Metastatic Adenosquamous Carcinoma Presenting As a Solitary Pancreatic Mass

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Case Report

A 36-year-old woman presented for evaluation of a pancreatic mass that had been discovered via computed tomography (CT). The patient had a 25-year history of ulcerative colitis (UC) complicated by primary sclerosing cholangitis. Significant medical history also included a total proctocolectomy performed 3 years earlier for treatment of a poorly differentiated adenocarcinoma (T1N0M0). Due to the presence of negative margins and the absence of lymphatic, venous, or perineural invasion, the patient had not undergone adjuvant chemotherapy.

The patient's current presentation was characterized by an insidious onset of epigastric pain that radiated to her back over the previous 3 months. On examination, left upper quadrant tenderness and epigastric fullness were noted without a palpable mass. CT revealed a large, bilobed, hypodense, infiltrating mass lesion in the neck of the pancreas and possibly 2 separate lesions measuring approximately 2.7 cm × 1.9 cm and 3.2 cm × 2.1 cm, respectively, that completely encased the superior mesenteric vein, left renal vein, and superior mesenteric artery (Figure 1). The patient's carcinoembryonic antigen level measured 7 ng/mL (normal, 0–3 ng/mL), and her CA 19-9 level measured 1,022 U/mL (normal, <37 U/mL). She was referred for endoscopic ultrasound (EUS) to obtain more definitive imaging and tissue diagnosis via EUS-guided fine-needle aspiration (FNA). EUS revealed multiple lymph nodes (up to 12 mm in size) in the peripancreatic space and 2 distinct lesions within the pancreas: a 30-mm heterogeneous mass in the pancreatic neck and a 35-mm hypoechoic mass within the body of the pancreas

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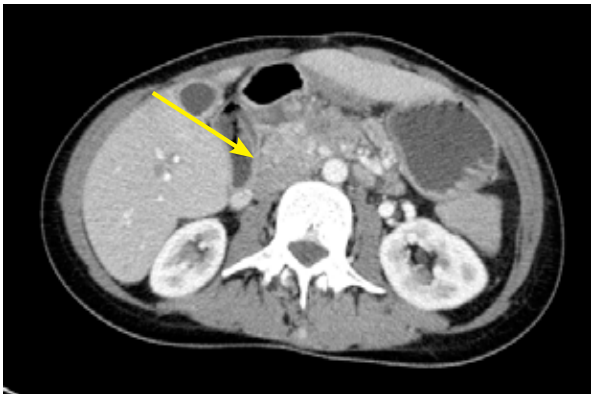

Figure 1. Enhanced axial computed tomography scan of a bilobed, hypodense, infiltrating mass lesion in the neck of the pancreas (yellow arrow). The lobes measured 2.7 cm × 1.9 cm and 3.2 cm × 2.1 cm, respectively.

(Figure 2). Direct smears prepared from FNA samples of the peripancreatic node revealed only normal lymphoid cells; surprisingly, samples of the body and the neck of the pancreas were positive for squamous-cell carcinoma (Figure 3). Combined fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT imaging demonstrated an intense FDG uptake corresponding to the pancreatic mass lesions (Figure 4). Metastasis to the retroperitoneal lymph nodes and the left supraclavicular node was suggested by moderate and intense FDG-avid activity, respectively. Repeat core biopsies of the pancreas revealed squamous-cell carcinoma with cytoplasmic keratinization and marked nuclear atypia (Figure 5). Immunohistochemical staining revealed that the tumor was strongly positive for CK5/6 and p16 but negative for CK7 and CK20. In situ hybridization testing for human papillomavirus was negative.

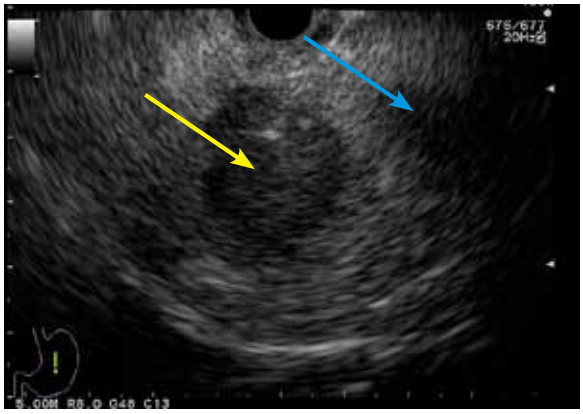

Figure 2. Linear endoscopic ultrasound image of a 30-mm heterogeneous mass in the pancreatic neck (yellow arrow) and a 35-mm hypoechoic mass within the body of the pancreas (blue arrow).

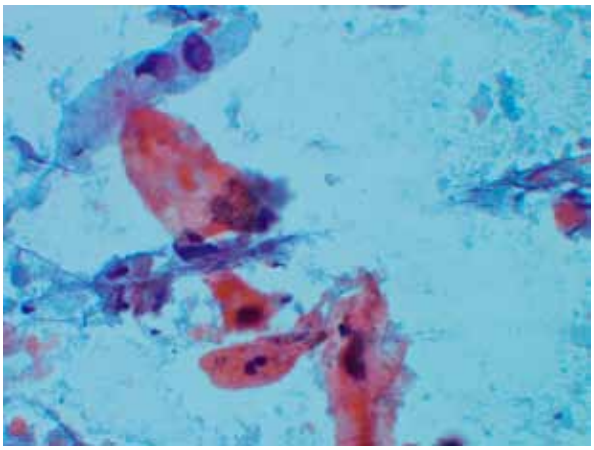

Figure 3. Fine-needle aspiration of a squamous-cell carcinoma in the body of the pancreas (Papanicolaou stain, 500× magnification).

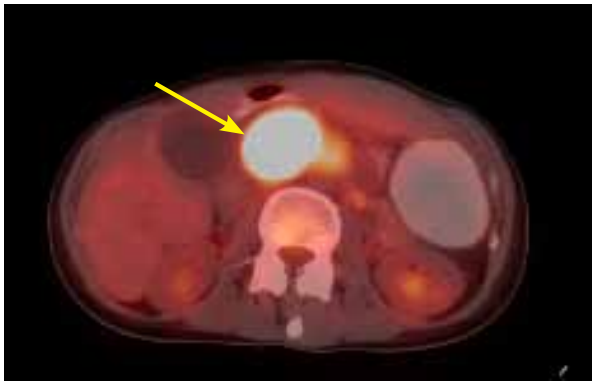

Figure 4. Combined fluoro-2-deoxy-D-glucose (FDG) positron emission tomography scan showing intense FDG uptake in the pancreatic mass (yellow arrow).

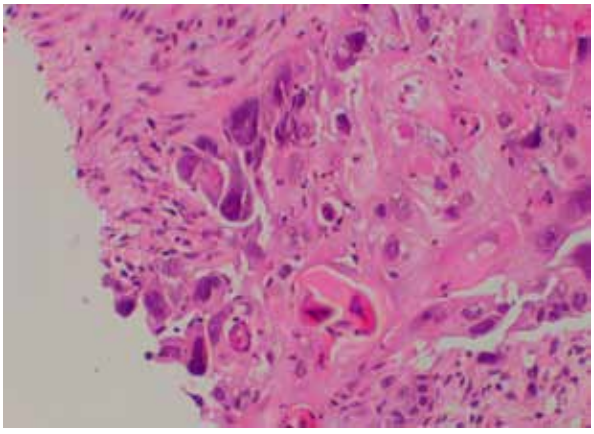

Figure 5. Core biopsies of the pancreas revealing squamous-cell carcinoma with cytoplasmic keratinization and marked nuclear atypia (hematoxylin and eosin stain, 250× magnification).

Due to the rarity of pancreatic squamous-cell carcinoma, slides from the patient's earlier total colectomy specimen were pulled and reviewed. Interestingly, foci within that tumor were suggestive of the squamous differentiation found in the pancreatic tumor (Figure 6). Additionally, the colonic malignancy was positive for p16 and negative for high-risk human papillomavirus. Given the low incidence of primary pancreatic squamous-cell carcinoma and the similar immunophenotype of the 2 tumors, the patient was thought to most likely have pancreatic metastasis from a primary colonic lesion, rather than a de novo lesion. At the time of this case report's submission, the patient had completed 2 cycles of palliative chemotherapy involving gemcitabine hydrochloride (Gemzar, Lilly), docetaxel (Taxotere, Sanofi Aventis), and capecitabine (Xeloda, Hoffmann La Roche), and her most recent CA 19-9 measurement was 29 U/mL.

Discussion

Primary pancreatic squamous-cell carcinoma is uncommon, with incidence rates ranging from 0.5% to 5%.[1] Statistically, the presence of pure squamous-cell carcinoma in the pancreas favors a metastatic lesion until proven otherwise; however, if abdominal carcinomatosis with secondary pancreatic involvement is appropriately excluded, a primary pancreatic neoplasm should be considered as a possibility.[1,2] In a retrospective review of 27 patients with metastatic lesions of the pancreas, Roland and associates found that epigastric pain was the most common presenting symptom that prompted diagnosis in 8 patients.[2] Although our patient

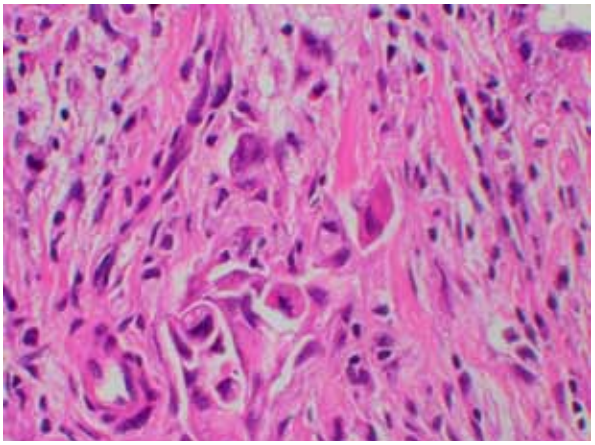

Figure 6. Squamous differentiation seen in the patient's colonic tumor (hematoxylin and eosin stain, 250× magnification).

also presented with epigastric pain, many patients with pancreatic metastases remain asymptomatic.[2,3] In many cases, metastatic lesions are discovered incidentally and are mistaken for primary pancreatic tumors on imaging, and appropriate endoscopic and tissue evaluation is required to rule out this possibility.[1,4]

A typical diagnostic approach for pancreatic lesions includes a contrast-enhanced abdominal CT scan, FNA of the pancreatic lesion under EUS or CT guidance, and, if indicated, either resection or palliative bypass.[3] Unfortunately, only 2% of pancreatic tumors that require operation are resectable, as patients typically present at an advanced stage.[3] The prognosis of metastatic disease to the pancreas is poor; the mean survival rate after diagnosis is 8.7 months.[3] Among the 27 patients with metastatic lesions of the pancreas who were reviewed by Roland and colleagues, 20 patients died within 1 year of diagnosis.[2] Ultimately, pancreatic metastasis is a preterminal event, and efforts for surgical care must be balanced against a limited life expectancy.[2]

The colon is one of the most common sites for primary tumors that are metastatic to the pancreas.[2] Although colorectal cancer (CRC) is the third most commonly diagnosed type of cancer and the second leading cause of cancer-related death in the United States, colorectal squamous-cell carcinoma and adenosquamous-cell carcinoma continue to be diagnostic rarities.[5,6] The infrequency of these tumors is further highlighted by the End Results Group, which found that combined pure squamous and mixed adenosquamous cancer accounted for 0.1% of the 60,193 CRC cases that were reviewed.[6,7] However, it should be noted that the relative incidence of colorectal squamous-cell carcinoma is higher in patients with UC (1.7%).[8,9]

Both pure squamous-cell carcinoma of the bowel and squamous elements in adenosquamous-cell carcinoma of the colon behave more aggressively than their glandular counterparts.[10] However, the mechanism that gives rise to either squamous or adenosquamous-cell carcinoma within the colon remains poorly understood to date. Nonetheless, several pathogenic theories have been proposed.[6] One theory suggests that uncommitted, or basal, cells proliferate in response to mucosal injury.[6,11] Proliferation may eventually lead to an adenosquamous, pure squamous, or mixed tumor.[11,12] Another theory proposes that squamous metaplasia of glandular epithelium may be the sequela of chronic inflammation.[6,9] Although not all case reports of these cancers have noted chronic irritation or inflammation, inflammatory changes may explain the relatively higher incidence of adenosquamous or squamous carcinomas in individuals with UC.[9,13]

Other researchers have proposed squamous differentiation of adenomas or adenocarcinomas as a cause of squamous-cell carcinoma. Williams and coworkers suggested that squamous differentiation may arise within adenomas; indeed, squamous differentiation with metastatic potential may be an explanation for our patient's disease.[14] Williams and associates have established diagnostic criteria for primary squamous-cell carcinoma of the colon, all of which were fulfilled in our case.[14] These criteria are: Metastasis from another site to the bowel must be ruled out; a squamous-lined fistulous tract must not involve the affected bowel, as this may be a source of squamous-cell carcinoma; squamous-cell carcinoma of the anus with proximal extension must be excluded; and squamous-cell carcinoma must be confirmed by histologic analysis.[14,15]

The rarity of colorectal squamous-cell carcinoma complicates the establishment of an accurate prognosis and increases the difficulty of treatment selection.[4,15,16] Copur and colleagues report that etoposide and 5-fluorouracil are an effective combination therapy in these patients.[17] Juturi and coworkers suggest that a combination of cisplatin, 5-fluorouracil, and leucovorin may be a possible treatment for patients with metastatic colorectal squamous-cell carcinoma.[16] Miyamoto and colleagues believe that surgical resection is a better first-line treatment approach for colorectal squamous-cell carcinoma.[15] Although the role of adjuvant chemotherapy or radiation remains unknown, adjuvant treatment may be considered if the patient has a good performance status.[15]

Both adenosquamous and squamous-cell carcinomas of the colon are uncommon.[5,6] Published reports suggest an increased incidence in patients with UC, as seen in this case study.[9] It is unclear from the limited available data whether inflammatory bowel disease is an etiologic factor in squamous-cell carcinoma of the colon.[13] In fact, Cheng and coworkers propose that the increased number

of squamous-cell carcinomas identified in patients with inflammatory bowel disease may be due to selection bias, as this group of patients undergoes surveillance colonoscopy more frequently than the general population.[13] Due to their rarity, adenosquamous-cell carcinoma and squamous-cell carcinoma of the colon, as well as squamous-cell carcinoma of the pancreas, remain enigmas. At present, any evidence-based conclusions regarding their etiology or treatment remain elusive, thus illustrating the need for further research.

References

1. Al-Shehri A, Silverman S, King KM. Squamous cell carcinoma of the pancreas. *Curr Oncol.* 2008;15:293-297.
2. Roland CF, van Heerden JA. Nonpancreatic primary tumors with metastasis to the pancreas. *Surg Gynecol Obstet.* 1989;168:345-347.
3. Liratzopoulos N, Efremidou EI, Papageorgiou MS, Romanidis K, Minopoulos GJ, Manolas KJ. Extrahepatic biliary obstruction due to a solitary pancreatic metastasis of squamous cell lung carcinoma. Case report. *J Gastrointestin Liver Dis.* 2006;15:73-75.
4. Moazzam N, Mir A, Potti A. Pancreatic metastasis and extrahepatic biliary obstruction in squamous cell lung carcinoma. *Med Oncol.* 2002;19:273-276.
5. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology*. 2008;134:1570-1595.
6. Landau D, Garrett C, Chodkiewicz C. A case of primary squamous cell colon cancer. *J Oncol Pharm Pract.* 2007;13:47-48.
7. Berg JW, Godwin JD 2nd. The epidemiologic pathology of carcinomas of the large bowel. *J Surg Oncol.* 1974;6:381-400.
8. Bargen JA, Gage RP. Carcinoma and ulcerative colitis: prognosis. *Gastroenterology*. 1960;39:385-393.
9. Michelassi F, Montag AG, Block GE. Adenosquamous-cell carcinoma in ulcerative colitis. Report of a case. *Dis Colon Rectum.* 1988;31:323-326.
10. Kontozoglou TE, Moyana TN. Adenosquamous carcinoma of the colon—an immunocytochemical and ultrastructural study. Report of two cases and review of the literature. *Dis Colon Rectum.* 1989;32:716-721.
11. Michelassi F, Mishlove LA, Stipa F, Block GE. Squamous-cell carcinoma of the colon. Experience at the University of Chicago, review of the literature, report of two cases. *Dis Colon Rectum.* 1988;31:228-235.
12. Vraux H, Kartheuser A, Haot J, et al. Primary squamous-cell carcinoma of the colon: a case report. *Acta Chir Belg.* 1994;94:318-320.
13. Cheng H, Sitrin MD, Satchidanand SK, Novak JM. Colonic squamous cell carcinoma in ulcerative colitis: report of a case and review of the literature. *Can J Gastroenterol.* 2007;21:47-50.
14. Williams GT, Blackshaw AJ, Morson BC. Squamous carcinoma of the colorectum and its genesis. *J Pathol.* 1979;129:139-147.
15. Miyamoto H, Nishioka M, Kurita N, et al. Squamous cell carcinoma of the descending colon: report of a case and literature review. *Case Rep Gastroenterol.* 2007;1:77-83.
16. Juturi JV, Francis B, Koontz PW, Wilkes JD. Squamous-cell carcinoma of the colon responsive to combination chemotherapy: report of two cases and review of the literature. *Dis Colon Rectum.* 1999;42:102-109.
17. Copur S, Ledakis P, Novinski D, et al. Squamous cell carcinoma of the colon with an elevated serum squamous cell carcinoma antigen responding to combination chemotherapy. *Clin Colorectal Cancer.* 2001;1:55-58.

Review

One More Piece of the Puzzle? Adenosquamous Carcinoma in a Pancreatic Mass

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Adebajo and colleagues present a rare case of what appears to be a pancreatic metastasis from a primary adenosquamous carcinoma of the colon and, in doing so, provide a piece of the puzzle that is gastrointestinal tract adenosquamous carcinoma.[1] Interestingly, the pancreatic mass—which was diagnosed via fine-needle aspiration on endoscopic ultrasound as well as a subsequent core biopsy—developed in a patient who had long-standing ulcerative colitis and in whom a T1N0M0 colonic adenocarcinoma had been removed 3 years earlier via total proctocolectomy. The pancreatic tumor was unresectable, but it responded to palliative chemotherapy consisting of gemcitabine hydrochloride (Gemzar, Lilly), docetaxel (Taxotere, Sanofi Aventis), and capecitabine (Xeloda, Hoffmann La Roche).

The case study's reference section provides a broad sampling of articles on these rare tumors. Based on the cited literature, as well as tumor marker studies performed on the index patient, Adebajo and associates conclude that the pancreatic mass and clinically positive lymph nodes were metastatic from the previous, albeit early-stage, primary colorectal cancer.[1] Several pieces of evidence support this conclusion: the proportionately high incidence of colorectal cancer as a source of pancreatic metastasis, the rarity of primary pancreatic squamous-cell cancer, the clinical finding of immunohistochemical similarities between the pancreatic and colonic tumors, and the retrospective identification of foci of squamous differentiation in the colonic tumor.[2,3] However, in colorectal cancer, squamous and adenosquamous histologies are also quite uncommon, with a reported incidence of 0.1% in over 60,000 cases.[4] Fewer than 100 squamous and adenosquamous colorectal cancers have been reported in the literature.[5]

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In the largest series of pancreatic adenosquamous carcinomas to date, microscopic evaluation of Armed Forces Institute of Pathology (AFIP) specimens uniformly demonstrated dual differentiation toward adenocarcinoma and squamous-cell carcinoma, and all of the specimens were immunoreactive with keratin CK1 and AE1:AE3.[6] Other keratin markers in the AFIP series were variably expressed, including CK5/6 (88%) and CK20 (26%). In the case report by Adebajo and coworkers, immunohistochemical staining of the patient's tumor was strongly positive for CK5/6 but negative for CK7 and CK20.[1]

Adebajo and colleagues provided a brief but concise summary of the known pathophysiologic hypotheses for the development of gastrointestinal squamous and adenosquamous tumors.[1] These theories include the proliferation of uncommitted, or basal, cells in response to mucosal injury, as well as squamous metaplasia of glandular epithelium as a sequela of chronic inflammation. A further hypothesis was that squamous differentiation may arise within adenomas, based on the observation of squamous differentiation in a small number of benign colonic adenomatous polyps.[7]

The report by Adebajo and colleagues provides an important addition to the literature surrounding these rare tumors, as well as to the reporting of immunohistochemical and serum-based tumor markers.[1] Of particular interest is p16 (CDKN2A)-positive staining of the primary and presumed metastatic tumor, as well as the initially high level of serum CA 19-9, which returned to normal after chemotherapy. Re-analysis of the original T1N0M0 colonic tumor showed foci with features of squamous differentiation and immunohistochemical positivity for p16 (CDKN2A), a cell-cycle checkpoint protein that binds to cyclin-dependent kinases, resulting in cell-cycle arrest at the G1/S checkpoint.[8]

In keeping with the favorable response to chemotherapy noted in the report by Adebajo and associates, a recent meta-analysis showed a somewhat tenuous, but favorable, prognostic significance for p16 in pancreatic tumors that is consistent with its tumor suppressor function; however, the authors of the meta-analysis were quick to point out that the small number of eligible studies precludes any meaningful conclusions regarding p16 expression as a reliable marker of prognosis.[1,9] Conversely, in a more robust database of 902 colorectal cancers from 2 independent cohort studies, p16 (CDKN2A) promoter hypermethylation was present in only 30% of tumors. Unlike the data available for pancreatic tumors, and despite p16's well-established role in carcinogenesis, p16 (CDKN2A) staining in colorectal cancer was not independently associated with patient prognosis.[10]

In addition to the data on p16, data on CA 19-9 are interesting. None of the articles cited by Adebajo and coworkers discussed CA 19-9.[1] In the previously mentioned AFIP series, immunohistochemistry was positive for CA 19-9 in 89% of cases; however, serum CA 19-9 data were not present. It was noted that the aggressive behavior of adenosquamous carcinoma observed in the AFIP study was analogous to that of anaplastic carcinoma, leading the authors to hypothesize that these 2 entities are related and represent different degrees of ductal adenocarcinoma differentiation.[6] Another observation relevant to the report by Adebajo and associates is the conclusion made by the AFIP study authors; after noting that some pathologists require that 30% of a specimen contain cellular elements, the AFIP study authors concluded that primary tumors of the pancreas that show any degree of definitive, malignant, squamous-cell differentiation on routine sectioning should be considered adenosquamous carcinoma.[1,6] By such a definition, presumably the pancreatic tumor in the report by Adebajo and associates would be considered adenosquamous, but the colonic tumor would not.[1]

Although the report by Adebajo and coworkers focuses on the question of whether the pancreatic tumor arose de novo from the pancreas or was metastatic from a T1M0N0 primary colonic tumor, there is, of course, a third possibility: a biliary-tract primary tumor.[1] Elevated preoperative serum CA 19-9 levels have been associated with a high risk of recurrence after curative resection of biliary-tract cancer.[11] The recurrence rate was significantly higher when the baseline CA 19-9 serum level was at least 55 U/mL (hazard ratio, 3.282; 95% confidence interval, 1.684–6.395; $P<.001$).[11]

Finally, the role of chronic inflammation and the development of adenosquamous tumors should be discussed. As noted by Adebajo and colleagues, the incidence of squamous and adenosquamous tumors was 0.1% in a large series of colorectal tumors; in patients with preexisting ulcerative colitis, the incidence increased to 9.5%.[1,12] The progression of squamous metaplasia to squamous-cell carcinoma has been documented in the setting of ulcerative colitis.[13] In the setting of chronic pancreatitis, squamous metaplasia of the pancreatic ductal epithelium is noted in adjacent ducts in 4% of adenocarcinomas.[14] Unlike anal cancer, there appears to be no association between human papillomavirus infection and squamous-cell carcinoma of the colon and upper rectum (>8 cm above the dentate line).[15]

In summary, the report by Adebajo and colleagues raises more questions than it answers, as should all such case reports.[1] From what organ and cell lineage did the tumor in question arise? What is the role of preexisting chronic inflammation? Are either p16 or CA 19-9 pathogenetic? Is there a prognostic significance to any of the studied tumor markers? Does the organ of origin make a difference in determining treatment? It is fair to conclude

that Adebajo and colleagues have not provided any definitive answers; however, they have contributed one more important piece of the puzzle.[1]

References

1. Adebajo CO, Dye CE, Abendroth CS, Moyer MT. Metastatic adenosquamous carcinoma presenting as a solitary pancreatic mass. *Gastroenterol Hepatol (N Y).* 2011;7:627-630.
2. Roland CF, van Heerden JA. Nonpancreatic primary tumors with metastasis to the pancreas. *Surg Gynecol Obstet.* 1989;168:345-347.
3. Al-Shehri A, Silverman S, King KM. Squamous cell carcinoma of the pancreas. *Curr Oncol.* 2008;15:293-297.
4. Berg JW, Godwin JD 2nd. The epidemiologic pathology of carcinomas of the large bowel. *J Surg Oncol.* 1974;6:381-400.
5. Landau D, Garrett C, Chodkiewicz C. A case of primary squamous cell colon cancer. *J Oncol Pharm Pract.* 2007;13:47-48.
6. Kardon DE, Thompson LD, Przygodzki RM, Heffess CS. Adenosquamous carcinoma of the pancreas: a clinicopathologic series of 25 cases. *Mod Pathol.* 2001;14:443-451.
7. Williams GT, Blackshaw AJ, Morson BC. Squamous carcinoma of the colorectum and its genesis. *J Pathol.* 1979;129:139-147.
8. Schutte M, Hruban RH, Geradts J, et al. Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. *Cancer Res.* 1997;57:3126-3130.
9. Smith RA, Tang J, Tudur-Smith C, Neoptolemos JP, Ghaneh P. Meta-analysis of immunohistochemical prognostic markers in resected pancreatic cancer. *Br J Cancer.* 2011;104:1440-1451.
10. Shima K, Nosho K, Baba Y, et al. Prognostic significance of CDKN2A (p16) promoter methylation and loss of expression in 902 colorectal cancers: cohort study and literature review. *Int J Cancer.* 2011;128:1080-1094.
11. Chung MJ, Lee KJ, Bang S, et al. Preoperative serum CA 19-9 level as a predictive factor for recurrence after curative resection in biliary tract cancer. *Ann Surg Oncol.* 2011;18:1651-1656.
12. Michelassi F, Mishlove LA, Stipa F, Block GE. Squamous-cell carcinoma of the colon. Experience at the University of Chicago, review of the literature, report of two cases. *Dis Colon Rectum.* 1988;31:228-235.
13. Cheng H, Sitrin MD, Satchidanand SK, Novak JM. Colonic squamous cell carcinoma in ulcerative colitis: report of a case and review of the literature. *Can J Gastroenterol.* 2007;21:47-50.
14. Chen J, Baithun SI, Ramsay MA. Histogenesis of pancreatic carcinomas: a study based on 248 cases. *J Pathol.* 1985;146:65-76.
15. Frizelle FA, Hobday KS, Batts KP, Nelson H. Adenosquamous and squamous carcinoma of the colon and upper rectum: a clinical and histopathologic study. *Dis Colon Rectum.* 2001;44:341-346.