent pancreaticoduodenectomy under general anesthesia. Post-operative pathological and immunohistochemical results confirmed a tumor located in the ampulla, measuring $1.5 \times 1 \times 1$ cm. The main component of the tumor was a moderately differentiated pancreaticobiliary adenocarcinoma (ADC), combined with squamous cell carcinoma (SCC) as well as small cell neuroendocrine carcinoma (SCNEC). The cancer tissue infiltrated the entire intestinal wall, with no invasion of microvessels, lymphatic vessels, or nerves observed. Until 46 months later, there was no tumor recurrence or distant metastasis. We present an uncommon case of ADC of the ampulla of Vater combined with SCC and SCNEC. Carcinoma of the ampulla of Vater may have mixed histological components; therefore, in cases of ampullary carcinoma, appropriate specimen collection is necessary, and further studies with more focus on histological origins are required.

Keywords: Ampullary carcinoma; Mixed histology components; Adenocarcinoma; Squamous cell carcinoma; Small cell neuroendocrine carcinoma

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1. Introduction

Carcinoma of the ampulla of Vater (AoV) is rare, accounting for only 0.2 – 0.5% of all gastrointestinal malignancies, and the majority of ampullary carcinomas are adenocarcinomatous.¹ We present an extremely rare case of ampullary carcinoma with three mixed histological components: Adenocarcinoma (ADC), squamous cell carcinoma (SCC), and small cell neuroendocrine carcinoma (SCNEC). A literature search for ampullary carcinoma with more than two histological components, including at least one neuroendocrine component, revealed only two cases.^{2,3} However, none of these cases reported SCNEC components.

2. Case presentation

A 62-year-old female presented to our hospital after having experienced persistent fever (up to 39.6°C) for 10 days and yellowing of the skin for 5 consecutive days. She reported pruritus, tea-colored urine, white clay-colored stool, and 2 kg loss of body weight over the last 15 days before seeking medical consultation. She had a poor mental state, appetite, and nutritional status; jaundice of the skin and sclera; and epigastric tenderness. Laboratory investigations revealed elevated levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ -glutamyl transpeptidase, total bilirubin, direct bilirubin, indirect bilirubin, total cholesterol, triglycerides, and cancer antigen 19-9. Ultrasonography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography (MRCP) revealed cholecystitis, dilated intra- and extra-hepatic bile ducts, and a dilated common bile duct (CBD). Abdominal computed tomography (CT) (Figure 1) revealed an enlarged gallbladder with a slightly thickened wall, dilated intra- and extra-hepatic bile ducts, a dilated CBD, irregular mass measuring 0.82×0.65 cm in the AoV, and obvious enhancement. Based on these findings, ampullary carcinoma was suspected. In light of the CT and MRCP findings confirming tumor invasion of the CBD, endoscopic retrograde cholangiopancreatography was

deemed inappropriate for further evaluation. Consequently, the patient was admitted for surgical management with the aim of achieving a complete tumor resection. A pancreaticoduodenectomy procedure was performed, entailing the resection of the ampulla mass, a portion of the pancreatic head, and a segment of the duodenum. In addition, an exploration of the regional lymph nodes was conducted to assess for metastatic involvement. The resected mass (Figure 2) was grayish-white in appearance, measuring $1.5 \times 1 \times 1$ cm.

Microscopically, the normal tissue structure of the pancreaticobiliary duct in the AoV has been replaced by tumor tissue, which has infiltrated the entire intestinal wall, including the submucosa of the duodenum and the entrance to the major duodenal papilla. The tumor consisted mainly of moderately-differentiated ADC (with varying-sized tubular structures or complex adenoid-like structures), and poorly-differentiated SCC (with solid growth patterns and occasional hyperkeratosis). In some areas of the tissue sample, it was observed that ADC gradually transitioned to poorly differentiated SCC. The SCNEC components accounted for approximately 15% of the tumors and were observed near the tumor surface and the ADC. The SCNEC components constituted approximately 15% of the tumor and were observed near the tumor surface and the ADC. Two distinct morphological variants were identified within the SCNEC components: The first variant consisted of a classic spindle-shaped, “oat”-like cell with a high nucleus-to-cytoplasm ratio and fine chromatin, characterized by the conspicuous presence of nuclear divisions (designated as NEC-1). The second variant was characterized by medium-sized oval cells arranged in an organoid, nested, or trabecular pattern, accompanied by small focal necrosis (designated as NEC-2). The SCNEC cells were more uniformly arranged, with vacuolated nuclei, and coarse granular chromatin (Figure 3). Immunohistochemistry further confirmed the coexistence of three components in this tumor: SCC, ADC, and SCNEC (Figure 4, refer

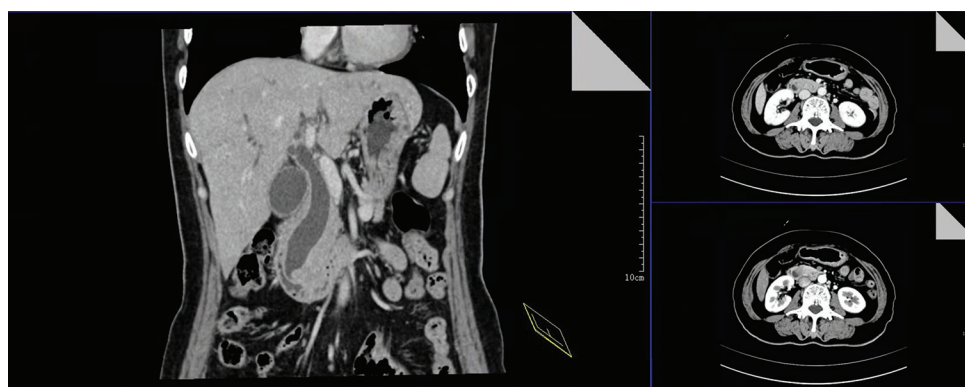


Figure 1. Abdominal computed tomography shows dilated intra- and extra-hepatic bile ducts, a dilated pancreatic duct, and an ampullary mass

to Table A1 for information on antibodies used in this assay). Immunohistochemistry of the ADC component revealed: CK7 (+), CK20 (+), P40 (-), and CgA (-). The SCC component showed: CK7 (weak +), CK20 (-), P40 (+), and CgA (-). The NEC component exhibited: CK7 (weak +), CK20 (-), P40 (-), and CgA (+). The proliferation index for all three components was similar, with a Ki67 positive percentage of more than 80%. (For additional immunohistochemical expressions, refer to Table A2).

No invasion of microvessels, lymphatic vessels, or nerves was observed; however, four lymph nodes were found next to the pancreas, one of which had a metastatic component of an ADC; the tumor was staged pT2N1M0 (stage IIIA).⁴ According to the request of the patient's family, the patient underwent six cycles of post-operative adjuvant chemotherapy in another hospital (but the specific treatment plan is not available).

This study was approved by Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences Institutional Review Board (approval number: YXLL-2021 – 036) for the publication of this case report and accompanying images.

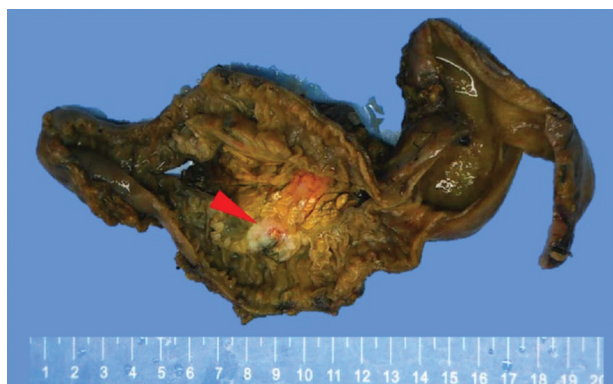


Figure 2. The tumor in the ampulla measures $1.5 \times 1 \times 1$ cm in dimension. The examined section appears grayish-white, solid, and brittle (indicated by the red arrow)

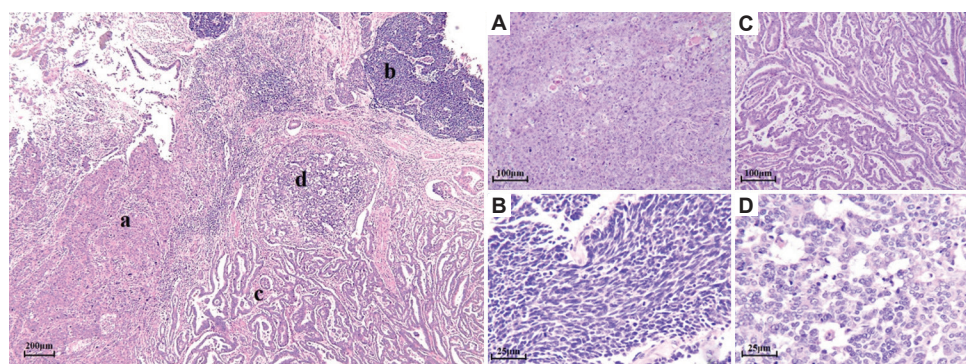


Figure 3. Hematoxylin-eosin stained section showing that the tumor is composed mainly of poorly-differentiated squamous cell carcinoma (A), moderately-differentiated tubular adenocarcinoma (C), and small cell neuroendocrine carcinoma (B and D)

3. Discussion

We report a rare case of ampullary carcinoma with mixed histological components: ADC, SCC, and SCNEC. The anatomical structure of the AoV is complex, including portions of the CBD and the main pancreatic duct. The histological structure of the AoV includes pancreaticobiliary duct-type epithelium, duodenal intestinal epithelium, and transition zone.⁵ Therefore, tumors occurring in this region may have multiple origins. Mitsuma *et al.*² reported an ADC with enteroblastoma and large-cell NEC (LCNEC). Sunose *et al.*³ presented a case of an LCNEC of the AoV with concurrent SCC and ADC. However, no cases like ours have been reported.

In our case, there were two different morphologies of SCNEC. Immunohistochemical staining for p53 and Rb1 proteins is helpful in the differential diagnosis of NEC. Diffuse overexpression and diffuse loss of p53 and Rb1 proteins, respectively, support NEC diagnosis⁶ (Figure 5). The results obtained in our case supported the definitive diagnosis of NEC (overexpression of p53 and no expression of Rb1). The NEC component was only 15%. In mixed ADC and NEC of the biliary tract, the NEC component determines the prognosis,⁷ and a high-grade NEC exhibits a more aggressive clinical course than limited advanced ADC.⁸ Therefore, though the NEC component was <30%,⁹ it was necessary for us to identify and quantify each tumor component in the pathological diagnosis for follow-up treatment.

The tumor in this case featured an SCC component of 45% and a moderately differentiated ductal ADC component of 40%, with a histological morphological transition observed between the two. There are two possible explanations for the origin of SCC. First, because the AoV is located at the confluence of two physiological ducts, the repeated flushing of digestive enzymes and related chemicals from the biliopancreatic system, and the stimulation of other lesions in this area may lead to

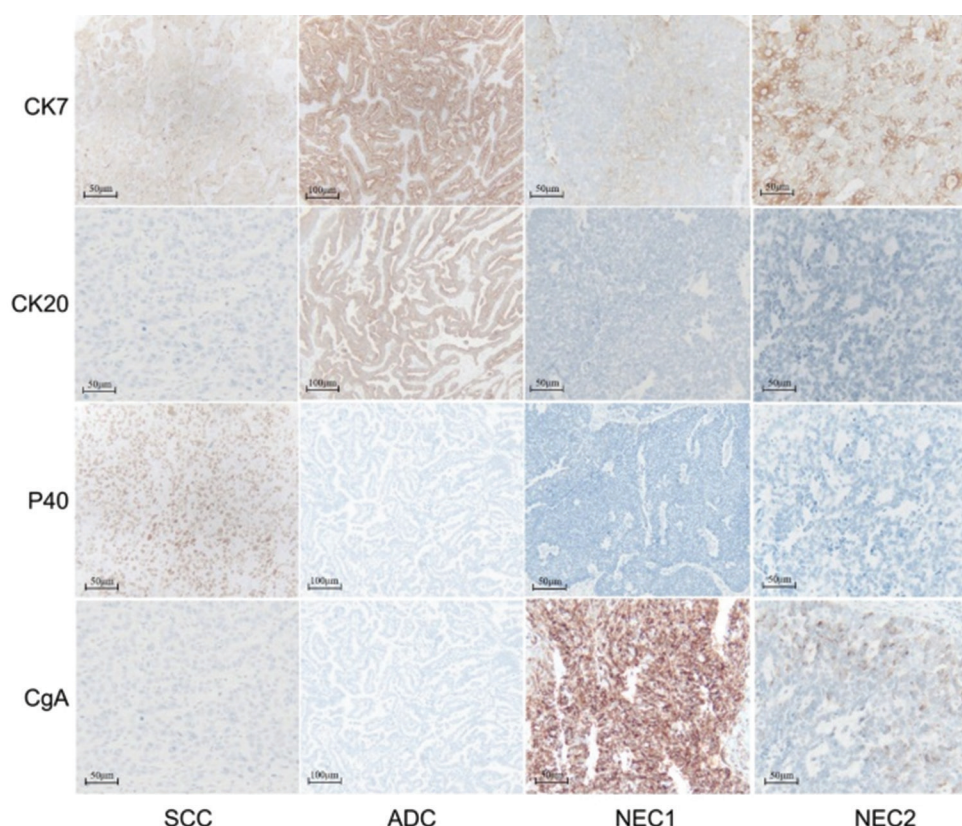


Figure 4. Immunohistochemical staining of squamous cell carcinoma, adenocarcinoma, and different morphological regions of small cell neuroendocrine carcinoma (NEC1 and NEC2)

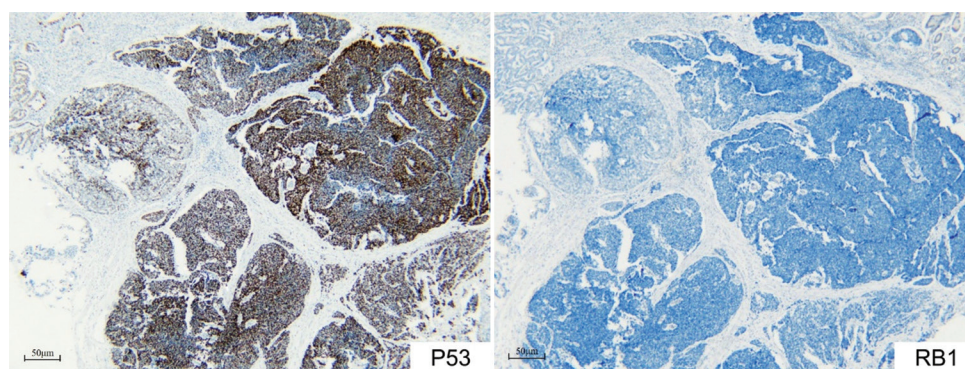


Figure 5. The overexpression of p53 and the lack of Rb1 expression support the diagnosis of a small-cell neuroendocrine carcinoma

squamous metaplasia of the normal glandular epithelium, followed by transformation into a malignant SCC. Second, ADC and SCC originate from the same multipotent stem cells,¹⁰ which have the potential to differentiate directly into ADC and SCC, or the ADC may transform into SCC during progression. We also hypothesized that the NEC component in this case might have originated from neuroendocrine cells in the AoV or from multipotent stem cells, which later acquired the ability to differentiate into glandular epithelial cells, squamous cells, and

neuroendocrine cells. While differentiating into the pancreaticobiliary-type ADC, part of the tumor tissue transformed into SCC and NEC, resulting in the unique aforementioned pathological features.

Pancreatic and gastrointestinal NECs are highly malignant, especially the small-cell type, which has an extremely poor prognosis and is prone to distant metastases.¹¹ In contrast, our patient had no distant metastases or recurrence at the time of follow-up and submission and showed a good prognosis (telephone

follow-up was performed 46 months after surgery). This may be attributed to the small tumor size, complete surgical resection, and a small percentage of SCNEC cells.

4. Conclusion

Ampullary carcinoma may exhibit multiple histopathological components, necessitating pathological examination of samples from various sections of the tumor. Future studies may need to focus on unraveling the histological origins of these components and the effects of these components on prognosis.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

This study was approved by Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences Institutional Review Board (approval number: YXLL-2021 – 036) for the publication of this case report and accompanying images. Verbal informed consent has been obtained from the patient's family members through telephone.

Consent for publication

Verbal consent for publication has been obtained from the patient's family.

Availability of data

Not applicable.

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Appendix

Table A1. List of used antibodies

Name	Manufacturer	Country	Clone number	Dilution ratio
AE1/AE3	ZSGB-Bio	China	AE1/AE3	1:150
CK7	ZSGB-Bio	China	UMAB16	1:150
CK19	ZSGB-Bio	China	UMAB2	1:150
CK20	ZSGB-Bio	China	EP23	1:150
CDX2	ZSGB-Bio	China	EP25	1:150
MUC1	ZSGB-Bio	China	GP1.4	1:150
MUC2	ZSGB-Bio	China	Ccp58	1:150
CK5/6	ZSGB-Bio	China	RM341	1:150
P63	ZSGB-Bio	China	UMAB4	1:150
P40	ZSGB-Bio	China	rabbit polyclonal antibody	1:150
Syn	ZSGB-Bio	China	OT11C9	1:150
CgA	ZSGB-Bio	China	LK2H10	1:150
CD56	ZSGB-Bio	China	UMAB83	1:150
CD117	Roche	USA	c-kit	Ready-to-Use
SSTR2	ZSGB-Bio	China	EP149	1:150
p53	ZSGB-Bio	China	DO-7	1:150
Rb1	ZSGB-Bio	China	13A10	Ready-to-Use
Ki67	ZSGB-Bio	China	UMAB101	1:150

Note: ZSGB-Bio: Beijing Zhongshan Golden Bridge Biotechnology Co. Ltd.

Table A2. Immunohistochemical staining results

Antibody	SCC	ADC	NEC1	NEC2
AE1/AE3	+	+	Weak +	Weak +
CK7	Weak +	+	Weak +	Weak +
CK19	+	+	Weak +	Weak +
CK20	-	+	-	-
CDX2	-	-	-	-
MUC1	Weak +	+	Weak +	Weak +
MUC2	-	-	-	-
CK5/6	+	-	-	-
P63	+	-	-	-
P40	+	-	-	-
Syn	-	-	+	+
CgA	-	-	+	+
CD56	-	-	-	-
CD117	-	-	+	+
SSTR2	-	-	weak +	+
Ki67	>80% +	>80% +	>80% +	>80% +

Notes: '+': Accurate localization with >75% cell staining, moderate to strong intensity; '-': No cell staining; 'Weak+': Accurate localization with >75% cell staining, mild intensity; '>80%+': Ki67 positivity >80%. Abbreviations: SCC: Squamous cell carcinoma; ADC: Adenocarcinoma; NEC1: Neuroendocrine carcinoma 1; NEC2: Neuroendocrine carcinoma 2.