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Review

Adenosquamous Carcinoma of the Pancreas: A Review of a Rare Neoplasm

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ABSTRACT

Adenosquamous cell carcinoma of the pancreas (PASC) is a rare and aggressive exocrine pancreatic neoplasm. This review sought to investigate the current literature regarding PASC to determine clinical and pathologic factors of PASC compared to Pancreatic Ductal Adenocarcinoma (PDAC).

Keywords: *Adenosquamous carcinoma; Pancreatic cancer.*

INTRODUCTION

Pancreatic cancer is a leading cause of cancer morbidity and mortality in the United States. Currently, it is the 4th leading cause of cancer-related death in the United States with a 5-year survival rate of less than 5%.[1] With an incidence of 7.5 to 10 per 100,000 person-years, it is also the tenth most common cancer in North America.[1-3] Adenocarcinoma in particular accounts for approximately 90% of pancreatic malignancies.[4] Adenosquamous carcinoma (PASC) comprises 1-4% of exocrine pancreatic malignancies.[5] PASC has also been referred to as adenocanthoma, mixed squamous, and adenocarcinoma and mucoepidermoid carcinoma.[6] The term "*adenocancroid*" was first used by Herxheimer when describing this malignant entity in 1907.[7] According to the Armed Forces Institute of Pathology, pancreatic adenosquamous carcinoma is defined as a neoplasm of the pancreas that is comprised of at least 30% squamous cell carcinoma mixed with ductal adenocarcinoma.[8]

In comparison to pancreatic adenocarcinoma, PASC represents a rare, aggressive subtype with a worse overall prognosis. Both neoplasms, however, have similar clinical presentations consisting of abdominal pain, weight loss, anorexia, and jaundice.[5,9-11] Diagnostic imaging for PASC includes computed tomography, endoscopic ultrasound and Endoscopic Retrograde Cholangiopancreatography (ERCP), with recent studies suggesting that PASC can be differentiated from adenocarcinoma radiographically.[5,12] On CT imaging, PASC is often round and lobulated with areas of necrosis and associated tumor thrombus in the portal vein system.[13] When resected, PASC is frequently associated with positive lymph nodes, vascular and perineural invasion, and poor tumor cell differentiation.[14] A rare entity, information on PASC comes from small, single-institution and retrospective studies, with the largest study having 307 patients.[5-6, 9-11,14-16]

Previous studies have demonstrated a poor prognosis for patients with PASC. The reported overall median survival is less than six months, and for patients who do not undergo surgical resection, the median survival is even lower.[11,16] Surgical resection with or without adjuvant chemotherapy has been shown to improve median survival from less than six months to 10-20 months in some studies; in other studies, the mean survival following resection was less than 8 months.[5,9-11,17-20] Resection margin status was shown to have prognostic significance in one small study, however, the small sample size in all previous studies does not allow for adequate evaluation of prognostic factors.[16]

DISCUSSION

Diagnosis

Patient with PASC is more likely to present with poorly differentiated, large tumors and be lymph node-positive at diagnosis.[6,15] These tumors are most commonly located within the body or tail of the pancreas.[21]

The rarity of PASC has led to the majority of knowledge regarding this disease to be based on small retrospective studies, which often report conflicting information. Two studies, one by Katz et al. with 95 patients with PASC and another by Boyd et al. with 415 PASC patients, concluded that PASC patients presented with larger tumors were more likely to be lymph node-positive, and more likely to undergo survival resection than patients with PDAC were.[6,15] Katz et al. used the California Cancer Registry, and as this study, Boyd et al. used the SEER database. Katz et al. evaluated and compared patients with PASC and PDAC that underwent surgical resection to those that did not. Their results attempted to evaluate tumor resectability as well as results in patients with PASC or PDAC. They reported that among patients with locoregional disease, 61.9% of patients with PASC were resected, while only 35.6% of patients with PDAC underwent resection. Furthermore, overall surgery was more frequently used with PASC than PDAC with surgery being used in 32.6% of PASC and only 16.5% of PDAC.[15] The study concluded that the higher incidence of body and tail cancers in patients with adenosquamous carcinoma may partially explain the observed differences in resectability, and they theorized that since a distal pancreatectomy is technically easier, surgeons less experienced in pancreatic surgery may be more willing to attempt distal pancreatectomy than pancreaticoduodenectomy.[15] Another proposed factor was that in pancreatic tumors that are diagnosed by biopsy, an inadequate sample may make it difficult for the pathologist to identify the 30% squamous cells in the specimen required for diagnosis. This may lead to an underestimation of the prevalence of adenosquamous carcinoma, and consequently, an overestimation of the frequency of resection of adenosquamous carcinoma, as more unresected tumors are being classified as adenocarcinoma rather than adenosquamous carcinoma. As with this study, Boyd et al. acknowledged that the evaluation of resectability might be limited by the accuracy of the information in the SEER extent-of-disease codes. They selected criteria for unresectability to include vascular invasion and invasion of organs outside the resection field.

Prognosis

Boyd et al, Kardon et al, Voong et al, and Smoot et al, reported overall survival of 12.0 months, 11.3 months, 17.9 months, and 13.1 months after resection, respectively.[6,11,14,16] Okabayashi reported 25.5% and 14% 1- and 2-year survival rates, respectively, for patients with resected adenosquamous carcinoma.[10] These studies used populations ranging from 6 to 415 patients with adenosquamous carcinoma. Again, in the study of 415 patients with adenosquamous carcinoma by Boyd et al., overall survival was 4 months, while survival after surgical resection was 12 months and nearly identical to the results achieved by Katz et al., in his analysis of 95 patients with adenosquamous carcinoma. In a recent review of the National Cancer Database by Hester et al., the difference in the overall survival rate of pancreatic adenosquamous carcinoma and pancreatic adenocarcinoma was not significantly different when surgical and non-surgical patient populations were combined. However, worse overall survival was reported with stage I/II resected patients with adenosquamous carcinoma.[21]

Treatment

The role of chemotherapy in patients with PASC is an area of study in need of further exploration, as limited studies exist. One study demonstrated a modest improvement in survival from 11 to 20 months with the use of adjuvant chemotherapy after resection. Wild et al. sought to discover the efficacy of platinum chemotherapeutic agents as adjuvant treatment for pancreatic adenosquamous carcinoma. Platinum containing medications, such as cisplatin and oxaliplatin, when used in addition to gemcitabine- or 5-FU-based chemotherapy, demonstrated a significantly longer overall survival period in patients who had undergone resection when compared to patients who did not receive a platinum-based chemotherapeutic agent. Patients who received platinum adjuvant therapy had a median survival of 13.9 months, whereas patients who did not receive this therapy had a median survival of only 6.8 months.[22] The true impact of this study, however, is difficult to ascertain, due to the lack of standardization of chemotherapeutic dose and duration. Katz et al. demonstrated an improvement in survival with the use of palliative radiation and chemotherapy but did not demonstrate an improvement in survival with the use of adjuvant chemoradiation.[15] The use of chemotherapy alone and in combination with surgical and radiological treatments is unclear and in need of further research.

Molecular Research

A recently active area of study involves the genomic profiling and immunohistochemically staining of PASC tumors. Fang et al. conducted a genomic analysis of 17 pancreatic adenosquamous carcinomas and 34 pancreatic ductal adenocarcinomas. They found that, compared to PDAC, PASC harbored an increased number of TP53 gene mutations and 3p loss with a frequency of 88% compared to 65% in PDAC.[23] In addition, 100% of the PASC had mutations of KRAS. Furthermore, PASC and PADC contained similar mutations, particularly alterations of KRAS and TP53.[23] These similar changes in genome suggests that PASC and PDAC may both be derived from the same progenitor cancer cell.[23]

Molecular analysis of adenosquamous carcinoma of the pancreas by Jordan et al. also revealed the PASC often included mutations in TP53, CDKN2A, and SMAD4 genes. Proto-oncogene KRAS, in particular, was mutated at codon 12 in all 16 samples analyzed in this study.[24] Furthermore, Jordan, et al. also investigated the immunohistochemical differences between squamous cell carcinoma and glandular adenocarcinoma. They found that PASC and PDAC had different keratin expression with the squamous cell carcinoma reacting with anti-CK5/6 and adenocarcinoma reacting with anti-CK7.[23]

In addition, Jordan, et al. found that CA19-9 and pCEA, two common markers of adenocarcinoma, not only stained glandular components but also showed focal reactivity in squamous cell areas.[23] These findings were thought to be evidence of PASC and PDAC being different phenotypes evolving from one neoplastic proliferation rather than developing from two separate and distinct progenitor cells. While current research has been limited due to a small number of cases and availability of viable tissue samples, this is a growing field of scientific inquiry. Further advances in the identification of specific genetic mutations and biomarkers could lead to targeted pharmacologic therapy for this malignant entity.

SUMMARY

While both PASC and PDAC are likely to present with metastatic disease and have dismal outcomes, PASC appears to be more aggressive about disease severity. Patient with PASC are more likely to present with tumors of a larger size, poorer grade and have distant metastases than in patients with PDAC. PASC was also more likely to present in the pancreatic body or tail. Surgical resection is the single strongest predictor of survival in patients with both PASC and PDAC. Further

research regarding efficacious treatment and genomic profiling is necessary, as no standard therapy for this disease exists.

CONFLICTS OF INTEREST

We have no conflicts of interest with nobody and have nothing to declare.

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