Unique Case of Primary Squamous Cell Carcinoma of Ampulla of Vater with microsatellite instability and response to pembrolizumab immunotherapy

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Research Article

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Abstract

Background: Primary squamous cell carcinoma is a very rare entity and there are only 11 reported cases to date. We describe a case of primary SCC of the ampulla of Vater with microsatellite instability (MSI) and response to pembrolizumab immunotherapy. To the best of our knowledge, this is the first reported case of SCC of ampulla of Vater with MSI. We also performed a review of literature to determine the treatment modalities for this pathology.

Case presentation: A 40-year-old male presented with direct bilirubinemia (total bilirubin: 10.7, direct bilirubin: 7.1) and was noted to have a pancreatic head mass which measured 6.6 x 5.5 x 5.5 cm. The patient underwent a pylorus preserving pancreateoduodenectomy with lymph node dissection. Pathology showed 5.5 x 3.5 x 3.5 cm squamous cell carcinoma of ampulla of Vater based on positive p40 and CK5 on immunohistochemistry. It was noted to be invading pancreatic head and duodenal mucosal. Surgical margins were negative.

Adjuvant chemotherapy with mFOLFIRINOX (irinotecan, 5-fluorouracil, oxaliplatin) was not performed because of active Hepatitis C infection. Chemoradiotherapy with capecitabine and radiation therapy was initiated however patient had progression of disease despite that. The patient was transitioned to Pembrolizumab in context of MSI high tumour with palliative intent. He had an excellent response to immunotherapy. The therapy was stopped after 18 cycles on patient request because of persistent symptoms of dizziness and lethargy. At the eight-month follow-up after the last cycle of immunotherapy (2.5 years after surgical resection), the patient had no evidence of relapse on CT scan.

Conclusions: Surgical resection is mainstay of treatment for primary squamous cell carcinoma of ampulla of Vater. Genetic testing for mismatch repair (MMR) genes should be performed for all patients and immunotherapy with Pembrolizumab should be considered in tumours with high microsatellite instability. Radiotherapy is not effective for this pathology.

Background

Periampullary cancers are rare and account for 0.2% of gastrointestinal cancers. They originate from the ampullary complex which is distal to the confluence of the common bile and pancreatic duct [1]. Adenocarcinoma is the most common primary malignant tumor originating from ampulla of Vater. Pure squamous cell carcinoma (SCC) or adenosquamous cell carcinomas (ASCC) have also been reported in literature, however, they are exceedingly rare [2]. An extensive literature review revealed only 11 cases of primary SCC of the ampulla of Vater with the first case being reported in 1952 [3]. We describe a case of primary SCC of the ampulla of Vater with microsatellite instability (MSI) and response to pembrolizumab immunotherapy. To the best of our knowledge, this is the first reported case of SCC of ampulla of Vater with MSI.

Case Description
Our patient is a 40-year-old male with a past medical history of intravenous drug abuse who presented to the emergency department with a three-week history of pruritus and a one-week history of jaundice. Associated symptoms included decreased appetite, unintentional 20-to-25-pound weight loss, and worsening heartburn. Family history was significant for colon cancer (maternal first cousin) and gastroesophageal cancer (maternal great grandmother). On physical exam, he appeared jaundiced with scleral icterus. His abdominal exam was benign. Lab workup was remarkable for direct bilirubinemia (total bilirubin: 10.7 mg/dL, direct bilirubin: 7.1 mg/dL). Computerized tomography (CT) of the abdomen and pelvis with IV contrast scan showed a pancreatic head mass that measured 6.6 x 5.5 x 5.5 cm with common bile duct and intrahepatic biliary dilatation (Fig. 1). Skull base to mid-thigh positron emission tomography (PET) scan showed a pancreatic lesion with a standardized uptake value (SUV) of 21 with metastatic adenopathy in the precaval region. Esophagogastroduodenoscopy (EGD) demonstrated a large, ulcerated mass lesion in the second portion of the duodenum involving greater than 50% of the wall near the ampulla of Vater (Fig. 2). Endoscopic ultrasound (EUS) showed a 3.6 x 3.1 cm hypoechoic mass in the head of the pancreas with no evidence of hepatic metastasis (Fig. 3). Endoscopic retrograde cholangiopancreatography could not be performed due to obstruction of the major papilla, requiring placement of a percutaneous biliary drain for biliary decompression. Biopsies of the duodenal lesion and fine needle aspiration (FNA) of the pancreatic head mass were performed and both were interpreted as poorly differentiated adenocarcinoma based on morphology.

The patient underwent a pylorus preserving pancreatoduodenectomy with lymph node dissection. Pathology showed a 5.5 x 3.5 x 3.5 cm poorly differentiated carcinoma of the ampulla of Vater with pancreatic and duodenal invasion. Surgical margins were negative. Immunohistochemistry (IHC) of the specimen was positive for p40 and CK5 consistent with squamous cell carcinoma. The tumor was MSH2 and MSH6 deficient. Multiple specimen sections did not reveal adenocarcinoma. One out of 21 lymph nodes were found to be positive resulting in a carcinoma staging of T3bN1M0.

The patient was scheduled for adjuvant chemotherapy with a modified regimen of oxaliplatin, leucovorin, irinotecan, and fluorouracil (mFOLFIRINOX). Pre-chemotherapy lab workup was significant for active hepatitis C with viral titer of 539,000 logs/mL and therefore, chemotherapy was deferred due to high risk of hepatic failure. He was referred to a quaternary center for further discussions of chemotherapy. Two months post-operatively, surveillance CT scan was completed showing a 6 cm mass at the resection site (Fig. 4). PET imaging revealed a lesion with an SUV value of 19 without evidence of metastasis. CT guided biopsy was performed, and pathology was consistent with SCC proving that it was recurrence at resection site. The patient was offered mFOLRINOX therapy, as was recommended by the quaternary center, versus radiotherapy (XRT) with a reduced dose of capecitabine as a radiosensitizer. The patient chose to pursue chemoradiotherapy. During his third week of treatment, he was noted to have progression of disease with CT imaging showing enlarging adenopathy with a new right retroperitoneal metastatic implant (Fig. 5). Given the poor prognosis, the patient opted for palliative management and the total dose of XRT was reduced from 4500 cGy to 3060 cGy.
Following completion of XRT, the patient was started on pembrolizumab based on high MSI with goals of palliative care. Patient had excellent response to pembrolizumab and CT imaging after 6 cycles of immunotherapy showed reduction in adenopathy, but two new nodules were seen in the liver (Fig. 6). CT guided biopsy showed benign hepatic parenchyma with prominent steatosis. The patient received a total of 18 cycles of pembrolizumab with complete resolution of recurrent mass at resection size and adenopathy. Pembrolizumab was discontinued at the patient's request due to adverse symptoms of recurrent dizziness and lethargy following each treatment. At eight months post-immunotherapy and 2.5 years post-operative follow-up, the patient had no evidence of relapse on CT imaging.

**Discussion**

Periampullary cancers

The ampulla of Vater is comprised of four histologic epithelial types: ampullary, duodenal, pancreatic, and biliary [4]. Ampulla of Vater carcinoma is classified based on anatomic location and histology with tumors in this region being broadly classified as periampullary adenocarcinomas (PAAC). PAAC can be delineated anatomically as either ampullary, distal common bile duct, duodenal or pancreatic ductal carcinoma [5]. The two main histological subtypes of PAAC are pancreatobiliary and intestinal with these subtypes having different pathogenetic and clinical characteristics [6]. Intestinal ampullary carcinomas originate from the intestinal epithelium overlying the ampulla, whereas pancreaticobiliary ampullary carcinomas originate from the epithelium of the distal common bile duct and distal pancreatic duct [7]. Periampullary SCC are rare and hence not included in broad classification of periampullary cancers.

SCC of the ampulla of Vater

Primary SCC of the ampulla of Vater is a rare pathology with only 11 reported cases. SCC of the ampulla of Vater has also been reported secondary to metastasis with two reported cases secondary to metastasis from the larynx and esophagus [8]. SCC of the ampulla of Vater appears as a pancreatic head mass and no specific radiological features have been reported. Hence, radiographic differentiation of ampullary adenocarcinoma from SCC is not possible and the diagnosis is based on histology. In our case, the tumor was poorly differentiated and was diagnosed as adenocarcinoma using FNA and duodenal biopsy based on morphology. IHC of the surgical specimen was suggestive of high-grade SCC based on positive p40 and CK5 tumor markers. This was also observed in the case of SCC of ampulla reported by Soni et al. in which the carcinoma was diagnosed as adenocarcinoma on ERCP biopsy, however, it was noted to be SCC one the surgical specimen [9]. Our case suggests that morphological diagnosis can be inaccurate, and IHC should be used to differentiate adenocarcinoma from SCC.

Management of SCC of the ampulla of Vater

There is no standard management algorithm of primary SCC due to its rare presentation. Our literature review reveals that pancreaticoduodenectomy was performed in nine out of eleven reported cases of primary SCC of the ampulla of Vater [2, 8–15]. The decision for surgical resection in our case was based
on facts that initial biopsy and FNA was interpreted as adenocarcinoma and the tumor was resectable on staging imaging.

The role of chemotherapy for SCC of the ampulla of Vater is unclear. However, literature suggests that SCC of the biliary tract has lower survival rates when compared to adenocarcinomas and adenosquamous carcinoma [9]. Therefore, inferring from this evidence, primary SCC of the ampulla of Vater should be treated more aggressively than adenocarcinoma and adjuvant chemotherapy should be considered. Adjuvant chemotherapy was only given in three out of the 11 documented cases with the regimen being paclitaxel plus carboplatin in one [13] and gemcitabine plus carboplatin in the remaining two cases [9, 15]. The affect of chemotherapy on survival can not be determined due to small sample size and absence of data on long-term follow-up.

XRT for SCC of the ampulla of Vater has only been used in one case and the patient expired from an unrelated complication before the effectiveness of XRT could be measured [10]. XRT has been attempted for unresectable biliary SCC and there is no current evidence for the efficacy of XRT in these patients [16]. Our patient received a total XRT treatment of 3060 cGy over 17 fractioned doses with a reduced dose of capecitabine due to concern of hepatic failure. His disease progressed despite XRT, and our case suggests that radiotherapy is unlikely to be beneficial in ampullary SCC and should not be considered as alternative to surgical resection.

Additionally, this case was unique based on the presence of microsatellite instability. Silva et al. reported that DNA mismatch repair deficiency occurs in biliary carcinoma and high-level MSI (MSI-H) is present in 5% of gallbladder and extra-hepatic ductal carcinoma, and in 10% of intrahepatic cholangiocarcinoma and ampullary carcinomas [17]. Our case is the first to discuss MSI with primary SCC of the ampulla of Vater. Pembrolizumab has been FDA approved for the treatment of unresectable or metastatic carcinoma with high MSI that are refractory to prior treatment [18]. Our decision to pursue immunotherapy with pembrolizumab was based on the presence of MSI-H tumor and failure of primary treatment. Previously reported cases of SCC of the ampulla of Vater did not mention the MSI status of the tumor. As such, IHC should be used to determine MSI status of SCC of the ampulla of Vater allowing for the use of adjuvant immunotherapy in case of MSI-H tumor.

Published follow-up data after surgical resection ranges from five months to one year and the mean survival time is unknown. Our patient had post-operative follow-up at 2.5 years without evidence of disease recurrence. To the best of our knowledge, our case is the longest reported disease-free survival.

Conclusion

SCC of the ampulla of Vater is a rare entity. It lacks any characteristic radiologic features to distinguish it from adenocarcinoma and histological analysis is required for diagnosis. Morphology analysis alone may lead to misdiagnosis and IHC is essential for identification of correct carcinoma subtype. Current literature recommends surgical resection as mainstay of treatment. Due to few reported cases it is not possible to compare the behavior of primary SCC of ampulla of Vater to ampullary adenocarcinoma,
however literature has shown that SCC of hepatobiliary region is a more aggressive than adenocarcinoma. Inferring from this data, adjuvant chemotherapy should be considered for all patients with SCC of the ampulla of Vater. Moreover, our case suggests that XRT may not be beneficial for SCC of the ampulla of Vater and treatment using this modality should be carefully considered. Screening for MSI should be performed and immunotherapy with pembrolizumab should be considered in patients with MSI-H tumors. It can also be considered an alternative treatment option for unresectable SCC of ampulla of Vater with MSI-H status. This report discussed a rare clinical entity with few documented cases and an unclear treatment algorithm. It is our hope that this report may be used to further direct treatment for individuals diagnosed with primary SCC of the ampulla of Vater.

**Abbreviations**

ASCC  
Adenosquamous cell carcinomas  
CT  
Computerized tomography  
EGD  
Esophagogastroduodenoscopy  
EUS  
Endoscopic ultrasound  
FNA  
Fine needle aspiration  
IHC  
Immunohistochemistry  
mFOLFIRINOX  
Modified oxaliplatin, leucovorin, irinotecan, and fluorouracil  
MSI  
Microsatellite instability  
MSI-H  
High-level microsatellite instability  
PAAC  
Periampullary adenocarcinomas  
PET  
Positron emission tomography  
SCC  
Squamous cell carcinoma  
SUV  
Standardized uptake value  
XRT  
Radiotherapy
Declarations

Ethics approval and consent to participate: IRB at Wellspan York Hospital has determined this project does not meet the definition of human subject research and was classified as exempt.

Consent for publication: Informed consent was obtained from the patient for publication of case report.

Availability of data and materials: All data is available in medical records.

Competing interests: None

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Authors' contributions: MS drafted initial report. MA reviewed. JS reviewed and revised. DP and DJ were mentors and performed final revision.

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**Figures**
Figure 1

CT scan showing pancreatic head mass

Figure 2

EGD showing partially obstructing, ulcerated lesion at major papilla
Figure 3

Hypoechoic mass in the head of the pancreas measuring 3.6 x 3.1 cm

Figure 4

Recurrent carcinoma in bed of surgical resection
Figure 5

Enlarging adenopathy and new retroperitoneal metastatic implant.

Figure 6

CT scan showing one of two new liver nodules.