

CASE REPORT

Bone Metastasis as the Only Site of Disease in a Patient 7 Years Post Treatment for a Locally Advanced Pancreatic Adenocarcinoma

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ABSTRACT

Context Pancreatic adenocarcinoma is one of the most challenging diseases to treat. Even patients able to undergo resection for potential cure have a high risk of recurrence and require close monitoring. The typical areas of recurrence and/or metastasis are the surgical bed, liver, and lungs. We present a rare case of a solitary bone metastasis identified seven years after a Whipple procedure for pancreatic adenocarcinoma. This is the first case report to demonstrate its ability to metastasize to bone in the absence of other systemic disease more than 7 years after surgical resection and adjuvant therapy. **Case report** The patient initially presented with a locally advanced pancreatic adenocarcinoma that was resected, pT3N1b. He was treated with 6 months of adjuvant chemotherapy, and monitored thereafter with quarterly MRI's of the abdomen and pelvis, and the CA 19-9 tumor marker. The patient had a good performance status (KPS 100), with no evidence of recurrence until over 7 years later, when an elevation in his CA 19-9 triggered a systemic workup. An isolated sclerotic lesion in the right sacral ala was identified on imaging and biopsied, found to be adenocarcinoma, consistent with pancreaticobiliary origin. **Conclusions** This case highlights the unusual ability of pancreatic adenocarcinoma to recur many years after treatment. It also shows the potential for pancreatic adenocarcinoma to metastasize to the bone as a solitary lesion and illustrates the role of CA 19-9 in monitoring tumor recurrence and treatment response. As patients may live longer with the recent advances in chemotherapy, this report may help inform providers about possible unusual patterns of recurrence.

INTRODUCTION

Pancreatic Cancer remains a significant health concern in the US, despite the trend of reduced incidence of many other cancers over the past decade. It represents about 3% of all new cancer cases, and 7% of cancer deaths [1]. It is estimated to become the third leading cause of cancer deaths in 2018. The American Cancer Society reports 55,440 people will be diagnosed in 2018, and of those, 44,330 will die from it. Treatment remains challenging, and it has one of the lowest 5-year survival rates of all cancers combined, at 8%. For patients diagnosed at later stages, the five-year survival rates drop significantly: 5% for stage IIb, 3% for stage III and 1% for stage IV [1]. Even for those patients with resectable local disease confined to the pancreas, tumor recurrence remains a risk. Many patients will recur within 12 months – 2 years, with 85% of metastases presenting in the liver; 12% in the lung, and 3% to the bone [2, 3].

CASE REPORT

Our patient is a 50 year-old male who presented with painless jaundice in October 2008. His past medical history was significant for ulcerative proctitis and HBsAg carrier status. He was a non-smoker, but had been exposed to second hand smoke at his workplace. MRI of the abdomen revealed a 3 cm head of pancreas mass. FNA done during stenting was positive for pancreatic adenocarcinoma. A staging PET CT was notable only for an FDG-avid mass in the pancreatic head, SUV 3. With no distant disease identified, the patient underwent a pancreaticoduodenectomy (Whipple procedure) and recovered without complications.

Pathology revealed moderately differentiated (G2) ductal adenocarcinoma, with evidence of venous/lymphatic and perineural invasion, chronic pancreatitis and pancreatic intraepithelial neoplasia (highest PanIN 2). Posterior margin was 1.5 mm from invasive carcinoma. He was stage III at diagnosis, pT3, per the pathology report, with tumor extended beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery; pN1b metastasis in multiple regional lymph nodes. Metastatic carcinoma was identified in 14/35 lymph nodes.

Pre-operative carcinoembryonic antigen (CEA) was normal, and CA19-9 was slightly elevated at 62 (<37 U/mL

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hospital lab). Therefore, this marker was used to monitor him post-op.

The patient's performance status was excellent (KPS 100). He was not diabetic and required no pancreatic enzymes. He enrolled in a clinical trial with Gemcitabine, Docetaxel, and Capecitabine, and received 6 months of adjuvant chemotherapy

He was followed thereafter with an MRI of the abdomen and pelvis every three months, along with BMP, LFT's, and CA 19-9, which remained normal throughout chemotherapy.

In 2010, he became febrile and was found to have e-coli bacteremia of unknown origin. He was treated successfully with IV Zosyn. Following that, he had recurrent febrile episodes with myalgias, accompanied by fevers and elevations of CA 19-9 up to 131 (<37 U/mL Hospital lab). Blood cultures were negative. Work up with infectious disease and rheumatology, imaging with PET, gallium scan, and MRI suggested the infection was from a biliary origin. Once recurrent adenocarcinoma was ruled out, the fevers were attributed to intermittent cholangitis. This was treated with a rotating course of oral antibiotics. The patient would become febrile approximately once every 4-8 weeks but fevers would resolve typically within 24 hours of starting oral antibiotic therapy.

In 2012, the patient was admitted to the hospital for new onset acute pancreatitis. The CA 19-9 was elevated during his attack but returned to normal after he recovered. MRI's remained without evidence of cancer recurrence.

The patient continued to be monitored with MRI and CA 19-9, along with an annual chest CT, none of which showed any changes concerning for disease recurrence.

Nearly eight years after his initial diagnosis, in June 2016, his CA 19-9 was found to be elevated at 48.8 on routine lab work (<41.3 U/mL - NSLIJ Core lab). The patient felt well with no complaints. His test was repeated 10 days later, and was 81.8 (<41.3 U/mL).

An MRI of the abdomen and pelvis showed no obvious recurrence in the pancreatic surgical bed, but it was notable for a solitary lesion in the right sacral ala, concerning for metastasis (**Figure 1**).

On PET/CT, the lesion in the right sacrum was hypermetabolic with an SUV of 3 (**Figure 2**). There were no other areas of increased FDG avidity.

The case was discussed at multidisciplinary tumor board, and the decision was made to proceed with a needle biopsy for tissue diagnosis. This was performed by interventional radiology (**Figure 3**).

The pathology specimen consisted of a small core biopsy of bone, measuring 0.7 × 0.2 × 0.2 cm. Microscopy revealed metastatic adenocarcinoma, composed of well-formed glands, without increased mitoses, pleomorphism or necrosis (**Figures 4a, b & 5**).

A panel of immunostains was performed to evaluate for a number of different possible primary malignancies. The tumor proved positive for markers suggestive of pancreatico-biliary origin (CA19.9, CK7) (**Figure 6**), while negative for prostate (PSA, PSAP), lung (Napsin, TTF1) and colon (CK20, CDX2).

In summary, overall histomorphology and IHC findings were consistent with metastatic adenocarcinoma of pancreatic origin. Review by a second pathologist at another institution agreed with the diagnosis.

The osseous lesion was treated with hypofractionated radiation therapy in three fractions, completed in July 2016, without side effects other than mild fatigue. Post-treatment, the patient was followed with serial imaging and his tumor marker, which trended downwards. His CA 19-9 was 241.4 in July 2016 (<41.3 U/mL). It reduced further in August to 109.8, and then to 61.3 in September.

At the three-month follow-up in October 2016, our patient was found to have additional osseous lesions. His MRI (**Figures 7a, b**) and bone scan (**Figure 8**) showed progression of disease outside the initial radiation fields

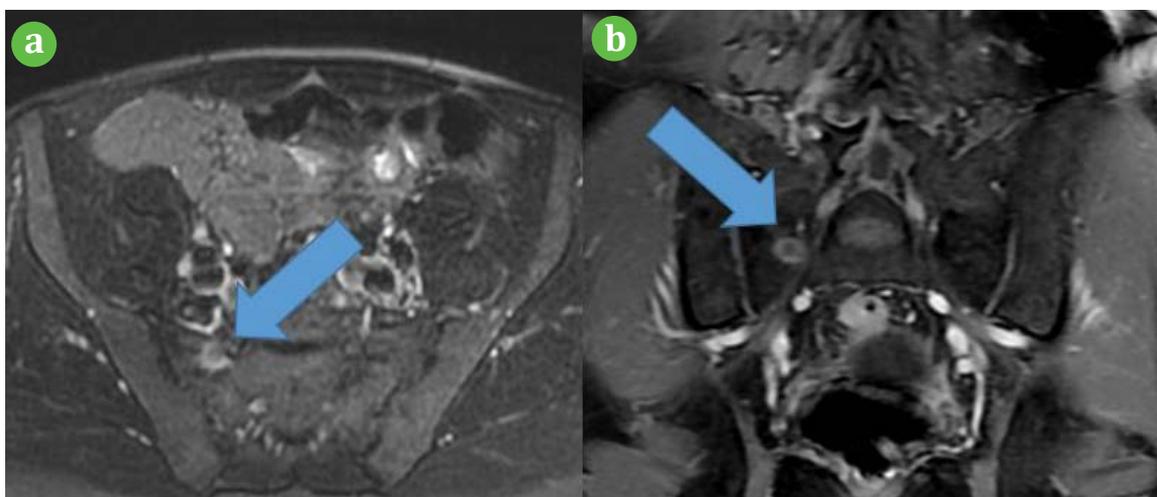


Figure 1. (a). Axial T2-weighted image with fat saturation. The arrow indicates a new 1.2 cm lesion right sacral ala, with hyper-intense rim surrounding hypo-intense center. **(b).** Post-contrast coronal T1-weighted image with fat saturation. The arrow highlights the lesion, which demonstrates a peripheral rim of enhancement.

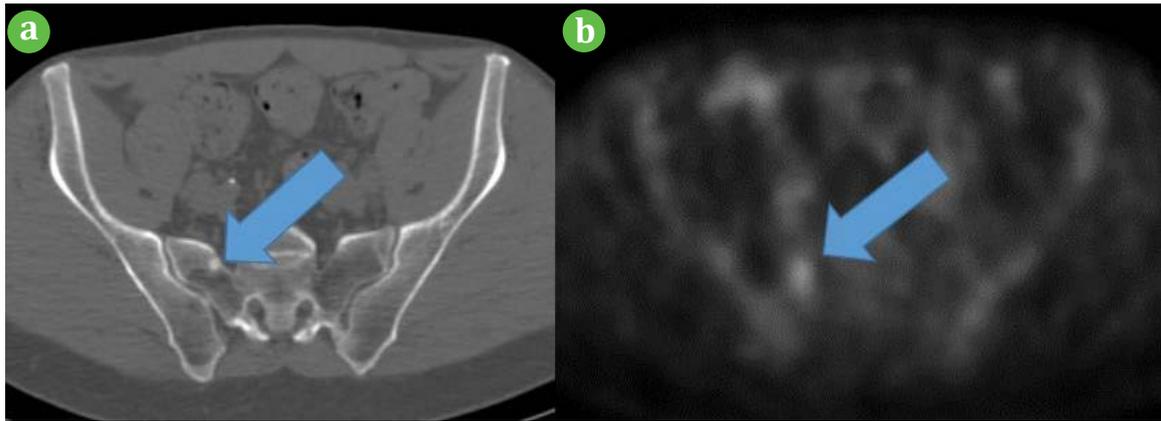


Figure 2. (a). Axial CT image with bone windows demonstrates a 6 mm sclerotic lesion of the right sacrum with density of 455 HU, indicated by the arrow. **(b).** Axial image from PET scan with an arrow to highlight the demonstration that the lesion is FDG-avid, with SUV max= 3.0 gm/mL.

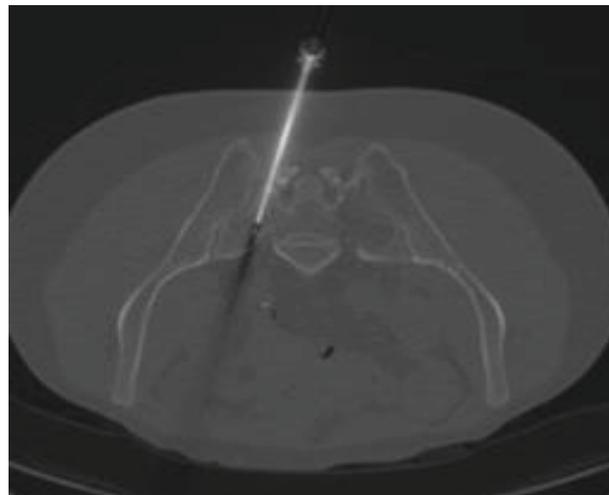


Figure 3. Axial CT image demonstrates CT-guided core biopsy of the right sacrum.

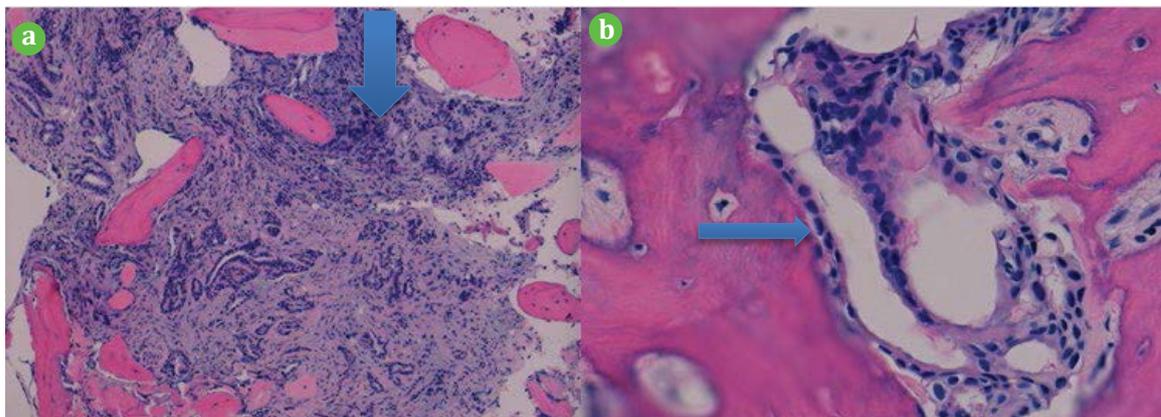


Figure 4. (a). Low power (10X); Metastatic adenocarcinoma with desmoplastic fibrous response (thick arrow). **(b).** High power (40X): Well differentiated glands replacing normal bone marrow (thin arrow).

in the sacrum. A right rib lesion was also identified. A 1 cm left sided superficial scalp lesion was also noted on exam. The CA 19-9 in October 2016 had increased to 306.6 (<41.3 U/mL). Given these findings, the decision was then made to initiate systemic therapy.

The patient began a course of gemcitabine and nanoparticle albumin-bound paclitaxel, with capecitabine as tolerated; he was also given xgeva to treat the bone lesions. He had further disease progression in the bony lesions noted on the follow up imaging, but he remained stable for a year on treatment, with no disease in the

pancreas, peritoneum, liver or lungs. His cutaneous scalp lesion was excised due to patient's discomfort, and was confirmed to be a metastasis as well.

Chemotherapy was stopped after a year due to neutropenia, fatigue, and worsening KPS (70). He developed further bone lesions seen on CT scan and PET/CT, and was transitioned to reduced dose liposomal irinotecan and 5FU. His main complaints were sacral pain, and fatigue and weakness from chemotherapy.

Due to worsening fatigue, increasing toxicity, and worsening KPS, chemotherapy was stopped, and the

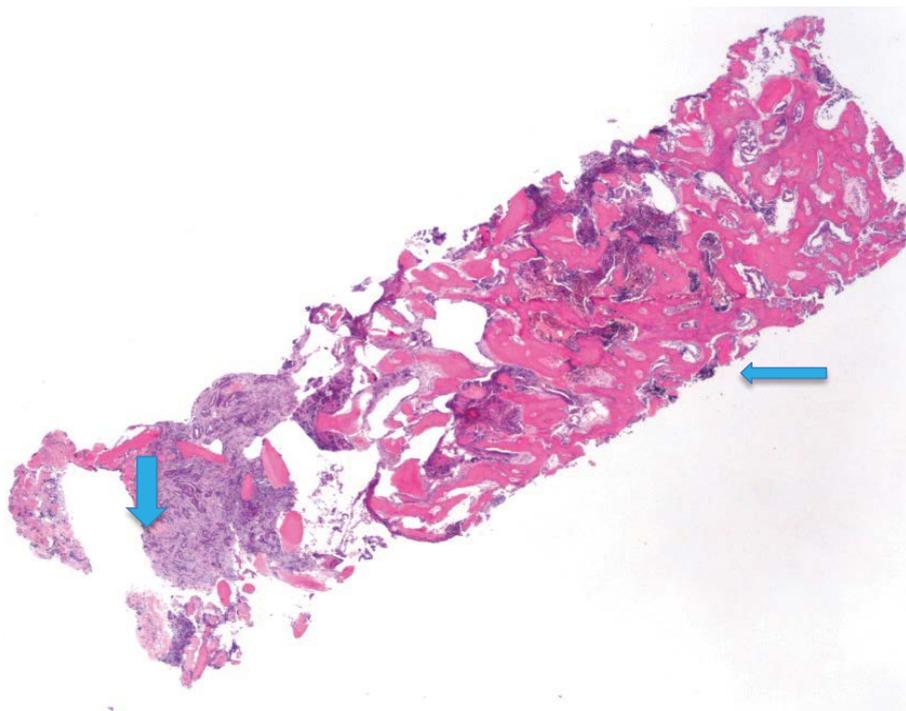


Figure 5. Core biopsy of bone, positive for metastatic adenocarcinoma (H&E). Focal desmoplastic response with fibrosis is noted (thick arrow), while in other areas tumor replaces marrow spaces without eliciting any reaction (thin arrow). Osteoblastic or osteoclastic activity is not appreciated, likely due to small specimen size.

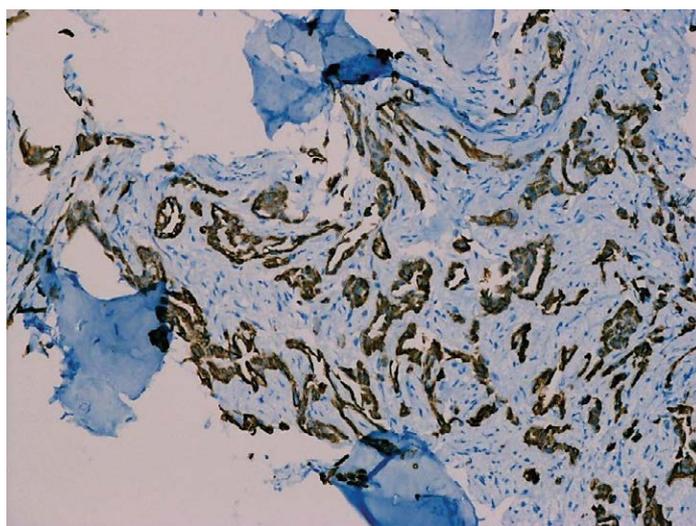


Figure 6. Immunohistochemistry demonstrates strong reactivity with CK7 consistent with pancreatic adenocarcinoma.



Figure 7. (a). Axial T2-weighted image with fat saturation demonstrates new hyperintense lesions of the right ilium (horizontal arrow) and in right sacrum (vertical arrow). **(b).** Coronal T2-weighted image demonstrates new lesions of the right ilium, indicated by the arrow.

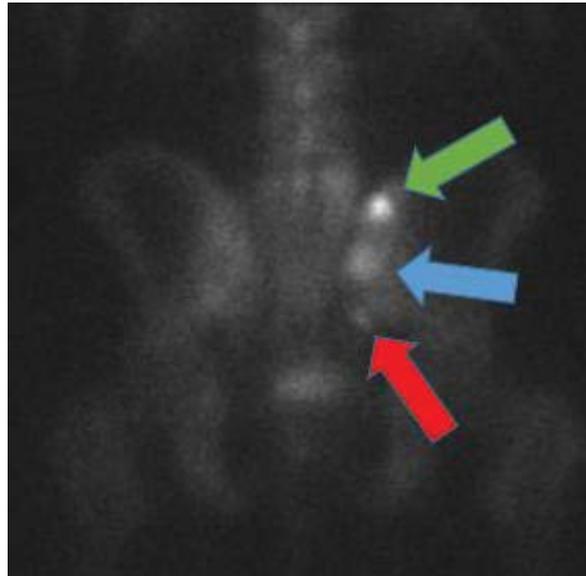


Figure 8. Posterior spot view of pelvis from bone scan demonstrates abnormal increased activity in new lesions in right ilium (top arrow), and superior aspect right sacrum (middle arrow), as well as the original lesion in the inferior sacrum (bottom arrow).

patient succumbed to his disease at the age of 60, almost ten years after his initial diagnosis.

DISCUSSION

Osseous metastases from pancreatic cancer are rare and have been reported to be as low as <2% [4]. Hess *et al.* reported on their tumor registry data gathered between 1994 - 1996 from 4399 patients. In their pancreatic adenocarcinoma cohort of 270 patients, they found 85% of metastases occurred in the liver; 12% occurred in the lung, and 3% went to the bone [2]. It is particularly uncommon to have progression of disease outside the abdomen in the absence of liver disease [2].

Borad *et al.* retrospectively reviewed a database of 323 patients with pancreatic adenocarcinoma from July 2005 – December 2007. In their cohort, they identified seven with skeletal metastases, both lytic and blastic, representing 2.2 percent of their population. All patients were at stage III or IV at initial diagnosis, and all but one had liver metastases. The most common sites of skeletal metastasis were the vertebrae, then hips, ribs. One patient had a symptomatic skull lesion [5].

The longest interval between initial diagnosis and development of metastasis was in a 53 year old male patient, stage III at diagnosis, 32 months. He also had the longest overall survival of the cohort, at 41 months. The other patients in the cohort developed bone metastases between 2-17.3 months after initial diagnosis; the median time to development was 5.5 months [5].

A literature review identified one other case report of solitary bone metastasis in pancreatic adenocarcinoma [6]. That patient was a 46-year-old African American female, s/p distal pancreatectomy and splenectomy. Her pathology grade was not specified (well differentiated, moderately differentiated, or poorly differentiated). She had 3/18 LN positive, and was stage IIB. She was treated with 6 cycles of adjuvant gemcitabine. Her bone metastasis

was discovered 2 years later after she complained of pain in her right clavicle. The lesion was PET FDG avid. She was radiated over two weeks, but before completing the course of radiation, she had further pain and was found to have multiple bone lesions in the left ischium, acetabulum, and femur, then in the left sacrum. Her disease progressed rapidly despite chemotherapy. Her CEA was elevated to 338 ng/ml but the CA 19-9 remained normal. She was reported to be on “best supportive care” within that year, and no survival time was given [6].

Our case of a solitary bone metastasis occurring 7 years after a Whipple procedure and adjuvant chemotherapy, with no visceral disease, is similar to the case mentioned above; however, he has had longer survival both since initial diagnosis, and after the development of metastases. Recently, Puri *et al.* reported in their observation of skeletal metastasis in 137 advanced pancreatic ductal adenocarcinoma patients that median OS from onset of skeletal metastasis was 4 months [4].

Characteristics that would portend a more favorable prognosis in our patient are his tumor grade (moderately differentiated and not poorly differentiated), negative surgical margin, and adjuvant chemotherapy [7].

However, his lymph node status, with 14/35 positive lymph nodes, would have suggested aggressive disease at the time of diagnosis. Lymph node involvement in pancreatic adenocarcinoma has been implicated in overall survival. Elshaer *et al.*'s review article found 17 studies that showed a high lymph node ratio was associated with decreased overall survival, and 11 studies revealed an increase in the number of positive nodes was associated with decreased overall survival [8]. Venous invasion has also been implicated in early recurrence [9]. These two factors in our patient's pathology would not have foretold 7 years' survival without recurrence.

Whether his participation in a clinical trial that used capecitabine adjuvantly in conjunction with gemcitabine

and docetaxel contributed to his PFS is unknown, but bears discussing. Cunningham *et al.* studied gemcitabine alone (which has been the standard of care) vs. gemcitabine plus capecitabine (GEM-CAP) in a phase III randomized study in patients with previously untreated locally advanced or metastatic disease [10]. They found improved 12-month PFS (8.4% vs. 13.9%) and a trend towards improved 12-month OS (22.0 months vs. 24.3). The authors recommended GEM-CAP as a first line option for advanced disease.

More recently, Neoptolemos *et al.* published data on their multicenter randomized phase 3 trial of gemcitabine vs. gemcitabine and capecitabine in patients with resected pancreatic adenocarcinoma [11]. Not only did they show a statistically significant benefit in median overall survival (25.5 months vs. 28 months), but long-term survival was improved. Overall survival at 5 years was extended from 16.3 % with gemcitabine alone to 28.8 % with gemcitabine and capecitabine [12]. The authors recommend the combination as a new standard of care for adjuvant chemotherapy.

This study also noted the patterns of relapse in their cohort of 730 patients, and 3% of those who recurred had bone lesions. Post-op CA 19-9 level was an independent predictor of survival [12]. In our patient, it was also a good reflection of treatment response and disease recurrence.

Finally, our patient's cutaneous scalp lesion is another rare finding in metastatic pancreatic adenocarcinoma, but not unheard of [13]. It generally indicates a poor prognosis [13, 14] but in this respect, again, this patient has surpassed the 17.5 % one-year survival rate after diagnosis of cutaneous metastasis documented by Horino *et al.* [14].

As for the treatment of this patient's disease, we attempted at every step to preserve quality of life. The 2016 American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for metastatic pancreatic adenocarcinoma states, "Goals of care, patient preferences, treatment response, psychological status, support systems, and symptom burden should guide decisions for treatments" [15]. The recommendation was "FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin; favorable comorbidity profile) or gemcitabine plus nanoparticle albumin-bound (NAB) -paclitaxel (adequate comorbidity profile) should be offered to patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1 based on patient preference and support system available" [15]. All of these aspects were considerations, as well the patient's prior durable response to the adjuvant triplet gemcitabine, taxotere and capecitabine.

Our patient's main concern was to preserve his quality of life. Despite his excellent KPS, given his history of 6 months of adjuvant chemotherapy, there was increased possibility of bone marrow suppression and other toxicities. Further, he was older, with diffuse disease as exhibited by the scalp

metastasis, and the goals of chemotherapy were strictly palliative. Therefore, the regimen agreed to was a reduced dose gemcitabine and nanoparticle albumin-bound paclitaxel, with low dose capecitabine as tolerated. Dose reductions were implemented in response to the patient's side effects.

The newest ASCO guidelines revised in 2018 do recommend FOLFIRINOX as first line and gemcitabine plus nanoparticle albumin-bound paclitaxel as second line [16]; however, at the time of this patient's recurrence, there was still concern and debate about the toxicity profile [17].

With further disease progression in the second year of systemic treatment, our patient was transitioned to liposomal irinotecan and 5FU, which has been recommended as second line for patients failing gemcitabine based therapy [18, 19]. The patient developed worsening side effects; chemotherapy was reduced, then interrupted, then stopped, working with the patient to balance his desire for ongoing treatment with concerns for increasing toxicity.

CONCLUSION

Though this is a unique case, we feel it will add to clinical knowledge in several ways. First, it illustrates the need for close surveillance in patients diagnosed with pancreatic adenocarcinoma, even after successful potentially curative surgery and adjuvant chemotherapy. Further, this case shows the potential for pancreatic adenocarcinoma to metastasize to the bone as a solitary lesion. Finally, it shows the role of CA 19-9 as useful in detecting tumor recurrence and treatment response in a patient whose marker was initially elevated at diagnosis. In our patient, the elevation was the only sign of recurrence and allowed detection of oligometastatic disease, which may have led to better disease control and, possibly, improved survival.

Conflict of Interest

The authors have no conflicts of interests to declare.

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