

CASE REPORT

Long-Term Survival in a Patient with Acinar Cell Carcinoma of Pancreas. A Case Report and Review of Literature

Monique Antoine^{1,2}, Marina Khitrik-Palchuk², Muhammad Wasif Saif²

¹Yale Cancer Center, Yale University School of Medicine. New Haven, CT, USA.

²Griffin Hospital. Derby, CT, USA

ABSTRACT

Context Acinar cell carcinoma of the pancreas is a rare malignancy that may have acinar and endocrine differentiation. Clinical practice guidelines exist for pancreatic ductal adenocarcinoma. However, treatment protocols for acinar cell carcinoma of the pancreas have not been standardized.

Case report We describe a case of a 44-year-old woman presenting with low grade fever and mid-abdominal tenderness secondary to a pancreatic mass with acinar and endocrine differentiation metastatic to the liver. The patient received multiple lines of conventional and investigational chemotherapy regimens. This included cycles of gemcitabine, irinotecan, oxaliplatin, docetaxel, capecitabine, octreotide, leucovorin, 5-fluorouracil, cisplatin, protein kinase C inhibitor, tyrosine kinase inhibitor, and a novel taxane. The patient developed *Clostridium difficile* colitis and septic shock resulting in death 37 months after the diagnosis of acinar cell carcinoma of the pancreas.

Conclusion This is a case of acinar cell carcinoma of the pancreas with an endocrine component, treated with multiple chemotherapeutic agents, in which the patient survived 37 months after diagnosis.

INTRODUCTION

The pancreas is composed predominantly of acinar cells. However, acinar cell carcinomas

comprise only 1-2% of exocrine pancreatic neoplasms [1, 2]. Acinar cell carcinoma occurs more frequently in men with a peak incidence at age seventy [3]. Patients present with vague clinical symptoms unless the tumor is associated with increased lipase levels [4]. Treatment protocols are lacking for this rare acinar cell malignancy. We report a young female patient with fever and an abnormal abdominal examination as the initial presentation of acinar cell carcinoma of the pancreas. After treatment with multiple chemotherapy regimens, this patient survived 37 months after the initial diagnosis.

CASE REPORT

A 44-year-old woman with no significant past medical history presented in June 2003 with low grade fever and mid-abdominal tenderness. A computed tomography (CT) scan of the abdomen was performed which revealed a large lesion in the left upper quadrant consistent with a pancreatic mass (4.8 cm) as well as synchronous hepatic metastasis (the largest being 3.2 cm). Fine needle aspiration of the lesion in the left upper quadrant of the abdomen revealed carcinoma with ninety percent acinar and ten percent endocrine differentiation, consistent with pancreatic origin. An FNA of the liver further confirmed carcinoma with endocrine and acinar differentiation compatible with pancreatic origin. This was similar to the prior specimen. Both the abdominal and liver lesions were immunohistochemically positive for trypsin, chromogranin A, chymotrypsin

and synaptophysin. Low-power microscopy of the tissue revealed solid, uniform sheets of cells with a monotonous appearance. At higher power, an abundant pink, eosinophilic cytoplasm, with granules was visible. The nuclei were not highly pleomorphic. This appearance was characteristic of acinar cell carcinoma. The diagnosis was confirmed by diastase periodic acid-Schiff (d-PAS) staining, which highlighted the cytoplasmic granules in the tumor cells. Immunohistochemical staining, verified the presence of alpha1-antichymotrypsin.

In late October 2003, the patient began combination therapy with gemcitabine 1,000 mg/m² and irinotecan 80 mg/m² weekly for two weeks followed by one week without treatment. This regimen was continued for seven cycles and stopped in May 2005 due to the development of an irinotecan hypersensitivity reaction. This reaction included blurred vision, chest tightness, and pharyngeal angioedema. The patient tolerated another cycle of gemcitabine plus irinotecan after premedication. However, enlargement of the liver metastases was seen on CT scan in June 2004 and the pancreatic mass measured 11.6x9.1 cm. Therefore, the chemotherapy regimen was changed to gemcitabine 1,000 mg/m² plus oxaliplatin 80 mg/m² (GemOx) biweekly. GemOx was continued for twelve cycles (six months).

In January 2005, a restaging CT scan revealed a pancreatic mass with foci of cysts, necrosis, and scattered calcifications, measuring 12.6x9.5 cm. At this time, the chemotherapeutic regimen was changed to docetaxel 30 mg/m² weekly for 2 weeks in a 21-day cycle, plus capecitabine 1,250 mg/m² orally twice daily on day one for fourteen days in the same 21-day cycle. After 6 cycles, in July 2005, a restaging CT scan showed further progression of disease with worsening of the liver metastases. There was also enlargement of the gastrohepatic ligament lymph node and the development of a new left pleural effusion. Subsequently, an octreotide scan was done which revealed somatostatin avid disease in the liver and left upper quadrant abdominal lesions. Therefore,

monthly octreotide acetate therapy was initiated and continued for 3 months.

A restaging CT scan in October 2005 demonstrated left retroperitoneal masses and worsening of the upper abdominal conglomerate adenopathy, although there was a mild decrease in the size of one liver metastasis. At this point, the patient began combination therapy with a bolus of 5-fluorouracil 400 mg/m², leucovorin 400 mg/m², and irinotecan 160 mg/m² (FOLFIRI protocol) on day one, followed by fluorouracil 1,000 mg/m² continuous infusion over 48 hours every two weeks. A CT scan in January 2006 confirmed progressive disease with enlarging foci of necrosis in the pancreatic tail and multiple hepatic lesions. There was also an increase in the extent of peritoneal disease, especially in the epigastrium, with a significant burden of adenopathy. Therefore, FOLFIRI was changed to gemcitabine 1,000 mg/m² weekly plus erlotinib 100 mg daily.

A follow-up CT scan in March 2006 revealed progressive disease with involvement of the lungs and an increased pleural effusion. Gemcitabine plus erlotinib was stopped, and the patient was enrolled in a phase I study of cisplatin plus a protein kinase C inhibitor. However, the patient was soon taken off the protocol due to further progression of her disease. Later in the spring of 2006, the patient was considered for other phase I studies at Yale University and was not eligible for any of the available protocols due to her poor performance status.

However in June 2006, the patient began therapy with sunitinib 50 mg daily for 28 days followed by 2 weeks off plus, sirolimus 8 mg orally every week starting day one. During the first cycle, the patient only experienced mild fatigue and anorexia, but the patient's clinical course was complicated by *Clostridium difficile* colitis which resulted in septic shock and death.

DISCUSSION

An estimated 37,170 new cases of pancreatic cancer are expected to occur in the United States in 2007, and pancreatic cancer is estimated as the fourth leading cause of

cancer deaths in the United States [5]. The pancreas is composed predominantly of acinar cells which are responsible for the production of digestive enzymes, including amylase, lipase, phospholipase and proteases [6]. Pancreatic neoplasms may be categorized as exocrine or endocrine, with subdivisions of solid or cystic. Acinar cell carcinomas comprise only 1-2% of exocrine pancreatic neoplasms [1, 2].

Acinar cell carcinoma of the pancreas is more common in men compared to women, in the ages of sixty to seventy, and is rare in

children [4]. Patients may present with Schmid's triad of subcutaneous fat necrosis, polyarthritits, and eosinophilia, as a result of increased lipase secreted by the neoplasm [1, 7]. However, the most common presentation is weight loss, abdominal pain, nausea and vomiting. Acinar cell carcinoma may also manifest with endocrine symptoms due to increased secretion of insulin, insulin-growth like factors and glucagon [4]. Our case of a 44-year-old female patient with fever and abnormal abdominal examination is unique, because it does not match the average age, sex or clinical profile of acinar cell carcinoma of the pancreas.

Acinar cell carcinoma may involve the head or the tail of the pancreas [2]. In a clinical imaging case series, Chiou *et al.* found that acinar cell carcinomas of the pancreas may arise in the uncinat process as well [8]. Acinar carcinoma of the pancreas tends to be larger than ductal carcinoma at presentation with a tumor of 10 cm not being rare [4]. The typical finding on computed tomography scan of acinar cell carcinoma is a solitary, well defined, heterogeneous hypodense mass with a well-defined enhancing capsule [8]. On computed tomography scan, our case similarly, revealed a large centrally cystic or necrotic mass with scattered calcifications arising from the pancreatic tail, and measured 12.6x9.5 cm in January 2005.

Acinar cell carcinomas of the pancreas are highly cellular tumors with minimal stroma and lack stromal desmoplasia [9]. Four patterns of growth have been described: acinar, cellular, trabecular, and glandular [4]. The tumor cells have hyperchromatic round nuclei in a polarized arrangement and their eosinophilic cytoplasm is positive for d-PAS [10]. d-PAS stain, is used to determine whether an entity that is PAS positive has zymogen granules [11] (Figure 1 taken from histological section). Electron microscopy of acinar cell carcinoma of the pancreas usually confirms zymogen granules in the cytoplasm [12].

According to a case series of acinar cell carcinoma of the pancreas by Stelow *et al.*, fine needle aspiration allows for accurate

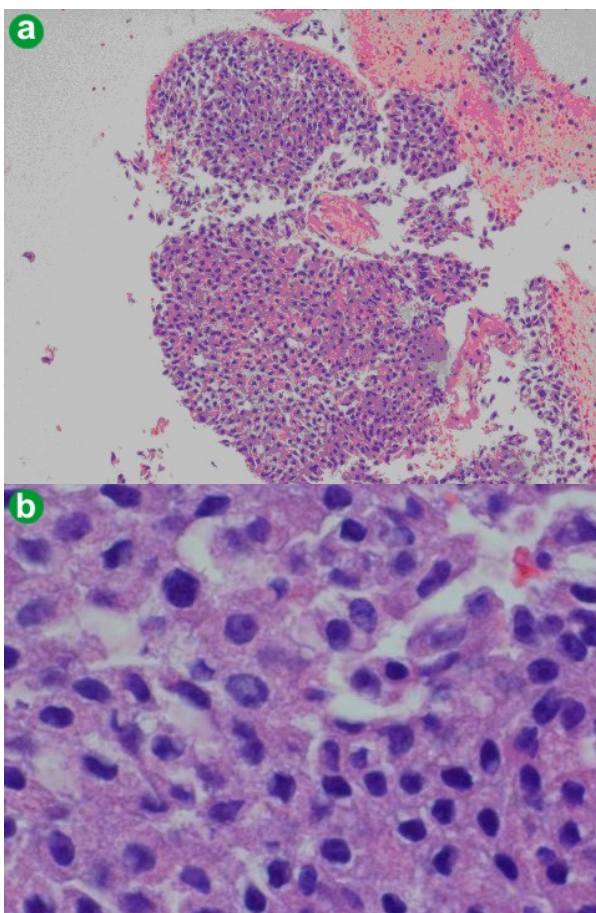


Figure 1. Light microscopic appearance of acinar cell carcinoma. **a.** At low-power microscopy, the tumor was hypercellular, with cords of cytologically uniform cells with granular eosinophilic apical cytoplasm reflecting the accumulation of zymogen granules. On cell block, the tumor cells arranged in thick trabeculae, poorly formed glands or acini. (H&E stain x4). **b.** At higher power microscopy, an abundant pink, eosinophilic cytoplasm, with granules was visible. Tumor cells with pleomorphic, centrally located nuclei, small to prominent nucleoli and scant to moderate amount of cytoplasm. Brisk and abnormal mitosis are evident. (H&E stain x40).

sampling and diagnosis of pancreatic lesions [13]. The definitive diagnosis of acinar cell carcinoma is obtained by immunocytochemistry. Because the pancreas secretes enzymes, the common immunohistochemical stains for acinar cell carcinoma of the pancreas include trypsin, chymotrypsin, amylase and lipase [14, 15]. Staining for amylase and lipase is technically difficult and not performed routinely. However, staining with antibodies against trypsin and chymotrypsin is confirmatory in 90% cases of acinar cell carcinoma [7]. Acinar cell carcinoma stains positive for synaptophysin and chromogranin A in thirty to fifty percent of all cases [14, 15]. There have also been cases of acinar cell carcinoma of the pancreas where insulin, glucagon, and somatostatin have been immunohistochemically identified [16].

In our case, the fine needle aspiration of a liver lesion stained positive for trypsin, chymotrypsin, chromogranin A and synaptophysin which favors metastatic acinar cell carcinoma. This is also consistent with the patient's history of a known primary acinar cell carcinoma of the pancreas. The reported case also had avid somatostatin disease treated with octreotide, and the presence of endocrine components identified by staining has been noted to have a better prognosis [17]. This may have contributed to the increased survival our patient. Our case does not classify as a mixed acinar-endocrine carcinoma of the pancreas, because the endocrine component is less than 25% of the neoplasm [9]. The histology of the FNA in our case revealed ninety percent acinar differentiation.

All pancreatic carcinomas have poor prognoses. Patient age and stage of disease are major prognostic factors [9]. Acinar cell carcinoma has a better prognosis than ductal carcinoma, but a worse prognosis compared to islet cell carcinoma. The mean survival is 18 months after diagnosis and 6 months for patients with unresectable tumors [18]. Surgery remains the treatment of choice for acinar carcinoma of the pancreas. For locally advanced unresectable pancreatic cancer,

chemotherapy and radiation may prolong survival.

Our case is unique not only because the patient lived beyond the mean survival for those with unresectable cancer, but also because she received multiple chemotherapy regimens. 5-fluorouracil (5-FU) and gemcitabine are the most common chemotherapeutic agents used in previous case reports of acinar cell carcinoma of the pancreas [4]. 5-FU was introduced in 1957 as a therapy for colorectal cancer [19]. Gemcitabine, an analog of cytosine arabinoside, is used as a first line agent in patients with unresectable pancreatic carcinoma and as a radiosensitizer of human tumor cells [18]. Chemotherapeutic agents used in the treatment of colorectal cancer may be effective in acinar cell carcinoma of the pancreas due to the genetic alteration in the APC/beta-catenin pathway noted in acinar cell of the pancreas [20].

When the biomodulator leucovorin was added to 5-FU, improved outcomes were noted in colorectal cancer, and therefore leucovorin is also used in pancreatic cancer. Irinotecan, a topoisomerase I inhibitor introduced in 1996, is a component of FOLFIRI protocol (5-FU, leucovorin, irinotecan) a combination chemotherapy revealed in 2004 [19]. Capecitabine, an oral agent which mimics intravenous 5-FU, and oxaliplatin a platinum based agent, were introduced for colorectal cancer in 1998 and 2002, respectively [19]. Each of these chemotherapeutic agents approved for colorectal cancer were used in the reported case. Also, docetaxel, a taxane derivative approved for non small cell lung cancer, was used in our case in combination with capecitabine from February to July 2005. Riechelmann *et al.* used paclitaxel in a case of acinar cell carcinoma and halted disease progression for a total of 4 months [21].

Experimental agents have been used in the treatment of acinar cell carcinoma of the pancreas, including TS-1 (5-chloro-2,4-dihydroxyuridine and potassium oxonate) and cisplatin I combination. Cisplatin may have been effective because acinar cell carcinoma

is morphologically and immunohistochemically related to pancreatoblastoma, and because cisplatin is a commonly used treatment for pancreatoblastoma [22, 23]. Abraham *et al.* suggest that acinar cell carcinoma of the pancreas shares the pathology and molecular genetics of pancreatoblastoma, a rare childhood cancer of the pancreas [20]. Combination chemotherapy with cisplatin and doxorubicin has been used as neoadjuvant chemotherapy for pancreatoblastoma [22]. Murakami *et al.* used consolidation chemotherapy with cisplatin, adriamycin, vincristine, and cyclophosphamide for pancreatoblastoma [23].

TS-1 is a novel agent designed to enhance anticancer activity and to decrease gastrointestinal toxicity [24]. It is an oral fluoropyrimidine (tegafur), a dihydropyrimidine dehydrogenase inhibitor and an orotate phosphoribosyltransferase inhibitor localized to the gastrointestinal tract [24]. Orotate phosphoribosyltransferase is an inhibitor of 5-FU phosphorylation localized to the gastrointestinal tract [25].

Ito *et al.* have used a novel inhibitor of mammalian target of rapamycin (mTOR) and gemcitabine in models of human pancreatic cancer. mTOR is considered to be an effector of cell growth and is found in human pancreatic cells. According to Ito *et al.* the combination of mTOR inhibitor and gemcitabine in an *in vivo* model achieved a better survival than gemcitabine and the mTOR inhibitor alone [26].

Safingol is another experimental agent that was used in the reported case during a clinical trial in combination with cisplatin. Schwartz *et al.* noted that safingol is a protein kinase C inhibitor that potentiates the effect of doxorubicin in tumor bearing animals [27]. As this patient received safingol and cisplatin in a clinical trial, perhaps the rationale is that safingol may also potentiate cisplatin. This re-emphasizes a possible link between acinar cell carcinoma of the pancreas and pancreatoblastoma due to a similar response to cisplatin.

Median overall survival for acinar cell carcinoma of the pancreas has been reported

to be 18.7 months with a 68% 1-year survival [28]. Cases of resectable acinar cell carcinoma have an average disease-free survival of 9 months [28]. We report an above average survival of 37 months after the initial diagnosis of acinar cell carcinoma of the pancreas. Increased survival may have been due to receiving multiple chemotherapy agents, and the unique histopathology and immunocytochemistry of the tumor. This case illustrates the lack of a standardized approach in the treatment of acinar cell carcinoma of the pancreas and emphasizes the need for further research.

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Abbreviations d-PAS: diastase periodic acid-Schiff; GemOx: gemcitabine plus oxaliplatin; mTOR mammalian target of rapamycin

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Correspondence

Muhammad Wasif Saif
Division of Medical Oncology
Yale University School of Medicine
333 Cedar Street, FMP 116
New Haven, CT 06520
USA
Phone: +1-203.737.1568
Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

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