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Case report

Squamous cell carcinoma of the ampullary region; the pitfalls and challenges in diagnosis

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Abstract

Introduction: Primary squamous cell carcinoma (SCC) of the ampulla of Vater is a very rare entity with only twelve reported cases to date.

Case report: A 61-year-old woman presented with painless obstructive jaundice of six weeks duration. On examination, she was deeply icteric and had tenderness over the right upper quadrant. Her liver enzyme levels were high. Imaging showed an ampullary mass associated with a dilated common bile duct (CBD) and a distal CBD stricture. The biopsy was reported as a poorly differentiated carcinoma. A Whipple procedure was done, and a tan-white, irregular tumour measuring 25x24x20 mm was seen centred on the ampulla. The entire tumour was submitted for histology, which comprised invasive clusters and sheets of malignant squamous cells. There was no adenocarcinoma component in the entire tumour. Special stains for mucin were negative. Immunohistochemistry showed that the tumour cells were strongly positive for CK7 and CA 19-9, focally positive for CK5/6 and negative for CK20. The features were compatble with a SCC of the ampulla. As pure SCC of the ampulla is rare, metastatic involvement of the ampulla was excluded clinically and radiologically.

Discussion and conclusionn: Due to rarity, the prognosis and biological behaviour of this type of carcinoma is largely unknown. Surgery is considered the mainstay of treatment. The possibility of adenosquamous carcinoma and metastasis from other sites should be excluded before making the diagnosis of primary SCC of the ampulla.

Keywords: squamous cell carcinoma, ampulla of Vater, ampullary carcinoma

Introduction

Primary carcinomas of the ampulla of Vater comprise up to 0.5% of all gastrointestinal malignancies out of which the majority are adenocarcinomas (1,2). The ampullary epithelium is devoid of squamous cells and the origin of primary squamous cell carcinoma (SCC) of the ampulla is unclear (3). Primary SCC of the ampulla is a very rare entity with only twelve cases reported thus far (1,4,5). The first case was reported in 1952 in a 68-year-old white woman in Sweden who developed obstructive jaundice (6). Another case coexisted with a separate well-differentiated adenocarcinoma of the distal pancreatic duct (3).

A pure SCC of the ampulla should raise suspicion of metastatic involvement of the ampulla from a primary elsewhere, which needs to be excluded clinically and radiologically (7). Three such cases were reported; primary laryngeal, oesophageal and uterine cervical squamous cell carcinoma (1), all of which metastasized to the ampulla.

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Adequate sampling and careful searching are necessary to identify any associated glandular component (7).

It is known that ampullary adenocarcinomas have a better prognosis after surgical resection compared to pancreatic head adenocarcinoma and adenocarcinoma of the lower common bile duct (8). However, due to the rarity of ampullary SCC, its biological behaviour, treatment options and prognosis are largely unknown (1). Hence it is extremely important to exclude metastatic involvement of the ampulla by an SCC elsewhere before diagnosing a primary. To our knowledge, this is the first case of primary SCC of the ampulla reported in Sri Lanka and the thirteenth worldwide. Its clinical, radiological and histological findings are highlighted.

Case report

A 61-year-old woman presented with painless obstructive jaundice of six weeks duration. She had loss of appetite, recent loss of weight (about 5 kg) and generalized fatigue. She had also experienced mild to moderate dyspeptic symptoms for three months.

On examination, she was deeply icteric. Abdominal examination revealed tenderness over the right upper quadrant without any palpable masses. Her liver enzyme levels were high with an increase in direct bilirubin. Serum CA19-9 was normal (Table 1).

An ultrasound scan showed a distended gallbladder without calculi and dilated intra and extra-hepatic biliary system. Contrast-enhanced computerized tomography (CECT) of the abdomen and pelvis showed similar findings with a common bile duct (CBD) diameter of 16 mm and a dilated main pancreatic duct. There was ampullary bulging with minimal hyperdensities. Pancreatic head masses were not seen. There were no intra-hepatic masses, other masses or enlarged intra-abdominal lymph nodes.

Magnetic resonance cholangiopancreatography (MRCP) revealed a stricture at the distal end of CBD causing obstruction with proximal dilatation. Endoscopic retrograde cholangiopancreatography (ERCP) showed a bulging, distorted ampulla of Vater with a tight distal CBD stricture. A biopsy taken at this time was reported as a poorly differentiated carcinoma.

A classical pancreaticoduodenectomy (Whipple procedure) was performed. At surgery, a tumour was seen in the regions of the ampulla of Vater, with dense adhesions to surrounding tissues.

On pathological examination of the specimen, a tan-white, irregular tumour measuring 25x24x20 mm was seen centred on the ampullary region. The rest of the pancreas was macroscopically normal.

The entire tumour was submitted for histology. The tumour comprised invasive clusters and sheets of malignant cells with a dense eosinophilic squamoid quality to the cytoplasm and nuclear atypia with frequent and atypical mitoses (Figure 1A and 1B). There was no definite keratinization of the tumour cells. There was no adenocarcinoma component in the entire tumour although pseudoglandular spaces were seen in areas of tumour cell necrosis (Figure 1C). Special stains for neutral and acid mucin were negative. Lymphovascular invasion and extension into

Investigation	**Result**
Serum alkaline phosphatase	2648 IU/L (98-279)
Total bilirubin	5.73 mg/dL (0.2-1.4)
Direct bilirubin	10 mg/dL (0.1-0.4)
Aspartate aminotransferase	290 U/L (<40)
Alanine aminotransferase	693.5 U/L (0-18.4)

Table 1. Investigation findings

peri-pancreatic connective tissue were present (Figure 1D). All peri-pancreatic lymph nodes contained tumour deposits. The background pancreas did not show squamous metaplasia or an adenocarcinoma in-situ component.

On immunohistochemistry the tumour cells were strongly positive for CK7 (Figure 2C) and CA19-9 (Figure 2B), focally positive for CK5/6 (Figure 2A) and negative for CK20 (Figure 2D). A melanoma was excluded with negative HMB45 and Melan A stains. The tumour cells were positive for CK5/6, supporting a diagnosis of SCC. Due to the unavailability of resources at the time of diagnosis, other squamous cell markers, such as p63 or p40, could not be performed.

Other possible primary sites for SCC were excluded by pan-endoscopy of the upper aerodigestive tract, inclusive of the paranasal sinuses, flexible sigmoidoscopy, colposcopy and biopsy of the uterine cervix and computed tomography (CT) of chest and abdomen.

The immediate postoperative period was uneventful. The patient defaulted follow-up treatment, and on inquiry, was found to have died eight months after surgery with liver metastasis.

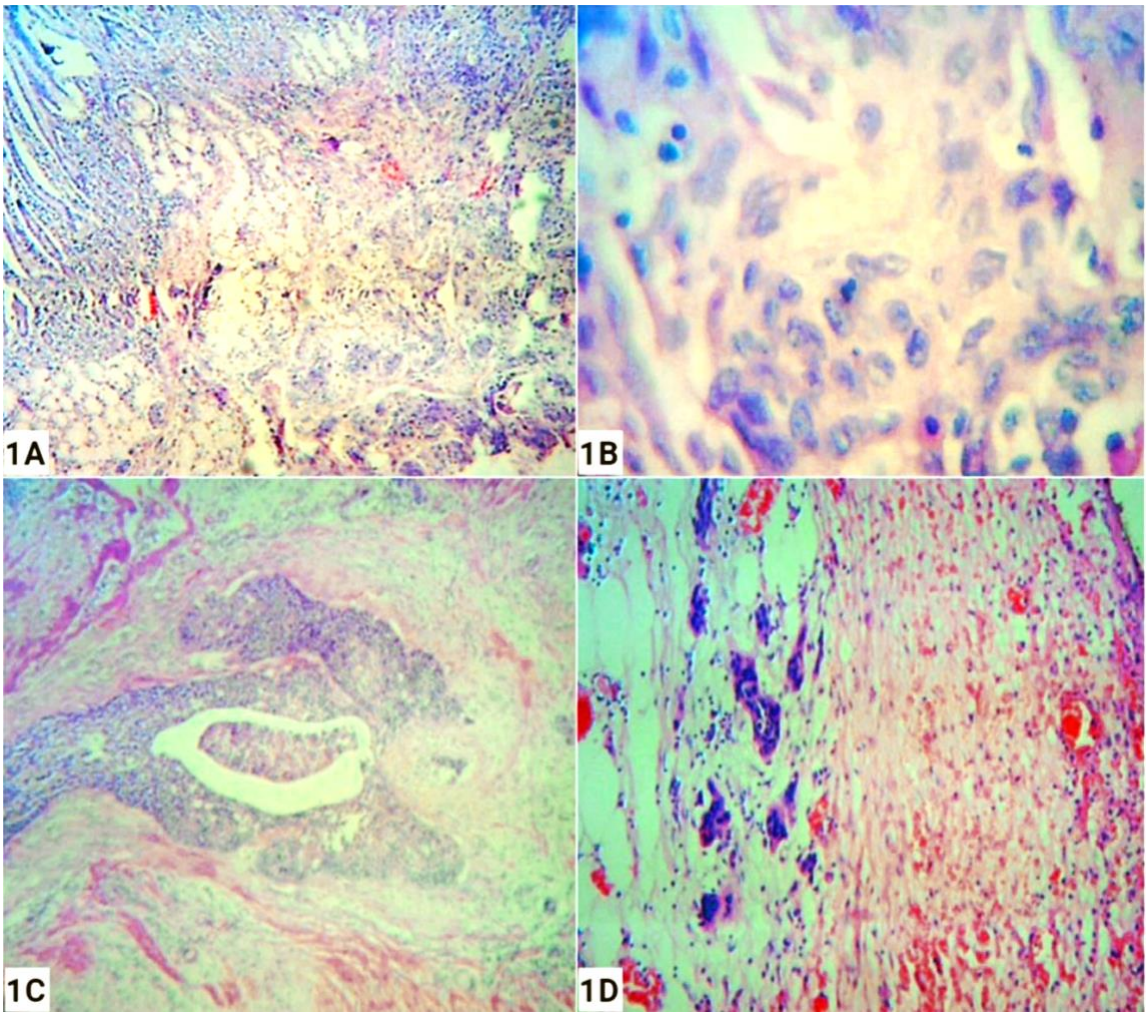

Figure 1. Microscopic appearance of the tumour (H&E stain) **1A** Tumour in the wall of duodenum (x40). **1B** Nests of squamoid cells (x400). **1C** Pseudoglandular spaces within the tumour (x100). **1D** Clusters of tumour cells seen at posterior margin (x400).

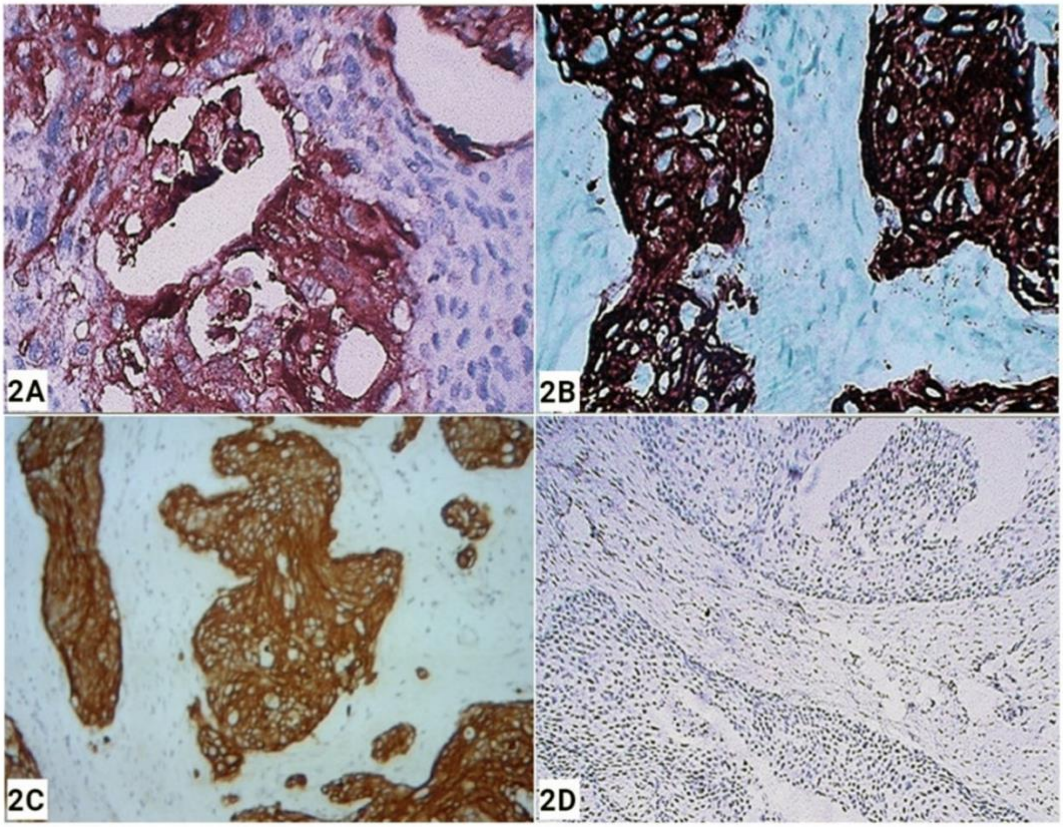

Figure 2. Immunohistochemistry **2A** CK5/6 (positive) **2B** CA 19-9 (positive) **2C** CK 7 (positive) **2D** CK20 (negative)

Discussion

It is hypothesized that squamous metaplasia of the pancreatic ductal epithelium following chronic inflammation plays an oncogenic role in the development of pancreatic SCC and a similar pathogenetic event may be involved in the development of SCC of ampulla (3). Reddy et al. proposed four possible mechanisms for the development of ampullary SCC (9). The first hypothesis is that SCC arises from pluripotent stem cells that can induce malignant transformation (9). Other hypotheses include squamous metaplasia of intestinal mucosa due to chronic inflammation caused by bile and pancreatic juice reflux, choledochal cyst and choledocholithiasis, malignant transformation of ectopic squamous epithelium and progression of adenocarcinoma to adenosquamous carcinoma and then to SCC (9).

According to the available demographic data, the mean age at diagnosis of ampullary SCC is 56 years (28–72 years), and the majority are females (83%) (9, 10). Almost all the patients presented with symptoms such as jaundice, abdominal pain and itching (9). Our patient had painless obstructive jaundice with deranged liver function tests. Some patients showed elevated serum CEA and CA19-9 levels (8). The clinical symptoms and signs are similar to that of ampullary adenocarcinoma and are not useful in differentiating the two (9). The demographic data, clinical features, the treatment offered and the outcomes of the 12 reported cases are summarized in Table 2.

Before making a confident diagnosis of primary SCC of the ampulla, it is important to exclude an adenosquamous carcinoma or a metastatic tumour from sites such as the larynx, oesophagus, lung, head and neck and uterine cervix in women (1,2,7). In this regard, sampling of the entire tumour and radiological

Author	Year	Age	Sex	Clinical features	Treatment given	Outcome
Walter J et al. (6)	1952	68	F	Obstructive jaundice and biliary colic	Surgery	Had lymph node metastases at diagnosis
Chen CM et al. (11)	1995	72	F	Obstructive jaundice and cholangitis	Surgery	Died due to disease
Singh DK et al. (5)	2008	30	F	Jaundice, pain and loss of appetite	Surgery	No metastases at the time of diagnosis
Gupta A et al. (12)	2009	28	F	Jaundice, abdominal pain and postprandial vomiting	Surgery	Not known
Sunose Y et al.* (13)	2011	73	F	General fatigue and jaundice	Surgery	Expired 13 months after surgery due to multiple bone and liver metastases
Pathak et al. (3)**	2011	50	F	Itching, jaundice and loss of appetite	Surgery	No recurrence after 8 months
Saleemuddin A et al. (4)	2012	36	M	Abdominal pain and pruritus	Surgery	Well postoperatively
Bolanki H et al. (8)	2014	68	M	Painless jaundice	Surgery	Liver metastases in 4 months Died in 5 months
Balci B et al. (14)	2016	54	F	Weight loss, jaundice and abdominal pain	Surgery + adjuvant chemotherapy	Not known
Reddy S et al. (9)	2016	65	F	Painless progressive jaundice, itching and loss of appetite	Surgery + adjuvant chemotherapy	No recurrence after 1 year
Sekhri R et al. (2)	2018	55	M	Jaundice and pruritus	Surgery + adjuvant chemotherapy	No recurrence after 6 months
Soni S et al. (1)	2021	38	F	Painless progressive jaundice, itching and melaena	Surgery + adjuvant chemotherapy	Asymptomatic one year after surgery

*with neuroendocrine and adenocarcinoma components
**with co-existent adenocarcinoma of pancreatic duct

Table 2. A summary of demographic data, clinical features, treatment offered and the outcomes of the previous 12 cases reported

and other investigations are important (7, 8). The tumour was totally sampled in our case and did not show an adenocarcinoma component, any neuroendocrine differentiation or squamous metaplasia. The radiology, including endoscopic studies, helped to exclude a primary SCC elsewhere in this patient.

Immunohistochemistry plays a supportive role in the diagnosis. This tumour showed strong positivity for CA 19-9, indicating a peri-ampullary origin in relation to the pancreas. It

was positive for CK7 and negative for CK20. This differs from the pattern seen in ampullary adenocarcinoma, which is usually CK20 positive with variably positive CK7 (11). There were no glandular areas in the entire tumour. Positivity for CK5/6 favoured an SCC. Only one of the reported cases mentioned CK7 expression. It was an SCC in the ampulla of Vater which showed CK7 negativity (2). Our case differs from this report and identifies the need to study the pattern of CK7 expression in ampullary SCC. The focal positivity for CK5/6 does not exclude an adenosquamous carcinoma on its own, but this tumour was examined morphologically in its entirety and there was no adenocarcinoma component. The diagnosis of SCC was thus made. Immunohistochemistry for p40 and p63 (if available) would further underscore the squamous origin.

Surgery is considered the mainstay of treatment for ampullary carcinomas (7, 8). Some authors have recommended multimodality treatment (9). Ampullary carcinomas treated by pancreaticoduodenectomy tend to have longer survival compared to pancreatic carcinoma (8). A single reported case was treated with percutaneous transhepatic biliary drainage combined with radiotherapy (9). The remainder were treated with surgery with or without adjuvant chemotherapy (1,2,10). However, due to the potential aggressive behaviour of ampullary SCC, it is believed that all patients should receive adjuvant chemotherapy (1). The role of chemo-radiotherapy in ampullary SCC is still debatable due to the limited data available (1).

Due to their rarity, the prognosis and the biological behaviour of this type of carcinoma are largely unknown (1). The 5-year survival rate of resected ampullary carcinoma is 45% (7). Evidence suggests that histological grade, histological type and tumour size play a less important role in predicting the outcome of ampullary carcinoma (7). In one reported case, the patient developed multiple liver metastases and died five months after surgery (1). Another died while receiving adjuvant radiotherapy (1). Three reported patients were alive with no recurrence for one year following adjuvant chemotherapy (1, 2). The other patients were free of disease progression at the time of reporting (1). Our patient also developed liver metastases and died eight months after surgery, underscoring the aggressive nature of this neoplasm. Saleemuddin et al. highlighted that further exploration of tumour histopathology and the molecular features may help to develop future medical therapies for ampullary SCC (4).

Conclusion

In conclusion, primary SCC of the ampulla is rare and likely to be aggressive. The possibility of adenosquamous carcinoma and metastasis from other sites should be excluded before making this diagnosis. A better understanding of the pathogenesis of this type of tumour may play an important role in planning the optimum treatment, prognostication and predicting the outcome.

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