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

Primary squamous cell carcinoma of the ampulla of Vater 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 the ampulla of Vater with MSI.

Our patient is a 40-year-old male who presented with direct bilirubinemia (total bilirubin: 10.7, direct bilirubin: 7.1) and was noted to have a pancreatic head mass that measured 6.6 x 5.5 x 5.5 cm. The patient underwent a pylorus-preserving pancreatoduodenectomy with lymph node dissection. Pathology showed 5.5 x 3.5 x 3.5 cm squamous cell carcinoma of the ampulla of Vater based on positive p40 and CK5 on immunohistochemistry. It was noted to be invading the 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 the context of MSI high tumor with palliative intent. He had an excellent response to immunotherapy. The therapy was stopped after 18 cycles at patient's 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 the CT scan.

Introduction

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 adenosqaumous 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 Presentation

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. He had no abdominal tenderness, involuntary guarding or rebound tenderness. 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 encroaching the second portion of the duodenum that measured 6.6 x 5.5 x 5.5 cm with common bile duct and intrahepatic biliary dilatation (Figure 1). The was no involvement of superior mesenteric artery or celiac trunk. The tumor was abutting the portal vein with less than 180-degree involvement and no associated thrombosis. 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 the mass invading the second portion of the duodenum involving greater than 50% of the lumen at the ampulla of Vater (Figure 2). Endoscopic ultrasound (EUS) showed a 3.6 x 3.1 cm hypoechoic mass extending from the ampulla of Vater to the pancreatic head with no evidence of hepatic metastasis or peripancreatic lymphadenopathy (Figure 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. Immunohistochemistry could not be performed because of insufficient tissue specimen.

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. MSH2 and MSH6 were absent on IHC reflecting microsatellite instability. 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 started on 8-week course of Mavyret (Glecaprevir/Pibrentasvir) to treat Hepatitis C and referred to a quaternary center for further discussion of chemotherapy. They recommended modified FOLRININOX therapy (oxaliplatin, leucovorin and 5-Flourouracil for 6 month) and repeating CT scan of chest, abdomen, and pelvis to restage the disease before initiating the chemotherapy. The CT scan revealed a 6 cm mass at the resection site (Figure 4). PET imaging revealed a lesion with a 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 mFOLRININOX therapy, as was recommended by the quaternary center. However, the patient requested alternative options due to side effects of mFOLRININOX therapy. Therefore, he was offered radiotherapy (XRT) with a reduced dose of capecitabine as a radiosensitizer as well as Pembrolizumab therapy in setting of MSI tumor. Patient decided to pursue immunotherapy with pembrolizumab, however radiotherapy and low dose capecitabine was initiated while awaiting approval for Pembrolizumab

therapy. During the 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 (Figure 5). Given the poor prognosis, the patient opted for palliative management and the total dose of radiotherapy was reduced from 4500 cGy to 3060 cGy.

Following completion of radiotherapy, the patient was started on pembrolizumab based on MSI-H tumor 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 (Figure 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. SSC 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 carcnoma [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 effect of chemotherapy on survival cannot 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 immediate recurrence after surgical resection. Previously reported cases of SCC of the ampulla of Vater did not mention the MSI status of the tumor. As such, immunohistochemistry 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. Morphologic analysis alone may lead to misdiagnosis and immunohistochemistry 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 to primary adenocarcinoma of ampulla of Vater, 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: Adenosqaumous 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.

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References

[1] Ahn DH, Bekaii-Saab T. Ampullary cancer: An overview. Am Soc Clin Oncol Educ B 2014. https://doi.org/10.14694/edbook_am.2014.34.112.

[2] Bolanaki H, Giatromanolaki A, Sivridis E, Karayiannakis AJ. Primary squamous cell carcinoma of the ampulla of vater. J Pancreas 2014;15. https://doi.org/10.6092/1590-8577/1649.

[3] Puderbach WJ, Bellamy J. Squamous-cell carcinoma of the ampulla of Vater. Surgery 1952;32. https://doi.org/10.5555/uri:pii:0039606052903085.

[4] Georgescu SO, Neacsu CN, Vintilã D, Popa P, Florea N, Mihailovici MS. The histopathologic type of the periampullary tumors. Is it important for survival? Chir 2009;104.

[5] A. Hester C, Dogeas E, M. Augustine M, Mansour JC, Polanco PM, Porembka MR, et al. Incidence and comparative outcomes of periampullary cancer: A population-based analysis demonstrating improved outcomes and increased use of adjuvant therapy from 2004 to 2012. J Surg Oncol 2019;119. https://doi.org/10.1002/jso.25336.

[6] Perysinakis I, Margaris I, Kouraklis G. Ampullary cancer - A separate clinical entity? Histopathology 2014;64. https://doi.org/10.1111/his.12324.

[7] Pea A, Riva G, Bernasconi R, Sereni E, Lawlor RT, Scarpa A, et al. Ampulla of Vater carcinoma: Molecular landscape and clinical implications. World J Gastrointest Oncol 2018;10. https://doi.org/10.4251/wjgo.v10.i11.370.

[8] Pathak G, Deshmukh S, Yavalkar P, Ashturkar A. Coexistent ampullary squamous cell carcinoma with adenocarcinoma of the pancreatic duct. Saudi J Gastroenterol 2011;17. https://doi.org/10.4103/1319-3767.87184.

[9] Soni S, Elhence P, Varshney VK, Suman S. Primary squamous cell carcinoma of the ampulla of Vater: Management and review of the literature. BMJ Case Rep 2021;14. https://doi.org/10.1136/bcr-2020-236477.

[10] Chen CM, Wu CS, Tasi SL, Hung CF, Chen TC. Squamous cell carcinoma of the ampulla of Vater: a case report. Changgeng Yi Xue Za Zhi 1996;19.

[11] Marin-Padilla M, Dewan CH. Squamous-cell carcinoma of ampulla of Vater. Case report and review of the literature. Guthrie Clin Bull 1960;29.

[12] Balci B, Calik B, Karadeniz T, Sahin H, Ugurlu L, Aydin C. Primary squamous cell carcinoma of the ampulla of Vater: A case report. Surg Case Reports 2016;2:2. https://doi.org/10.1186/s40792-016-0130-0.

[13] Reddy S, Wani A. Multi-modality therapy for primary squamous cell carcinoma of the ampulla of vater - Report of a rare Case with Literature Review. J Pancreas 2016;17:679–82.

[14] Gupta A, Kumar K, T.S K, Gupta S, Makhija M, Singh B. Primary squamous cell carcinoma of the ampulla of Vater - A rare entity. Internet J Surg 2009;22:1–4.

[15] Sekhri R, Kamboj M, Gupta G, Sunil P. Primary squamous cell carcinoma of the ampulla. Indian J Pathol Microbiol 2018;61:300–2.

[16] Kang M, Chung DH, Cho HY, Park YH, Kim NR. Squamous cell carcinoma of the extrahepatic common hepatic duct. J Pathol Transl Med 2019;53. https://doi.org/10.4132/jptm.2018.09.03.

[17] Silva VWK, Askan G, Daniel TD, Lowery M, Klimstra DS, Abou-Alfa GK, et al. Biliary carcinomas: Pathology and the role of DNA mismatch repair deficiency. Chinese Clin Oncol 2016;5. https://doi.org/10.21037/cco.2016.10.04.

[18] Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res 2019;25. https://doi.org/10.1158/1078-0432.CCR-18-4070.

Figures

Figure 1

CT scan showing pancreatic head mass

Figure 2

EGD showing partially obstructing, ulcerated lesion at major papilla

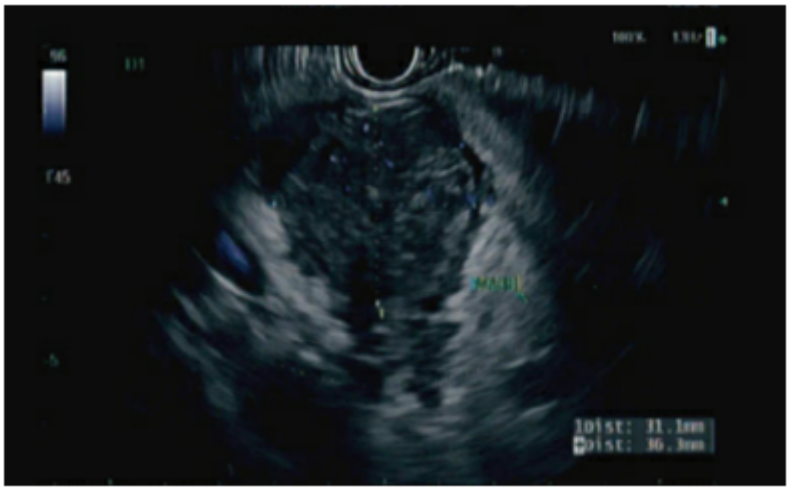

Figure 3

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

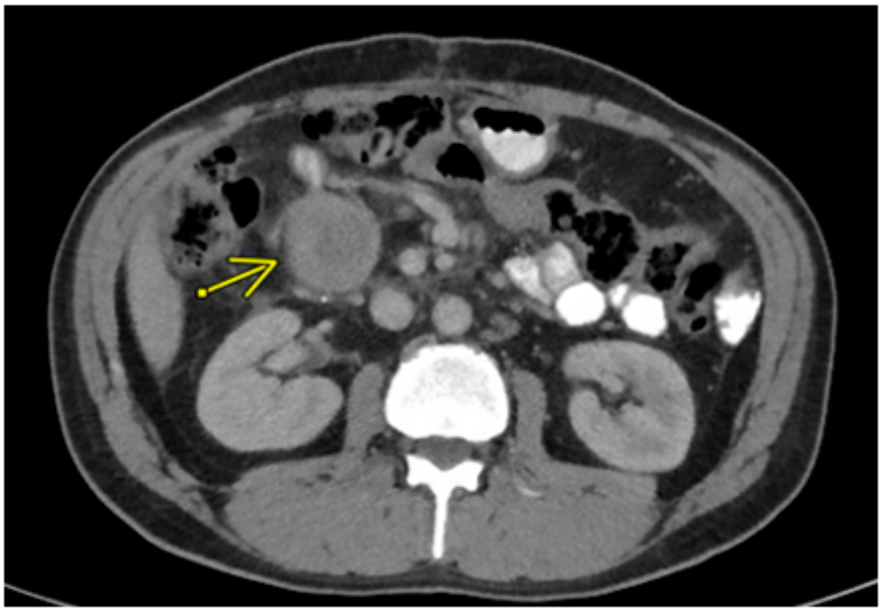

Figure 4

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.