Adenosquamous Carcinoma of the Pancreas

James A. Madura, MD; Benjamin T. Jarman; Michael G. Doherty; Moo-Nahm Yum, MD; Thomas J. Howard, MD

Hypothesis: Adenosquamous carcinoma of the pancreas is a rare but particularly virulent variant of invasive ductal carcinoma. This review will demonstrate the aggressive biologic activity, histopathologic features, and DNA flow cytometric characteristics of this aggressive lesion. In addition, the outcome is less favorable than in other pancreatic neoplasms, in spite of aggressive surgical and postoperative adjuvant therapy.

Design: A retrospective review of 6 patients treated during an 8-year period.

Setting: A major urban university tertiary referral hospital.

Patients: There were 6 patients with this unusual tumor seen between 1990 and 1998. There were 4 men and 2 women, all white, with a mean ± SD age of 63.5 ± 14.7 years. Symptoms were similar to those in patients with more common pancreatic malignant neoplasms.

Results: Four patients with tumors in the head of the pancreas had pancreatoduodenectomy, and 2 with body and or tail lesions had distal pancreatectomy and splenectomy. Pathologically, all the tumors were poorly differentiated and aneuploid, and 5 of the 6 were locally metastatic. All but 1 patient had postoperative complications, but there were no operative deaths. One half of the patients received postoperative adjuvant chemotherapy and radiation therapy. Only 1 patient is still alive at 9 months after surgery, but has known residual cancer around his portal vein noted during palliative distal pancreatectomy.

Conclusions: Adenosquamous carcinoma of the pancreas is an uncommon variant of exocrine pancreatic neoplasm. It is characterized by an admixture of adenomatous and squamous cell elements and demonstrates aggressive biologic behavior. This series of 6 patients is similar to the 134 cases reported since 1907, in that survival is short despite aggressive surgical therapy. Few patients with this disease live more than 1 year. Aggressive therapy should be tempered by the realization of the uniform poor prognosis associated with this malignant neoplasm.

Arch Surg. 1999;134:599-603

INVASCIVE DUCTAL carcinoma accounts for the majority of pancreatic malignant neoplasms and has a poor prognosis with the exception of a series of highly selected patients undergoing radical surgical therapy for cure. Adenosquamous carcinoma of the pancreas is an unusual variant of pancreatic neoplasm. It has been variously referred to as adenoacanthoma, mixed squamous and adenocarcinoma, and mucoepidermoid carcinoma. These tumors are histologically characterized by adenomatous cell populations mixed with varying amounts of keratinized squamous cell elements. Major institutional reviews of autopsy and/or surgical specimens suggest an incidence of approximately 4% of all pancreatic neoplasms; however, only 134 cases have been reported in the accessible world's literature. Most of the reports have been small series or single case reports, and, of the large autopsy or surgical tissue reviews, only a few reports detail clinical, histopathologic, and patient outcome data. Survival times have been short in those patients found to have unresectable tumors, as well as in those who have undergone aggressive resection for attempted cure. The prognosis of this uncommon lesion appears to be even less favorable than the invasive ductal tumor, with only a few patients surviving more than 1 year. Because of its rarity, only anecdotal studies of adjunctive radiation or chemotherapy are available.

This series of 6 cases over an 8-year period demonstrates the aggressiveness of this tumor, and its rapid course from discovery to death, despite aggressive surgical treatment.
RESULTS

There were no postoperative deaths, but 5 of the 6 patients had postoperative complications, including 3 with ventilator dependence and 2 with pancreatic fistulas that responded to nonoperative management. Postoperatively, survival was short, with a mean ± SD survival of 5.04 ± 3.58 months. Three of the patients died of their malignancy at 1, 3, and 5 months postoperatively. One patient with a large tumor invading the duodenum presented with upper gastrointestinal tract bleeding and anemia. Physical findings included upper abdominal tenderness in 4 patients, jaundice in 2 patients with tumors in the head of the pancreas, and a palpable abdominal mass in 1 patient. Laboratory studies were unremarkable with the exception of elevated bilirubin and alkaline phosphatase levels in the 2 patients with jaundice and moderately elevated serum carbohydrate antigen 19-9 (Ca 19-9) of 200 U/mL (reference value, ≤70 U/mL) in 1 patient. Computed tomography and endoscopic ultrasound both accurately demonstrated and localized a pancreatic mass in all 6 patients (Figure 1). Endoscopic retrograde cholangiopancreatography was performed in 5 patients and demonstrated pancreatic ductal obstruction by tumor in the head or body, which corresponded with the tumor location on the imaging studies (Figure 2). Three patients had preoperative fine-needle aspiration biopsy of the tumor mass but none of the specimens were diagnostic of adenosquamous carcinoma. All 3 of the patients with tumors in the head of the pancreas underwent pancreatectoduodenectomy, and those with tumors in the body and/or tail of the pancreas were treated by distal pancreatectomy and splenectomy.

PATIENTS AND METHODS

Between 1990 and 1998, six patients were diagnosed as having adenosquamous carcinoma of the pancreas and treated at the Indiana University Medical Center Hospitals, Indianapolis. There were 4 men and 2 women, all white, whose mean ± SD age was 63.5 ± 14.7 years. The duration of symptoms prior to presentation was 4.3 ± 3.9 months, and symptoms included abdominal pain and weight loss in 5 of the 6 patients, nausea and vomiting in 3 patients, and anorexia and jaundice in 2 patients. A single patient with a large tumor invading the duodenum presented with upper gastrointestinal tract bleeding and anemia. Physical findings included upper abdominal tenderness in 4 patients, jaundice in 2 patients with tumors in the head of the pancreas, and a palpable abdominal mass in 1 patient. Laboratory studies were unremarkable with the exception of elevated bilirubin and alkaline phosphatase levels in the 2 patients with jaundice and moderately elevated serum carbohydrate antigen 19-9 (Ca 19-9) of 200 U/mL (reference value, ≤70 U/mL) in 1 patient. Computed tomography and endoscopic ultrasound both accurately demonstrated and localized a pancreatic mass in all 6 patients (Figure 1). Endoscopic retrograde cholangiopancreatography was performed in 5 patients and demonstrated pancreatic ductal obstruction by tumor in the head or body, which corresponded with the tumor location on the imaging studies (Figure 2). Three patients had preoperative fine-needle aspiration biopsy of the tumor mass but none of the specimens were diagnostic of adenosquamous carcinoma. All 3 of the patients with tumors in the head of the pancreas underwent pancreatectoduodenectomy, and those with tumors in the body and/or tail of the pancreas were treated by distal pancreatectomy and splenectomy.

Figure 1. Computed tomographic scan of a patient with large adenosquamous carcinoma of the mid-body of the pancreas.

Figure 2. The endoscopic retrograde cholangiopancreatogram of the patient in Figure 1, demonstrating pancreatic ductal cutoff in the mid-body of the pancreas.

Figure 3. Histologic sections showing the adenosquamous carcinoma. A, Low-power view showing the mixture of ductal and squamous cell components. B, Higher magnification showing the glandular component with large vesicular nuclei and prominent nucleoli. C, Higher magnification showing the squamous component with hyperchromatic nuclei and eosinophilic cytoplasm.

Histologically, the tumors all displayed a mixture of ductal adenocarcinoma and squamous cell carcinoma, with the latter comprising more than 30% of the lesion. In a single case, the squamous cell component exceeded the glandular component by a 9:1 ratio. The adenocarcinoma consisted of ductlike structures lined by columnar cells having large vesicular nuclei and prominent nucleoli. Most of these cells had pale to clear cytoplasm with occasional mucin vacuoles. The malignant squamous cells were large and polygonal, having large hyperchromatic nuclei and eosinophilic cytoplasm with intercellular bridges and occasional squamous pearls. They were arranged in diffuse sheets and lobules. These squamous and glandular components were for the most part intimately admixed (Figure 3). The tumors elicited a desmoplastic response, which accounted for the firmness appreciated on gross examination. Peripancreatic fat and neural invasion was present in all 6 cases. Lymphatic invasion was noted in 4 cases and the duodenal wall was invaded by tumor in 3 of the 4 tumors located in the head of the pancreas. Lymph node metastases were found in 5 of the 6 patients. DNA flow
cytometry demonstrated aneuploidy in 5 patients with
S-phase determination between 5.2% and 30.0% (Table 1).

## COMMENT

Exocrine tumors of the pancreas have been classified his-
tologically in several large institutional reviews. The
majority of cases are recognized as invasive ductal carci-
nomas. Other recognized variants include the mucin-
ous tumors; pleomorphic, anaplastic, and large cell types;
acinar cell carcinoma; spindle cell tumors; microadeno-
carcinomas; and oncocytic cancers. Adenosquamous and
squamous cell carcinomas are recognized much less fre-
quently and probably account for 1% to 4% of all re-
ported tumors.

The first known report of adenosquamous carcino-
oma in the literature is credited to Herxheimer in 1907 in
which he referred to this lesion as “cancroide.” Subse-
quently, other authors have referred to this tumor of
mixed columnar adenocarcinoma and keratin-
containing squamous cell elements as mixed squamous
and adenocarcinoma, mucoepidermoid carcinoma, and
adenoacanthoma. This admixed tumor has been seen
more commonly in other organ systems, such as the
lungs, esophagus, colon, stomach, salivary glands, and
the female reproductive organs. Several reports describe
pancreatic tumors with a more unicellular squamous
appearance without the glandular component. Most
pure squamous lesions of the pancreas are thought to
represent metastatic disease, and it is suggested that in
the absence of another primary lesion the squamous
pancreatic lesion will usually be found to have a gland-
ular component with more careful histological inspec-
tion. Since the pancreas does not normally contain
any squamous cell elements, it has been proposed that
squamous metaplasia occurs as a result of ductal
inflammation due to chronic pancreatitis or obstruction
by an adenomatous tumor. Currently, there are several
theories, none well proven, of the origin of the adeno-
squamous tumor. The most favored theory is that of
squamous metaplasia occurring as a result of obstruc-
tion and inflammation and differentiating into a malig-
nant form. The “collision theory” suggests that 2 his-
tologically different tumors arise independently and
join or coalesce. No reports have proven this transition
phenomenon, but rather have demonstrated squamous
cell components intermingled in the body of the pre-
dominantly adenocarcinoma. Electron microscopy has
demonstrated 2 clearly different cell types. The adeno-
carcinoma cell demonstrates abundant endoplasmic
reticulum and well-developed Golgi apparatus and
secretory vesicles. The other cell has scant amounts of
endoplasmic reticulum but prominent bundles of tono-
filaments, similar to cells seen in other squamous cell
tumors. A final theory is that of malignant differentia-
tion by a pluripotential duct cell into the 2 histological
types. This theory has received support by an immu-
nocytocchemical study demonstrating positive stains for
Ca 19-9, ST 439, and keratin in varying degrees in both
the squamous and adenomatous cells. There is a
report demonstrating carcinoma in situ in squamous
metaplasia. In addition, there is a single report of an
adenosquamous tumor focus in an equally unusual mucin-
cystic neoplasm.

The incidence of this unusual lesion is really not
known, but estimates from review and classification of
pancreatic tumors from autopsy and/or surgically re-
sected specimens have been demonstrated to be approxi-
mately 4% (Table 2). Of the reported series, the incidence
ranges from 0.9% to 11.1%, but this latter estimate
was from a series of 27 surgical specimens. A number
of reports suggest that many of these lesions are large and
inoperable; therefore, analysis limited to surgical cases
may not be totally indicative of the true incidence since
many of these patients have not undergone subsequent
surgery or autopsy.

A comprehensive review of 31 available reports be-
tween 1907 and 1997 identified 134 patients with aden-
osquamous tumors (Table 3). From those re-
ports with detailed clinical data, there were 69 men and
45 women, a ratio of 1.53:1. The mean age of these
patients was 62.4 ± 11.7 years, with a range of 33 to 86 years.
The major symptoms were no different than those of the
usual invasive ductal lesions of the pancreas, and in-
cluded abdominal and back pain, weight loss, anorexia,
and jaundice in patients with lesions in the head of the

### Table 1. Histopathological Characteristics and Flow Cytometric Data in 6 Patients With Adenosquamous Carcinoma of the Pancreas

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Tumor Size, cm</th>
<th>Nodes, Positive/Total</th>
<th>DNA Cytometry</th>
<th>S-Phase, %</th>
<th>DNA Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.0 x 0.8 x 0.3</td>
<td>0/15</td>
<td>Aneuploid</td>
<td>30</td>
<td>1.45</td>
</tr>
<tr>
<td>2</td>
<td>4.6</td>
<td>1/1</td>
<td>Diploid</td>
<td>15</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>5.0 x 2.5 x 1.7</td>
<td>1/3</td>
<td>Aneuploid</td>
<td>15</td>
<td>1.74</td>
</tr>
<tr>
<td>4</td>
<td>6.0</td>
<td>3/5</td>
<td>Aneuploid</td>
<td>20</td>
<td>1.52</td>
</tr>
<tr>
<td>5</td>
<td>6.5 x 5.0 x 3.0</td>
<td>2/2</td>
<td>Aneuploid</td>
<td>13</td>
<td>1.86</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>6/9</td>
<td>Aneuploid</td>
<td>6</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*All tumors were poorly differentiated.*
pancreas. Tumor location was in the head of the pancreas in 31 patients, head and body in 4, body in 7, body and tail in 6, and tail in 8. It was diffuse in 4.

Whether or not surgical resection was attempted, survival was short, averaging 5.7 ± 4.1 months in 72 patients for whom survival data were available. Few studies report tumor marker data or flow cytometry results, but the present series provides evidence that these lesions are poorly differentiated, metastatic, and have aneuploid DNA characteristics. Because of the small numbers of reported cases, only anecdotal reports of adjunctive therapy are available and none of the therapies seem to prolong survival in this aggressive lesion.20

Accurate preoperative diagnosis of this lesion is difficult. There are no characteristics on imaging studies to differentiate it from the more common exocrine neoplasms of the pancreas. A recent report by Kuhl et al21 suggests that these lesions may selectively take up gallium 67 and be visualized by nuclear scanning. In several recent case reports, preoperative percutaneous and intraoperative cytologic studies have been diagnostically correct, but this did not alter treatment decisions or survival.22-23

Once these lesions are identified, with or without accurate preoperative or intraoperative cytologic diagnosis, the question arises as to the extent of treatment. Since survival appears to be uniformly poor, should aggressive resection be undertaken, even if it appears potentially curative at the time of operation? From the review of the literature, there are only 5 known patients who have survived 1 year or longer, in contrast to reported series of highly selected patients with invasive ductal carcinomas in whom 5-year survival rates of 20% to 30% have been reported. In addition, mean survival with or without resection is less than 6 months in the present series, as well as those accumulated cases in the literature. One has to consider the risk and complications of major resective surgery in light of this rather short postoperative survival. If these lesions are small and there is no intraoperative evidence of nodal or distant metastasis, should these patients be denied an attempt at curative resection? Since pancreaticoduodenectomy and distal pancreatectomy can currently be done with acceptably low morbidity and mortality, these procedures are probably the best palliative procedures available. In the near future, more effective chemotherapy combined with radiation may allow better survival with an acceptable quality of life.

Presented at the 106th Scientific Session of the Western Surgical Association, Indianapolis, Ind, November 18, 1998.

Reprints: James A. Madura, MD, Department of Surgery, Indiana University School of Medicine, 545 Barnhill Dr, EM 244, Indianapolis, IN 46202-5125.

REFERENCES


Table 2. Incidence of Adenosquamous Carcinoma in Major Retrospective Autopsy and Surgical Studies

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Specimens</th>
<th>No. (%) of Adenosquamous Carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Autopsy</td>
<td>Surgical</td>
</tr>
<tr>
<td>Halpert et al, 1965</td>
<td>120 0</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Cihak et al, 1972</td>
<td>90 0</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Baylor and Berg, 1973</td>
<td>5075 0</td>
<td>46 (0.9)</td>
</tr>
<tr>
<td>Kissane, 1975</td>
<td>225 0</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Cubilla and Fitzgerald, 1980</td>
<td>525 120</td>
<td>20 (3.1)</td>
</tr>
<tr>
<td>Ishikawa et al, 1980</td>
<td>0 27</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Morohoshi et al, 1983</td>
<td>167 97</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Chen and Baithun, 1985</td>
<td>275 116</td>
<td>13 (3.4)</td>
</tr>
<tr>
<td>Motojima et al, 1992</td>
<td>145 57</td>
<td>6 (3.0)</td>
</tr>
</tbody>
</table>

Table 3. Details of Reported Patients With Adenosquamous Carcinoma of the Pancreas

<table>
<thead>
<tr>
<th>Literature Review</th>
<th>Present Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of reported patients, 1907-1997</td>
<td>134 8</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>69:45 42</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>62.4 ± 11.7 63.5 ± 14.7</td>
</tr>
<tr>
<td>Location in pancreas, No.</td>
<td>Head 31 4</td>
</tr>
<tr>
<td></td>
<td>Head and body 4 0</td>
</tr>
<tr>
<td></td>
<td>Body 7 0</td>
</tr>
<tr>
<td></td>
<td>Body and tail 8 2</td>
</tr>
<tr>
<td></td>
<td>Tail 5 0</td>
</tr>
<tr>
<td></td>
<td>Diffuse 4 0</td>
</tr>
<tr>
<td>Survival, mo</td>
<td>5.7 ± 4.1 5.0 ± 3.6</td>
</tr>
<tr>
<td>Range</td>
<td>0.06-18 1.03-12.03</td>
</tr>
</tbody>
</table>

* Not all reports contained complete data about each patient.
Gerard V. Aranha, MD, Maywood, Ill: Dr Madura has presented us with 6 cases of adenosquamous carcinoma of the pancreas, a very rare variant of the usual adenocarcinoma. There were 4 patients with head lesions and 2 with lesions in the body; all were resected, but none survived more than 12 months, suggesting also a poorer prognosis than patients with adenocarcinoma. The pathology evaluation revealed that 5 of the 6 patients had peripancreatic or perineural invasion as well as lymph node metastasis and that 5 of the 6 had aneuploid tumors, all harbinger of poor prognosis. As far as theories go, there are many, but the one that makes the most sense is the one that you first alluded to—the one that says that there may be squamous metaplasia in an adenocarcinoma that leads to 2 pathologic entities in one tumor.

In your lymph node metastasis, which of the elements metastasized, was it the glandular type or the squamous type? Can you conjecture why the prognosis was so bad in these patients? Is it possible that squamous metaplasia occurs more often in adenocarcinoma and that we do not find it because we do not search enough for it? The incidence of this tumor you said was 4%, but in a Japanese study, it was 11%. If this variant occurs more, should we be reconsidering our adjuvant therapy? Our therapy now is geared toward adenocarcinoma. Should we be changing the chemotherapy or combining it with something geared toward squamous, let’s say, platinum-based therapy?

You talked about ERCP (endoscopic retrograde cholangiopancreatography). If you had these patients first and you saw a CT scan clearly showing you a mass, would you put them through an ERCP?

Finally, one other question about biopsy. Because you saw 6 cases of this variant with bad prognosis, are you going to change your philosophy? I suspect you are like me and do not do a biopsy preoperatively or intraoperatively. Would you change your philosophy based on these 6 patients?

Dr Madura: Dr Aranha, your first question was about the cellular pattern of the lymph node metastases. We reviewed all of the lymph nodes in the 3 patients with metastases. Three of these patients had mixed adenocarcinoma and squamous cell carcinoma in the nodes, while 2 patients, interestingly, had only squamous cell elements. We also evaluated the pancreatic lesions for the total content of each of the 2 specific cell types and found that 5 of the patients had 30% squamous cell cancer in their tumor, while 1 patient had more than 90% squamous cells in his tumor. You asked whether these patients should be treated with a chemotherapeutic regimen more suited for the squamous cell element. Unfortunately, these lesions are very unusual, and there are no series of patients treated with such an approach. Our sole survivor at this point has known residual disease but has survived nearly 9 months and he has been treated with gemcitabine and irradiation. I am not sure of this agent’s efficacy with squamous cell tumors, but it does have some advantage in adenocarcinomas. I think your concept may be correct and in the future, we might change our adjuvant therapeutic approach.

You asked if we had diagnosed any of these lesions ahead of time, and, with the exception of those patients arriving with previous biopsy, we do not attempt a preoperative aspiration nor do we do any tissue sampling in the operating room. If the lesion looks amenable to removal on preoperative assessment and in the operating room, we go ahead with the resection. One of these patients gave us no choice since her tumor had eroded into the duodenum and was bleeding. I do not think that a diagnosis of adenosquamous carcinoma preoperatively would change our approach. It would give us an opportunity to inform the patient and their family about the prognosis, and perhaps allow us to stimulate our oncologic colleagues to consider a different postoperative regimen.