



An Unusual Case of Biliary Obstruction Because of Human Papillomavirus–Associated Metastatic Squamous Cell Carcinoma From Head and Neck Primary

Maneera Chopra, MD¹, Dimpal Bhakta, MD², Songlin Zhang, MD, PhD³, and Tomas DaVee, MD, MSCI²

¹Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center, Houston, TX

²Interventional Gastroenterology at UTHealth, McGovern Medical School, The University of Texas Health Science Center, Houston, TX

³Department of Pathology and Laboratory Medicine, McGovern Medical School, The University of Texas Health Science Center, Houston, TX

ABSTRACT

Secondary pancreatic tumors are uncommon, with the majority originating from primary gastrointestinal or lung cancers. We present the case of a 42-year-old woman with squamous cell carcinoma of the pancreas, found to be human papillomavirus–positive on *in situ* hybridization. After extensive work-up, the patient was determined to have a previously undiagnosed, asymptomatic head and neck primary malignancy. There is sparse literature discussing metastatic human papillomavirus–positive squamous cell carcinoma to the pancreas. This report highlights the importance of including this diagnosis when considering a differential for secondary pancreatic tumors, especially squamous etiology.

INTRODUCTION

Human papillomavirus infection (HPV) is a risk factor in the development of squamous cell carcinoma of the cervix, genitalia, and oral cavity. HPV viral DNA multiplies rapidly after infecting epithelial cells and manifests as warts or papillomas in low-risk subtypes and neoplasia in high-risk subtypes.¹ The most common high-risk HPV subtypes predisposing to malignancy include HPV 16, 18, 31, 33, 35, and 45. A common biomarker used to distinguish HPV-related malignancies is p16, a tumor suppressor protein that is overexpressed in cancerous cells. Secondary/metastatic pancreatic tumors most often originate from epithelial lining, including lung and gastrointestinal primary tumors or renal cell carcinoma.² Although squamous cell carcinoma (SCC) can be present in many different organs, SCC of the pancreas is rare, with an incidence of 0.5%–5% of all pancreatic malignancies. Metastatic squamous cell carcinoma to the pancreas lacks glandular components and other features typical of adenocarcinomas, and most cases occur as metastases of gynecological or head and neck cancers. Pancreatic primary squamous cell carcinomas are usually associated with ductal obstruction and inflammation, which is not caused by HPV-related changes. Metastatic SCC of the pancreas presents similarly to pancreatic adenocarcinoma, with symptoms dependent on the anatomic location of the tumor(s). Presentations may include painless jaundice, abdominal pain, nausea, vomiting, or loose stools. Weight loss may be seen with advanced metastatic disease or pancreatic exocrine insufficiency. There is limited literature available regarding survival rates and treatment options for patients with metastatic SCC to the pancreas, likely because of the disease's aggressive nature. In this case report, we discuss a patient with pancreatic metastasis with pathological results indicative of HPV-positive squamous cell carcinoma secondary to a previously undiagnosed head and neck primary cancer.

CASE REPORT

A 42-year-old woman with a history of anemia presented with 5 months of epigastric pain radiating to the back. The patient reported decreased appetite with nausea and vomiting and a 30-pound unintentional weight loss. Her epigastric pain worsened in intensity over several weeks and was associated with darkened urine. She endorsed several weeks of constipation but denied pale-colored stools or steatorrhea. The patient had a family history significant for colorectal cancer in multiple family members. She denied a history of

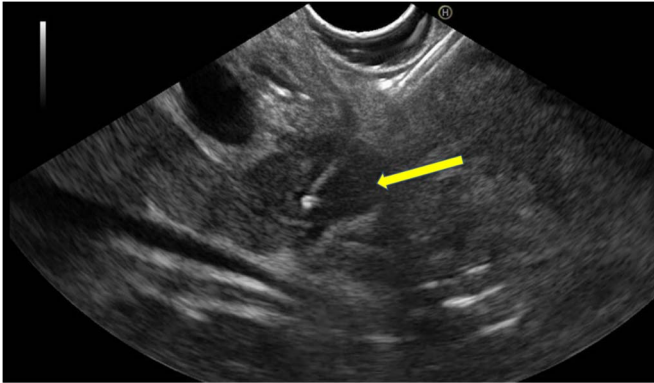


Figure 1. Endoscopic ultrasound–guided fine-needle biopsy of the pancreas mass. Yellow arrow points to positive uptake in the left supraclavicular lymph node.

smoking but reported alcohol use. Physical examination was notable for jaundice. Initial laboratory test results revealed hyperbilirubinemia and transaminasemia: total bilirubin 5.9 mg/dL, alkaline phosphatase 551 U/L, aspartate aminotransferase 703 U/L, and alanine aminotransferase 479 U/L. An initial right upper quadrant ultrasound was concerning for common bile duct (CBD) dilation to 12 mm and a distended gallbladder with stones. Magnetic resonance cholangiopancreatography was pursued and displayed intrahepatic and extrahepatic biliary ductal dilation secondary to obstruction by a stone or mass. Interventional Gastroenterology at UTHHealth was consulted for further management. Endoscopic ultrasound (EUS) identified a 35-mm mass of the head and uncinate process of the pancreas. The mass was deeply hypoechoic, well-defined, and appeared to obstruct the CBD (Figure 1). EUS-guided fine-needle biopsy (FNB) was performed with use of a core needle (SharkCore; Medtronic, Minneapolis, MN). Endoscopic retrograde cholangiopancreatography demonstrated the absence of contrast in the distal bile duct with upstream biliary dilation, consistent with a CBD stricture and obstruction by the pancreas mass (Figure 2). Subsequent, pancreatic protocol computed tomography (CT) confirmed the pancreas mass with extension along the axis of the celiac artery, superior mesenteric artery, and portal venous system (Figure 3). Positron emission tomography (PET)/CT scan showed increased tracer uptake of the cricoarytenoid, left supraclavicular lymph node, pancreatic mass, and retroperitoneal lymph nodes (Figure 4).

Interestingly, tissue acquired by EUS-FNB of the pancreatic mass identified squamous morphology, malignant cells diffusely positive for p40 and p16. HPV in situ hybridization study showed tumor cells were positive for high-risk HPV subtypes 16/18 (Figure 5). The tissue biopsy was CK7-negative.

Because of the pathology results showing high-risk HPV-positive tumor cells, there was a high suspicion for a gynecological or head and neck primary tumor. The patient had a history of a cervical conization in 2000 because of cervical dysplasia and was HPV-negative at the time; since then, her pap

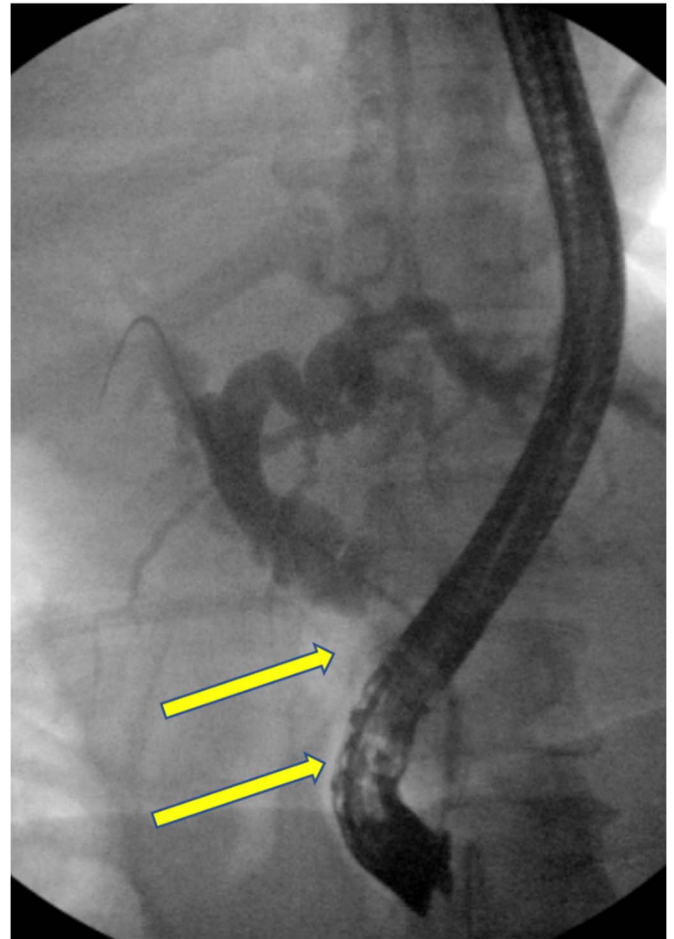


Figure 2. Endoscopic retrograde cholangiopancreatography showing the absence of contrast in distal bile duct consistent with obstruction by pancreas mass. Yellow arrow points to positive uptake in the left supraclavicular lymph node.

smears had been normal and HPV-negative. The patient's last normal pap was in July 2019. Colposcopy was performed in August 2019 without evidence of dysplasia or malignancy of the vulva, vagina, or cervix. The patient's PET/CT scan did not reveal a soft-tissue mass of the head and neck; however, there were several areas of increased tracer uptake in the regional lymph nodes of the neck and cricoarytenoid cartilage. The PET/



Figure 3. Coronal view of computed tomography pancreatic protocol showing a mass lesion in the pancreas.

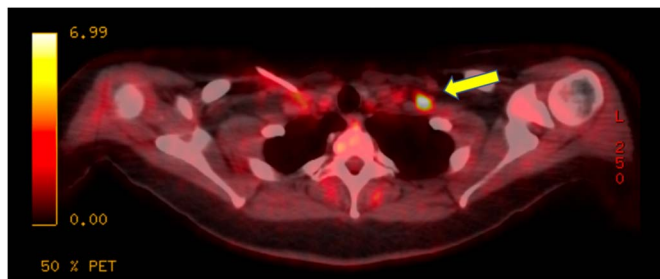


Figure 4. Positron emission computed tomography of supraclavicular lymph nodes.

CT scan showed extensive disease of the head and neck, chest, and abdomen but no avidity of the inguinal, pelvic, or obturator nodes, or anywhere in the female reproductive tract. The patient's CT scan of the head and neck and soft tissues of the neck showed no masses; however, the patient was noted to have prominent nasopharyngeal adenoid tissue and oropharyngeal tonsils. The primary tumor of HPV-positive squamous cell carcinoma from the head and neck may be occult by radio-tracer. As a result, it was concluded that the patient's pancreatic mass was metastatic SCC secondary to an eye, nose, throat (ENT) primary source. The patient was scheduled to follow-up with ENT and oncology for treatment with a platinum- or taxane-based chemotherapy regimen at the time of the initial study. She was subsequently lost to follow-up after 3 months.

DISCUSSION

This case illustrates the importance of thoroughly investigating additional primary tumor sources for metastatic squamous cell carcinoma of the pancreas. Most previously reported cases cite ovarian or lung primary tumors, and HPV-positive tumors were most often attributed to cervical or ovarian malignancy.³ Cervical cancer spreads in variable ways, including lymphatically, hematogenously, and by direct extension to the obturator, para-aortic, and pelvic or iliac lymph nodes. The patient had a history of cervical dysplasia, which initially seemed to be the most plausible primary tumor site. However, per tumor board discussion, a cervical source was ruled out as the patient had normal pap smears, a normal colposcopy, and a PET/CT scan without evidence of regional pelvic lymph node spread. In addition, tissue biopsy was negative for CK7, a phenotypic marker for genitourinary malignancies, which makes a primary gynecologic malignancy unlikely. The patient had multiple suspicious lesions of the head and neck on PET/CT. Despite lack of oropharyngeal symptoms, HPV-positive squamous cell carcinoma of the head and neck may present with neck mass or can be discovered incidentally. Metastatic squamous cell carcinoma of the head and neck is often occult, with up to 80% of these cancers eventually found to be HPV-positive.⁴ Finally, it is doubtful that the patient developed a primary HPV-positive squamous cell carcinoma of the pancreas with metastases because the pancreas normally lacks squamous cells, and this

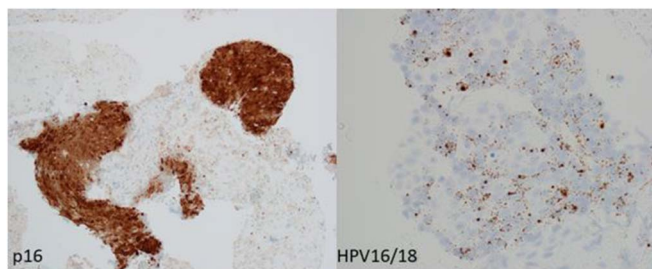


Figure 5. Immunohistochemical staining and in situ hybridization study. Pathology images of p16- and HPV 16/18-positive staining.

is a diagnosis of exclusion if no other primary tumor can be identified. Case reports of primary pancreatic squamous cell carcinomas have not shown head and neck metastases.

From a literature review, 3 case reports highlight squamous cell carcinoma of the head and neck region metastasizing to the pancreas. One case was a pancreatic cystic tumor, which was diagnosed by EUS-FNA as squamous cell carcinoma.³ A case series followed 4 patients with p16- and HPV 16/18-positive squamous cell carcinoma of the head and neck with 1 patient who had metastases to the pancreas, which was also found to be p16, but not HPV-positive.⁵ The third case reported basaloid squamous cell carcinoma originating from the maxillary sinus spreading to the pancreas.⁶ Interestingly, most cases of metastatic squamous cell to the pancreas describe cystic or mucinous lesions of the head of the pancreas on EUS. Our patient was found to have a large, infiltrating heterogenous mass on EUS, which may suggest a pattern to the appearance of these aggressive lesions. In addition, most cases of HPV-related squamous cell carcinoma with metastases to the pancreas also resulted in p16- or HPV 16/18-positive immunohistochemical staining. This finding raises a question as to whether this disease is preventable with the widely available HPV vaccination.

HPV-positive squamous cell carcinoma is generally highly treatable with chemoradiation therapy compared with non-HPV cancers and pancreatic adenocarcinomas. Although our patient was lost to follow-up, a chemotherapy regimen of cisplatin and taxotere would have likely been appropriate. Unfortunately, from most previous case reports, patients respond poorly to treatment and succumb to their disease around 30 months after diagnosis. Because of the rare occurrence and aggressive nature of this malignancy, studies are limited. In conclusion, our report underscores the importance of early identification of metastatic HPV-positive squamous cell pancreatic cancer and consideration of the head and neck as the tumor origin site.

DISCLOSURES

Author contributions: M. Chopra wrote the manuscript. D. Bhakta wrote the manuscript and revised the manuscript for intellectual content. S. Zhang revised the manuscript for

intellectual content. T. DaVee provided the images, revised the manuscript for intellectual content, and is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received October 3, 2020; Accepted March 30, 2021

REFERENCES

1. Hennessey PT, Westra WH, Califano JA. Human papillomavirus and head and neck squamous cell carcinoma. *J Dent Res*. 2009;88(4):300–6.
2. Adsay N, Andea A, Basturk O, Kilinc N, Nassar H, Cheng J. Secondary tumors of the pancreas: An analysis of a surgical and autopsy database and review of the literature. *Virchows Archiv*. 2004;444(6):527–35.
3. Glass R, Andrawes SA, Hamele-Bena D, Tong GX. Metastatic tonsillar squamous cell carcinoma masquerading as a pancreatic cystic tumor and diagnosed by EUS guided FNA. *Diagn Cytopathol*. 2017;45:1042–5.
4. Chernock RD, Lewis JS. Approach to metastatic carcinoma of unknown primary in the head and neck: Squamous cell carcinoma and beyond. *Head Neck Pathol*. 2015;9(1):6–15.
5. Müller S, Khuri FR, Kono SA, Beitler JJ, Shin DM, Saba NF. HPV positive squamous cell carcinoma of the oropharynx. Are we observing an unusual pattern of metastases? *Head Neck Pathol*. 2012;6(3):336–44.
6. Ozgursoy OB, Yorulmaz I, Tulunay O. Rapid and unusual spread of basaloid squamous cell carcinoma of the maxillary sinus. *B-ENT*. 2008;4(4):233–8.

Copyright: © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of The American College of Gastroenterology. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.