Pancreatology 16 (2016) 153–156

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Case report

Multimodal approach and long-term survival in a patient with recurrent metastatic acinar cell carcinoma of the pancreas: A case report

Sarah F. Jauch, Van K. Morris, Corey T. Jensen, Ahmed O. Kaseb*

The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit Number: 426, Houston, TX 77030, USA

ARTICLE INFO

Article history:
Available online 28 September 2015

Keywords:
ACC
Acinar cell
Maintenance capecitabine
Metastatic pancreatic cancer
Pancreatic panniculitis
XELOX chemotherapy

ABSTRACT

Pancreatic acinar cell carcinoma is an uncommon neoplasm of the exocrine pancreas associated with a poor prognosis, especially when found to be metastatic. Since there are a lack of large studies and prospective, randomized data, no consensus treatment guidelines are available. Here, we report a case of a patient with recurrent metastatic acinar cell carcinoma involving the liver who had presented initially with pancreatic panniculitis. She received chemotherapy with capecitabine and oxaliplatin prior to resection of her primary tumor and liver metastases, after which she experienced a 30 months recurrence-free survival. Upon relapse, she was treated with a combination of capecitabine and oxaliplatin followed by maintenance capecitabine. Now, more than seven years after initial diagnosis, the patient remains stable without evidence of active disease. This case highlights the possibility of therapeutic success even for a patient initially deemed unresectable due to a poor performance status who responded to fluoropyrimidine-based therapy.

Introduction

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States [1–3], with approximately 40,000 deaths estimated in 2015 [1]. The vast majority of pancreatic neoplasms arise from the exocrine pancreas, and over 85% of all pancreatic malignancies are pancreatic ductal adenocarcinomas (PDAC) [4]. However, acinar cell carcinoma (ACC) is a rare subgroup of 1–2% of pancreatic exocrine tumors in adults [4,5] with a prevalence of less than one per million in the United States [6]. The diagnosis of ACC is challenging due to various morphologic characteristics [7] and non-specific clinical symptoms [5,6,8–11]. A distinctive but rare syndrome called Schmid's Triad is characterized by subcutaneous fat necrosis, eosinophilia and polyarthralgia, secondary to lipase hypersecretion [11]. Associated subcutaneous nodules can be misdiagnosed as erythema nodosum [10]. The overall five-year survival of pancreatic ACC from prior reports has ranged from 6 to 50% [5,6,11–13]. These series have suggested that survival outcomes in ACC may be more favorable than for patients with adenocarcinoma [6,12]. In the absence of prospective data for this rare disease, no standard therapeutic approach exists [14]. Surgery is the treatment of choice for patients with localized disease [10]. In addition, chemotherapeutic agents established in PDAC and colorectal carcinoma are often used [14].

We report a multimodal approach in a patient diagnosed with stage IV pancreatic ACC who remains without evidence of active disease on maintenance capecitabine.

Case report

In June 2007, a 61-year-old Caucasian woman with a past medical history notable for vasculitis presented with partially ulcerated, erythematous/violaceous subcutaneous nodules and swelling throughout her lower extremities. With a presumed diagnosis of erythema nodosum (given her aforementioned history of autoimmune disease), she was started empirically on prednisone yet developed rapid progression of her skin lesions. Biopsy of the skin demonstrated septal panniculitis with areas of necrosis. Infection was excluded as an etiology with negative blood and wound cultures. Further diagnostic evaluation included a computed tomography (CT) scan (Fig. 1A + B), which detected a

* Corresponding author. Tel.: +1 713 792 2828; fax: +1 713 563 0541.
E-mail address: akaseb@mdanderson.org (A.O. Kaseb).

http://dx.doi.org/10.1016/j.pan.2015.09.006

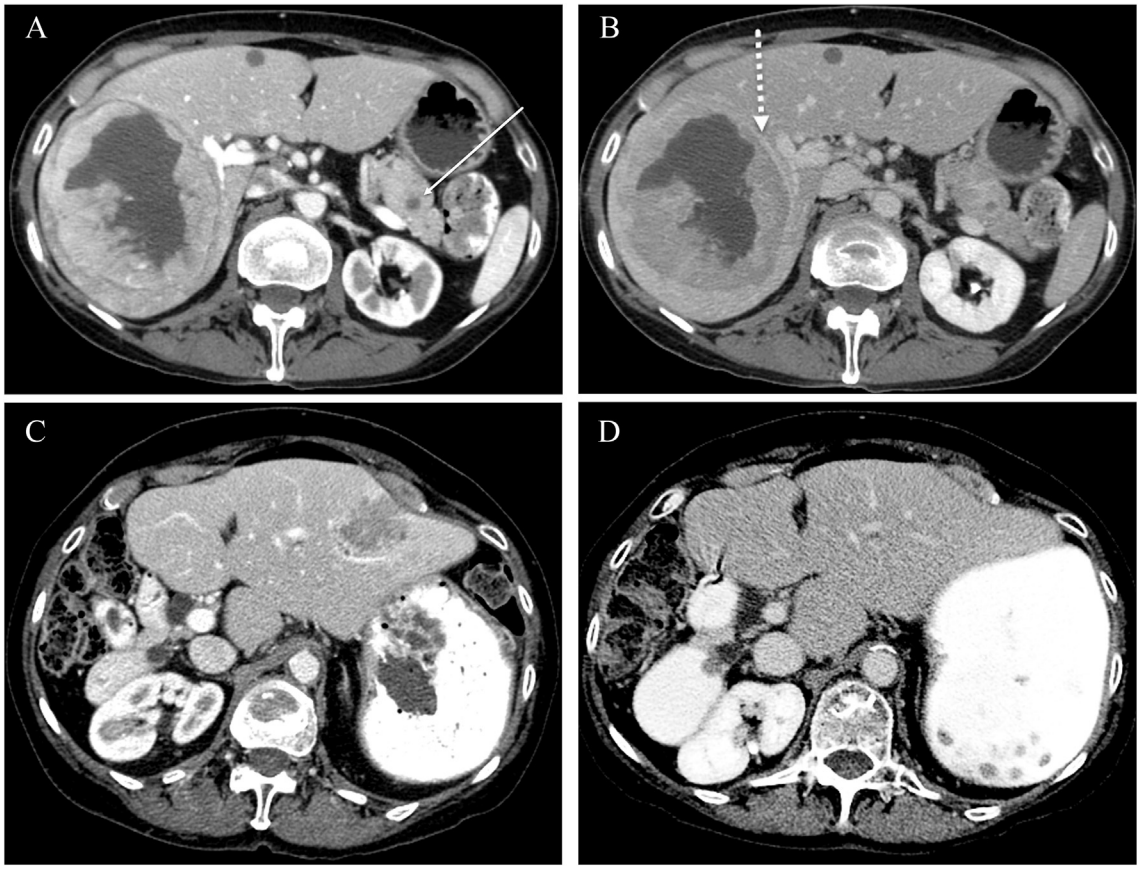

Fig. 1. Abdominal CT scans at diagnosis demonstrate the A) pancreatic tail mass with small cystic change (arrow) and the dominant hypervascular hepatic metastasis with B) washout and pseudocapsule (dashed arrow) on delayed imaging. Three years later, C) recurrent tumor was identified in the liver with D) subsequent complete response to therapy.

3.1 × 2.4 cm pancreatic mass between the gastric fundus and distal pancreatic tail. In addition, numerous bilobar liver metastases, the largest in the right lobe measuring 10 × 8 cm, were noted. CT guided biopsy of a suspected liver metastasis was consistent with acinar cell carcinoma. Pathological analysis of the tumor revealed strong immunohistochemical staining for chymotrypsin, lipase, alpha-1 antitrypsin, and pankeratin; and scattered positivity for carbohydrate antigen 19-9 (CA 19-9) and trypsin. Neuron-specific enolase (NSE), synaptophysin, chromogranin and beta-catenin were all negative.

Subsequently, the patient was referred to our institution for further recommendations of metastatic pancreatic ACC. Upon initial evaluation, she was noted to have an Eastern Cooperative Oncology Group (ECOG) performance status of 3 and to be underweight with a body-mass index (BMI) of 17.3 kg/m^2. Her physical exam was otherwise notable for violaceous lesions across her abdomen and lower extremities. Laboratory results showed increased CA 19-9 of 345.6 U/mL, alpha-fetoprotein (AFP) of 343.5 ng/mL, lipase of 7459 U/L, albumin of 3.3 mg/dL, and lactate dehydrogenase (LDH) of 865 IU/L. Carcinoembryonic antigen (CEA), amylase, total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were all within normal limits. Because of her unfavorable performance status and her poor nutritional status, the patient was not considered to be a candidate for surgical resection. Rather, she received eight cycles of chemotherapy with capecitabine plus oxaliplatin (XELOX). After her first three cycles, laboratory analyses revealed normalization of her CA 19-9, lipase, and LDH laboratory values. After eight cycles, the panniculitis had resolved completely, and both her ECOG performance status and her BMI had improved, findings compatible with clinical improvement. Imaging studies confirmed resolution of the primary tumor and reduction in the size of her right hepatic lesions. Given this profound response to XELOX chemotherapy, surgical evaluation was reassessed, and four months after completion of chemotherapy, the patient underwent distal pancreatectomy, splenectomy, cholecystectomy and right hepatectomy. Pathology revealed a residual moderately differentiated ACC in the pancreas measuring 6 mm in diameter with negative surgical margins, one of eleven regional lymph nodes with tumor, and six tumor nodules in the liver, with the largest containing 30% viable tumor cells (ypT1N1M1, AJCC 6th edition). Due to her slow recovery after surgery and residual sensory neuropathy from oxaliplatin, the patient did not receive adjuvant chemotherapy. She remained disease free for the following 30 months, at which point she was found to have a newly elevated lipase (1111 U/L) and new liver lesions concerning for recurrent metastases (Fig. 1C). Given her initial response to XELOX, this regimen was reintroduced with imaging studies after three cycles showing a response in all measurable lesions. After a total of six cycles of XELOX, the oxaliplatin was dropped, and she has continued on single-agent capecitabine (1000 mg/m^2/day) for the past three and a half years. Most recent imaging studies show complete eradication of all disease with no evidence of macroscopic tumor visualized (Fig. 1D). Her performance status is now 0, and her previously mentioned elevated laboratory values are all within normal limits.

Table 1
Overview of case reports with synchronous metastases and a survival longer than five years.

Report	First-line therapy	Second-line therapy etc.	Survival
Hashimoto et al. [13]	distal pancreatectomy, left hepatectomy and limited resection of liver segment six	1) repeated limited hepatic resections 2) hepatic intraarterial infusion chemotherapy (5-FU, cisplatin, mitomycin c), based on the regimen of Ukei et al. [24] (41 months of complete response)	63 months after the first operation
Sumiyoshi et al. [21]	see discussion		
Ang et al. [18]	gemcitabine and cisplatin followed by gemcitabine and oxaliplatin due to renal insufficiency	1) FOLFIRI 2) hepatic arterial infusion of floxuridine and dexamethasone [grade 2 elevation in alkaline phosphatase] and intravenous irinotecan 3) intravenous irinotecan and cetuximab 4) FOLFIRI and cetuximab 5) subsequently addition of bevacizumab (response/disease stability for almost two years) 6) FOLFOX, cetuximab and bevacizumab	seven years after diagnosis
Armstrong et al. [20]	distal pancreatectomy, splenectomy, re-resection of the margin and hepatic radiofrequency ablation (RFA) adjuvant therapy with gemcitabine and cisplatin followed by radiation to the pancreatic bed accompanied by cisplatin cycles	1) hepatic RFA followed by thalidomide [deep vein thrombosis] with paclitaxel 2) capecitabine 3) imatinib 4) etoposide 5) liposomal doxorubicin [potential cardiac toxicity]; hepatic intraarterial brachytherapy with Sirspheres 6) hepatic RFA and cryotherapy; stereotactic radiosurgery of a pericardial lymph node 7) sorafenib and temozolomide 8) external beam radiation (liver) 9) albumin-bound paclitaxel (Abraxane) [neuropathy] and bevacizumab [confusion]	ca. eight years since initial presentation
Cananzi et al. [19]	docetaxel, irinotecan and cetuximab distal pancreatosplenectomy with right hepatectomy adjuvant treatment with docetaxel, irinotecan and cetuximab	1) gemcitabine/oxaliplatin [neutropenia] and cetuximab (disease free for ca. three years) 2) resection of liver/peritoneal metastases, extensive lymphadenectomy; oxaliplatin [hypersensitivity reaction] later carboplatin, gemcitabine, cetuximab and bevacizumab 3) repeated hepatic RFA; carboplatin (later stopped), gemcitabine, cetuximab and bevacizumab [proteinuria] 4) repeat para-aortic lymphadenectomy, intraoperative hepatic RFA 5) gemcitabine, capecitabine, cetuximab 6) right/left partial adrenalectomy, partial peritonectomy, extensive lymphadenectomy 7) liposomal doxorubicin followed by nab-paclitaxel with panitumumab 8) resection of a retroperitoneal mass and completion of left adrenalectomy 9) left frontal brain metastasis resection 10) nab-paclitaxel and panitumumab	over eleven years since diagnosis

Abbreviations: 5-FU: 5-fluorouracil; FOLFIRI: folinic acid, 5-FU, irinotecan; FOLFOX: folinic acid, 5-FU, oxaliplatin; [side effects causal for termination].

Discussion

Pancreatic acinar cell carcinoma is a rare and aggressive malignancy with a reported median overall survival of 19 months for all patients and 14 months for those presenting with metastatic disease [10,15]. It is important to note that the literature of acinar cell carcinoma is non-uniform, since ACC has been mixed to pancreatoblastoma and mixed acinar-endocrine tumor [11]. At presentation, approximately half of the patients have metastatic disease [5,15] with the liver as the most frequent site for distant spread [15]. An additional 23% of patients develop metastases after initial diagnosis [5]. Due to the paucity of information regarding this disease, no treatment guidelines according to expert consensus for ACC exist. Surgery significantly improves the outcome with a five-year survival between 36.2% and 71.6% [6,16]. Based on results from a retrospective study of 865 patients with ACC and on literature review, Schmidt and colleagues [16] recommend neoadjuvant therapy for locally unresectable or metastatic tumors in order to achieve downstaging and possible surgical resection. However, this will likely not be assessed prospectively given the low annual incidence of ACC. Nevertheless, a high rate of disease recurrence [57% (median follow-up of 15 months) [17] - 100% (median follow-up of 31.4 months) [11]] [11,15,17] has been described in various studies, even after R0-resection (56%) [15] and partially neo-adjuvant or adjuvant therapy [11,15,17]. Recurrences develop more commonly at distant sites, suggesting the presence of micro-metastases as opposed to occurring at the site of resection of the primary tumor [15]. With this high rate of disease recurrence, surgery alone may not be sufficient to cure ACC [11]. Adjuvant therapy may be warranted to treat micrometastases [15], even though retrospective studies [16] question the benefit of adjuvant chemotherapy and/or radiation, restricted by the lack of details regarding the varying regimens utilized in ACC. However, in patients with metastatic ACC, aggressive multimodal treatments incorporating chemotherapy, radiotherapy and surgery appear to be of clinical benefit.

Currently, there are only five reports of pancreatic acinar cell carcinoma with synchronous metastases and a survival longer than five years (Table 1): Hashimoto et al. [13] describe a case with subcutaneous fat necrosis and recurrent metastases to the liver. A long-term survival of seven years in a case with metastatic intrahepatic cholangiocarcinoma as a presumed diagnosis is presented by Ang et al. [18]. Cananzi et al. [19] report a eleven-year survival in a patient, first diagnosed as a poorly differentiated PDAC (pT3N1aM1) metastasized to the liver. A multimodal personalized approach based on genomic profiling and cell line development

combined with a survival over five years is demonstrated by Armstrong et al. [20]. Sumiyoshi et al. [21] describe a case with peritoneal dissemination and a recurrence-free survival over six years after distal pancreatectomy, partial gastrectomy and resection of disseminated nodules followed by oral S-1 chemotherapy (tegafur, gimeracil, oteracil potassium).

Furthermore, ACC with metachronous metastases and a total survival of fifteen years after surgery and six years after peritoneal recurrence, treated with intraperitoneal cisplatin, is presented by Kobayashi et al. [22]. Suzuki and colleagues [23] describe a repetitive surgical approach in a patient with recurrent liver metastases, who has survived 65 months since initial diagnosis and almost five years since the first liver lesions have occurred.

Here, we would like to highlight the relevance and therapeutic implications of the presented case: in contrast to other reports, the poor general condition of this patient resolved with systemic chemotherapy and reversed her candidacy for surgical resection. This clinical improvement, indicated by performance and nutritional status recovery as well as by paraneoplastic syndrome clearance, correlated with a biomarker and positive radiographic response, despite large tumor involvement in the liver at diagnosis. As a result, surgical resections of remnant lesions enabled this patient to achieve a marked disease-free survival benefit. Reduced XELOX regimen and subsequent maintenance capecitabine resulted in remission of her recurrent metastatic ACC.

We report, to our knowledge, the first use of capecitabine alone as maintenance therapy as a means to treat metastatic ACC and prevent disease recurrence. For patients with poor performance status who cannot tolerate combination regimens, single-agent capecitabine may exhibit activity in this disease and provide rationale for a fluoropyrimidine-based strategy. Additionally, upfront chemotherapy may resolve clinical symptoms and convert a patient with metastatic ACC from a nonresectable to resectable surgical candidacy.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.

[2] Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009;6:699–708.

[3] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011;378:607–20.

[4] Reid MD, Bagci P, Adsay NV. Histopathologic assessment of pancreatic cancer: does one size fit all? J Surg Oncol 2013;107:67–77.

[5] Klimstra DS, Heffess CS, Oertel JE, Rosai J. Acinar cell carcinoma of the pancreas. A clinicopathologic study of 28 cases. Am J Surg Pathol 1992;16:815–37.

[6] Wisnoski NC, Townsend Jr CM, Nealon WH, Freeman JL, Riall TS. 672 patients with acinar cell carcinoma of the pancreas: a population-based comparison to pancreatic adenocarcinoma. Surgery 2008;144:141–8.

[7] La Rosa S, Adsay V, Albarello L, Asioli S, Casnedi S, Franzi F, et al. Clinicopathologic study of 62 acinar cell carcinomas of the pancreas. Insights into the morphology and immunophenotype and search for prognostic markers. Am J Surg Pathol 2012;36:1782–95.

[8] Klimstra DS. Nonductal neoplasms of the pancreas. Mod Pathol 2007;1(20 Suppl.):S94–112.

[9] Toll AD, Hruban RH, Ali SZ. Acinar cell carcinoma of the pancreas: clinical and cytomorphologic characteristics. Korean J Pathology 2013;47:93–9.

[10] Mortenson MM, Katz MH, Tamm EP, Bhutani MS, Wang H, Evans DB, et al. Current diagnosis and management of unusual pancreatic tumors. Am J Surg 2008;196:100–13.

[11] Butturini G, Pisano M, Scarpa A, D'Onofrio M, Auriemma A, Bassi C. Aggressive approach to acinar cell carcinoma of the pancreas: a single-institution experience and a literature review. Langenbecks Arch Surg 2011;396:363–9.

[12] Matos JM, Schmidt CM, Turrini O, Agaram NP, Niedergethmann M, Saeger HD, et al. Pancreatic acinar cell carcinoma: a multi-institutional study. J Gastrointest Surg 2009;13:1495–502.

[13] Hashimoto M, Miki K, Kokudo N, Beck Y, Makuuchi M. A long-term survivor of metastatic acinar cell carcinoma. Pancreas 2007;34:271–2.

[14] Lowery MA, Klimstra DS, Shia J, Yu KH, Allen PJ, Brennan MF, et al. Acinar cell carcinoma of the pancreas: new genetic and treatment insights into a rare malignancy. Oncologist 2011;16:1714–20.

[15] Holen KD, Klimstra DS, Hummer A, Gonen M, Conlon K, Brennan M, et al. Clinical characteristics and outcomes from an institutional series of acinar cell carcinoma of the pancreas and related tumors. J Clin Oncol 2002;20:4673–8.

[16] Schmidt CM, Matos JM, Bentrem DJ, Talamonti MS, Lillemoe KD, Bilimoria KY. Acinar cell carcinoma of the pancreas in the United States: prognostic factors and comparison to ductal adenocarcinoma. J Gastrointest Surg 2008;12:2078–86.

[17] Seth AK, Argani P, Campbell KA, Cameron JL, Pawlik TM, Schulick RD, et al. Acinar cell carcinoma of the pancreas: an institutional series of resected patients and review of the current literature. J Gastrointest Surg 2008;12:1061–7.

[18] Ang C, Herran LA, Lagunes DR, Klimstra DS, Kemeny NE. A case report of a patient with advanced acinar cell carcinoma of the pancreas: long-term survival with regional, systemic and targeted therapy. Tumori 2013;99:e61–4.

[19] Cananzi FC, Jayanth A, Lorenzi B, Belgaumkar A, Mochlinski K, Sharma A, et al. "Chronic" metastatic pancreatic acinar cell carcinoma. Pancreatology 2013;13:549–52.

[20] Armstrong MD, Von Hoff D, Barber B, Marlow LA, von Roemeling C, Cooper SJ, et al. An effective personalized approach to a rare tumor: prolonged survival in metastatic pancreatic acinar cell carcinoma based on genetic analysis and cell line development. J Cancer 2011;2:142–52.

[21] Sumiyoshi T, Shima Y, Okabayashi T, Kozuki A, Iwata J, Saisaka Y, et al. Long-term survival following pancreatectomy and S-1 chemotherapy for pancreatic acinar cell carcinoma with peritoneal dissemination: a case report and literature review. Med Baltim 2015;94:e378.

[22] Kobayashi S, Ishikawa O, Ohigashi H, Yamada T, Sasaki Y, Imaoka S, et al. Acinar cell carcinoma of the pancreas successfully treated by en bloc resection and intraperitoneal chemotherapy for peritoneal relapse: a case report of a 15-year survivor. Pancreas 2001;23:109–12.

[23] Suzuki A, Sakaguchi T, Morita Y, Oishi K, Fukumoto K, Inaba K, et al. Long-term survival after a repetitive surgical approach in a patient with acinar cell carcinoma of the pancreas and recurrent liver metastases: report of a case. Surg Today 2010;40:679–83.

[24] Ukei T, Okagawa K, Uemura Y, Miyauchi K, Kaneko T, Mizunoya S, et al. Effective intra-arterial chemotherapy for acinar cell carcinoma of the pancreas. Dig Surg 1999;16:76–9.