Primary Ampullary Adenosquamous Carcinoma: Report of Two Cases

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Case Report: 
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Abstract: Introduction: Adenosquamous carcinoma of the ampulla of Vater is a rare neoplasm with its clinicopathological profile limited to a few case reports. Here we report clinical profile, morphology and outcome of two cases of this rare entity. Case report: Case 1 was a 57 year old male who presented with features of obstructive jaundice; Case 2 was a 55 year old female with complaints of pain abdomen. Imaging studies suggested a pre-emptive diagnosis if periaompillary malignancy for which both patients underwent Whipple’s pancreaticoduodenectomy. Histopathological examination revealed an ampullary malignancy with variable proportions of adenocarcinoma and squamous cell carcinoma. Case 2 also showed concurrent region lymph node metastasis. Case 1 was alive at 15months follow up with no recurrence/metastasis while case 2 survived for only 10 days post surgery. Conclusion: Adenosquamous carcinoma occurring at the ampulla of Vater is a rare event with less than 15 cases documented in the English literature so far. It is an aggressive tumour and is associated with a dismal prognosis. Here we add two more cases to the literature for better understanding of this rare neoplasm.

Key Words: Adenosquamous carcinoma. Ampullar of Vater, Pancreatocoduodenectomy, Periampullary malignancy, Perineural invasion

Introduction: 
Ampullary carcinomas constitute of around 10-20% of all malignancies in the periampillary region. Most of these cases are adenocarcinomas. Adenosquamous carcinoma (ASC) of the ampulla of Vater is an uncommon neoplasm constituting of about 1% of ampullary tumours [1]. ASC are characterised by presence of variable proportions of glandular and squamous elements. WHO classification of tumours of the digestive system characterises ASC as tumours with at least 25% squamous cell carcinoma component. ASC are documented in various other organ systems and are said to be aggressive neoplasms with a poor prognosis than their adenocarcinoma counterparts [2]. The clinicopathological profile of ampullary ASC is limited to a few case reports in the English literature. The following two cases add to the sparse literature for a better understanding of this rare neoplasm.

Case Report

Case 1: A 57 years old male presented with yellowish discolouration of sclera and palms since one month. He complained of intense itching and passing high coloured urine and clay coloured stools for 15 days and a significant loss of weight. Laboratory parameters revealed an elevated serum direct bilirubin (16.7 mg/dl), aspartate aminotransferase (121 IU/L) and alkaline phosphatase (313.0 IU/L) levels. Magnetic resonance imaging (MRI) of abdomen suggested a periampillary carcinoma followed by an endoscopy which revealed a bulky, irregular, ulcerated ampulla of Vater. A small biopsy was done which suggested a well differentiated adenocarcinoma on histopathology. Patient was undertaken for surgery and a Whipple’s pancreaticoduodenectomy with feeding jejunostomy was done. The gross examination of the excision specimen revealed an ulcer-infiltrative growth measuring 2.5x2x2cm, arising from the ampulla and infiltrating the head of pancreas. Histopathological examination confirmed an ulcerated and infiltrating tumour composed predominantly of nests, cords, and sheets of malignant squamous cells [Figure 1]. Adenocarcinoma component was seen as foci of glands and scattered signet ring cells with intracytoplasmic mucin, accounting for approximately 15% of the tumour [Figure 2]. The tumour was infiltrating the head of pancreas and sub mucosa of the duodenum; there were foci of lymphovascular invasion however all the resected lymph nodes were free of tumour. The
The patient was followed up for 1 year and is doing well after the closure of the feeding jejunostomy.

**Case 2**: A 55-year-old female presented with pain abdomen for 3 months. Careful review of the history revealed that the patient had similar complaints for 2 years. A past computed tomographic (CT) scan of the abdomen had revealed a peripancreatic mass causing obstructive jaundice following which she had undergone stent placement in common bile duct to relieve the jaundice. Laboratory investigations revealed a raised serum alkaline phosphatase (187 U/L), rest of the liver enzymes and bilirubin levels were within normal limits. The serum CA19-9 levels were raised (530 U/ml). A repeat CT scan revealed a growth surrounding the CBD stent with soft tissue overgrowth at the distal end simulating a distal cholangiocarcinoma, along with a pulmonary nodule (?metastasis) and multiple intra-abdominal lymph nodes. Patient was taken up for Whipple’s pancreaticoduodenectomy. Gross examination of the specimen revealed an ampullary growth measuring 3x1.5cm, infiltrating into the pancreas and duodenal wall [Figure 3]. Histopathological examination showed an infiltrating tumour composed of glandular component (approximately 10%) and malignant squamous element (approximately 90%) as sheets, singly scattered dyskeratotic cells and keratin pearls. Perineural invasion was seen by the tumour cells [Figure 4]. The squamous element showed positivity for p40 [Figure 5] while the adenocarcinoma element was negative. Tumour deposits were noted in the lymph nodes along the superior mesenteric artery. The patient succumbed to acute renal failure and sepsis following the surgery.

**Discussion**

The histogenesis of ASC is not clear, however the most acceptable prevailing hypotheses include; 1) tumour derived from the pluripotent stem cells which induce malignant change in both cell types, 2) tumour arising from the metaplastic change in intestinal mucosa, 3) adenocarcinoma with malignant metaplastic transformation, and 4) collision of adeno and squamous cell carcinoma [3]. The most acceptable belief is that of an adenocarcinoma undergoing a malignant metaplastic transformation. This was demonstrated by Hoshimoto et al [3], using immunohistochemistry to demonstrate the squamous and glandular differentiation, they outlined the elements and negated the bidirectional differentiation.
A review of the English literature revealed that there less than 15 cases of primary ASC of ampulla of Vater documented so far (Table 1), of which Yang et al [6] reported the largest series of 4 cases. The clinicopathological data from published literature suggests that ASC of ampulla of Vater is more common in elderly (median age of 68 years) males. Most of the patients presented with initial complaints of abdominal pain, jaundice and associated weight loss.

Of various surgical modalities available, pancreatectoduodenectomy and pylorus preserving pancreatectoduodenectomy are the most commonly used surgical approach, along with abdominal lymph node dissection [7,8]. Pancreatectoduodenectomy has significant morbidity associated with it in the form of pancreatic fistula, infections and anastomotic leaks. Ampullectomy is a less damaging procedure; however, its efficacy in the management of malignant tumours has not been established. Post resection nodal status is said to be an important prognostic factor [12]. Both the cases in the present study underwent Whipple’s pancreatectoduodenectomy.

Hoshimoto et al [3] in their review stated the mean size of the tumour as 26.8 mm and 50% cases with lymph node metastasis. In the present cases, the tumour size was 25 mm and 30mm respectively, in the greatest dimension and one case showed intra-abdominal lymph node tumour deposits. Microscopically, ASC are characterized by varying proportions of adenocarcinoma and squamous cell carcinoma. WHO Classification of tumours of the digestive tract gives a cut off of presence of at least 25% of squamous cell carcinoma element in the tumour for the diagnosis of ASC; however, even a minor glandular component in an otherwise squamous tumour is enough for the diagnosis. Extracellular and intracellular mucin (signet ring cells) can be seen [6,7]. In the present study both cases showed predominant squamous elements comprising around 85% (case1) and 90% (case2) of the tumour. IHC positivity for P63 and CK5/6 can be used to demonstrate the squamous differentiation in difficult cases, also it shows strong positivity for MUC1 [3,13]. Ampullary ASC exhibit frequent lymphatic and perineural invasion with local and distant lymph node metastasis detected concurrently or on follow up [6,7,9]. In the present cases, owing to the evident characteristic morphology of the aden and squamous elements IHC was not performed. Lymphovascular and perineural invasion was seen in both, however, only case 2 showed concurrent nodal tumour deposits.

Squamous cell carcinoma has an aggressive biological nature and a shorter doubling time than adenocarcinoma. The aggressive nature and poor survival rates seen in ampullary ASC was attributed to the squamous cell carcinoma component by Hoshimoto et al [3]. The median survival post-surgery in ampullary ASC is 8.5 months [3], but in the present cases, case 1 was alive without recurrence at 15 months of follow up, while case 2 succumbed within 10 days of surgery.

Conclusion
Here we add two more cases of ASC of ampulla of Vater to the existing literature. Ampullary ASC is a rare neoplasm and has a clinically aggressive course and poor survival than the conventional adenocarcinomas. The clinicopathological profile and survival rates are debatable owing to the sparse documentation of the cases, hence warrants larger studies to establish the diagnostic and prognostic indicators.

References

Table 1: Review of reported cases of primary adenosquamous carcinoma of ampulla of Vater along with the present cases.

<table>
<thead>
<tr>
<th>Study</th>
<th>Case</th>
<th>Age/sex</th>
<th>Management</th>
</tr>
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<tbody>
<tr>
<td>Ueno et al [1]</td>
<td>1</td>
<td>47/M</td>
<td>Pancreatectoduodenectomy</td>
</tr>
<tr>
<td>Ri et al [2]</td>
<td>2</td>
<td>62/F</td>
<td>Pylorus preserving pancreatectoduodenectomy</td>
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<tr>
<td>Lee et al [4]</td>
<td>3</td>
<td>48/M</td>
<td>Pylorus preserving pancreatectoduodenectomy</td>
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<tr>
<td></td>
<td>4</td>
<td>80/F</td>
<td>Pylorus preserving pancreatectoduodenectomy</td>
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<tr>
<td>Song et al [5]</td>
<td>5</td>
<td>76/M</td>
<td>Stenting</td>
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<tr>
<td>Yang et al [6]</td>
<td>6</td>
<td>82/M</td>
<td>Ampullectomy</td>
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<td></td>
<td>7</td>
<td>68/M</td>
<td>Pancreatectoduodenectomy</td>
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<td></td>
<td>8</td>
<td>34/F</td>
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<td></td>
<td>9</td>
<td>77/M</td>
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<td>Kshirsagar et al [7]</td>
<td>10</td>
<td>58/M</td>
<td>Pancreatectoduodenectomy</td>
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<tr>
<td>Patel et al [8]</td>
<td>11</td>
<td>45/F</td>
<td>Pancreatectoduodenectomy</td>
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<tr>
<td>Dekate et al [9]</td>
<td>12</td>
<td>77/F</td>
<td>Pancreatectoduodenectomy</td>
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<tr>
<td>Hoshimoto et al [3]</td>
<td>13</td>
<td>81/F</td>
<td>Pylorus preserving pancreatectoduodenectomy</td>
</tr>
<tr>
<td>Present cases</td>
<td>14</td>
<td>57/M</td>
<td>Pancreatectoduodenectomy</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>55/F</td>
<td>Pancreatectoduodenectomy</td>
</tr>
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</table>

Laboratory investigations show direct hyperbilirubinemia along with elevated serum alkaline phosphatase levels. Levels of tumour marker CA19-9 is also elevated as reported by Dekate et al [9], however no such finding was reported by Yang et al [6]. Kau S Y et al [10] outlined the prognostic role of serum levels of CA19-9 and affirmed it as an independent prognostic marker in both resectable and non resectable periampullary malignancies. Kurthara C et al [11] too backed the prognostic value of CA19-9; however they also deduced that the levels are not associated with a histologic type and hence the serum levels of CA19-9 and the histopathological subtypes are two independent survival predictors in malignancies of ampulla of Vater. In the present report both the cases had an elevated serum alkaline phosphatase and one had elevated serum CA19-9.

Imaging studies like CT and MRI have been employed to successfully detect the lesion and help in staging of the lesion however the prediction of histological subtype is difficult owing to absence of any specific features. ASC of ampulla of Vater usually presents as a soft tissue density in the scans [6]. ERCP is a useful investigation as it provides the real time image of the lesion. It also provides a means to stent the CBD, which relieves the symptoms and to take a small biopsy which could be used to confirm the diagnosis. The utility of small biopsies is limited by their high false negative rate owing to difficulty in obtaining a representative sample in cases of intra ampullary lesion and rare variants [12]. In the present cases, imaging studies had successfully detected the lesion, and a differential diagnosis of distal cholangiocarcinoma was also considered in case 2 owing to the overlapping radiological features. A small biopsy was done in case 1 which revealed only the adenocarcinoma component, a potential pitfall in the diagnosis of the rare subtypes on limited tissue sampling.


