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CNS Involvement in Pancreatic Adenocarcinoma: a Report of Eight Cases from the Johns Hopkins Hospital and Review of Literature

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Abstract

Purpose—CNS metastasis of pancreatic cancer is extremely rare, although systemic metastasis is very common. We present eight such cases with various forms of nervous system involvement.

Methods—Data was gathered from chart review of 800 patients with pancreatic cancer treated between 2004 and 2012 of which eight patients are described with CNS metastases.

Results—The median age of patients was 61.5 years and the median time to develop CNS metastasis was 29 months. Interestingly, two patients had no other sites of metastasis. The treatment modalities tried included resection followed by radiation, resection alone, or whole brain radiation.

Keywords

CNS metastasis; Pancreatic adenocarcinoma; SMAD4; P53

Introduction

Pancreatic cancer is a universally fatal disease. The only chance of cure is complete surgical resection of the tumor. This is particularly difficult as the disease often presents late in its course. Although metastatic disease is very common, metastasis to CNS is rare. We present eight such cases with CNS involvement from primary pancreatic cancer.

Purpose and Methods

We describe eight patients who were diagnosed with CNS involvement from pancreatic adenocarcinoma at The Johns Hopkins Hospital from 2004 to 2012 from a database of over 800 patients with resected pancreas cancer, therapeutic modalities tried, and their course and outcomes. Patient data was gathered from chart review, and patient characteristics, presentation, treatment of the primary, and treatment used or tried for the metastatic disease were reviewed.

The median age of the patients at the time of diagnosis of pancreatic cancer was 61.5 years with range of 49–70 years, and the median time from diagnosis of pancreatic cancer to development of CNS metastasis was 29 months (range 2–57 months). All patients had imaging to show CNS involvement. Patients 1 and 2 also had brain biopsies to support the diagnosis. Patient 3 had a lumbar puncture. Three patients presented with extremity weakness of some degree. Two patients presented with imbalance, two with blurry vision; one patient had tongue weakness; and one patient presented with headaches, diplopia, and CN VI palsy.

Patients 1,3,5,6, and 7 had adenocarcinoma located in the head of the pancreas. Patient 2 had ampullary adenocarcinoma; Patient 4 had a primary in the tail of the pancreas. Patient 8 had poorly differentiated adenocarcinoma in the head of the pancreas arising from IPMN.

Patients 1, 2, and 7 had P53 mutation and SMAD 4 wild type (Fig. 1). The others were not tested for the same.

Apart from CNS metastasis, patients 1 and 2 had no other metastatic disease. Patient 3 had extensive disease including a paratracheal LN metastasis causing SVC syndrome, subcutaneous tissue, and bone metastasis. Patients 4 and 5 had liver and vertebral involvement. Patient 6 had lungs as the only other metastatic site. Patient 7 had mesenteric lymph node involvement and lung metastasis. Patient 8 had mesenteric, supraclavicular, and retroperitoneal lymph node involvement and lung metastasis.

CNS metastasis for patient 1 included recurrent brain metastasis to left parieto-occipital regions, and the patient underwent three craniotomies and resection followed by whole brain irradiation during the course. Patient 2 had a right parietal mass (Fig. 2) and underwent successful resection of the same with no evidence of recurrence for 9 years when the patient was lost to follow-up (the only surviving patient in the group). Patient 3 had extensive metastatic disease including involvement of CN XII with corresponding features of tongue deviation. The patient was tried with a trial of XRT and gemcitabine-based chemotherapy. Patient 4 developed cerebellar lesions and numerous intra-axial brain lesions including a

large posterior left frontal lesion which extended through the bone and scalp. This patient was tried with whole brain irradiation. Patient 5 presented with imbalance and vertigo post pylorus preserving pancreaticoduodenectomy and was found to have involvement of the clivus and the pituitary stalk and CNVI involvement. Patient 6 had metastasis to anterior vermis herniating to the fourth ventricle (Fig. 3). Patient 7 had metastasis to choroid. Patient 8 had multiple cystic metastasis to cortical/sub-cortical interface most notably in the right middle frontal gyrus and right temporal gyrus (Fig. 4).

Patient 1 was treated with a classic Whipple surgery followed by chemotherapy and radiation. Symptoms of CNS involvement developed approximately 22 months after Whipple. Patient 2 had pylorus preserving pancreaticoduodenectomy followed with chemoradiotherapy. Symptoms of CNS involvement developed 13 months after the pancreaticoduodenectomy. Patient 3 had partial pancreatectomy with standard lymph node dissection and subsequent trial therapy with a GM-CSF-transfected tumor allogenic vaccine. The patient developed diffuse disease along with CN XII involvement 53 months after the Whipple. Patient 4 was diagnosed with metastatic disease and given trial therapy with gemcitabine plus S1. The patient presented with cerebellar metastatic disease 2 months after the initial diagnosis. Patient 5 underwent a classic Whipple surgery, and imaging 2 months post Whipple showed metastasis to the clivus and the stalk. Patient 6 underwent Whipple followed by chemoradiation and developed evidence of metastasis to the vermis herniating in to the fourth ventricle and underwent fractionated stereotactic radiotherapy 43 months after the initial surgery. Patient 7 underwent a Whipple and had chemotherapy with multiple agents. The patient developed choroidal metastasis 36 months after the diagnosis of pancreatic cancer. Patient 8 underwent distal pancreatectomy with spleenectomy followed by chemoradiation. He subsequently developed lung metastasis and later blurry vision 57 months after the initial diagnosis and surgery of the pancreatic carcinoma.

Discussion

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the USA [1].

An estimated 43,920 new cases of pancreatic cancer are expected to occur in the USA in 2012. Since 2004, incidence rates of pancreatic cancer have been increasing by 1.5 % per year. An estimated 37,390 deaths are expected to occur in 2012. For all stages combined, the 1- and 5-year relative survival rates are 26 and 6 %, respectively. Even for those people diagnosed with local disease, the 5-year survival is only 22 %. More than half of patients are diagnosed at a distant stage, for which 5-year survival is 2 % [2].

Local tumor extension or hepatic involvement is common; other common sites include the peritoneum and lungs [3]. On the contrary, pancreatic cancer metastases to the brain are exceedingly rare (0.33 % of pancreatic adenocarcinoma cases as per Pauline et al. [4] vs. 0.57 % as per Park et al. [5]), perhaps owing to the aggressive nature of pancreatic adenocarcinoma and the fact that most patients do not survive long enough to experience clinical manifestations of brain metastasis. It is also a possibility that the actual incidence is higher than reported as many patients may not be evaluated for a CNS lesion as first presentation late in the course of the disease is extremely common with pancreatic

carcinoma. This hypothesis is supported by a higher incidence rate in autopsy studies (7.9 %) [3].

In contrast to previous report [5] by Park et al., the median time after diagnosis of pancreatic cancer to CNS symptoms in our group of patients was 29 months (range 2–57 months).

Three patients, who were tested for Smad4 (Fig. 1), all contained SMAD wild type and mutated P53 further reinforcing the fact that genetic status of pancreatic cancer may in the future have a bigger role in predicting metastatic potential as shown by Donahue et al. [6]. Molecular basis of CNS involvement by pancreatic tumor has not been well studied [7]; however, some parallels may be drawn from well-known perineural [8] affinity of the pancreatic adenocarcinoma.

Surgery appears to have significant benefit in both patients 1 and 2 and, in our opinion, should be considered whenever feasible. Matsumura [9] et al. also reported a case which was treated with surgery and postoperative radiation and was alive for at least 22 months after the surgery and radiation. Lemke et al. [7] also reported two cases who benefitted from surgery.

CNS involvement of various forms of pancreatic cancer including pancreatic somatostatinoma [10] and acinar cell tumor [11] has been reported. This is the largest case series ever reported to the best of our knowledge, and this is only case series reported after the advent of gemcitabine.

Although the survival improvements in pancreatic carcinoma have not been as high as in some other malignancies, as survival improves [12], we will possibly identify more CNS involvement. It is important to recognize that CNS involvement can occur and palliative resection could be of benefit if diagnosed early. Also, given the rarity of pancreatic cancer brain metastasis, neuroimaging surveillance does not appear to be indicated.

Chorioidal metastasis also is a rare phenomenon; incidence was reported at 0.4% by Shah et al. [13].

There are approximately nine [13–16] reported cases in the literature, five of which were reported in a case series by Shah et al. [13].

Cerebellar metastasis appears to be even rarer than choroid and intraparenchymal brain metastasis. A search in PUBMED with key words “cerebellar,” “metastasis,” and “pancreatic adenocarcinoma” shows only one more case reported by Caricato et al. [17]. Thus, the two cases presented above are the second and third cases to the best of our knowledge.

To conclude, we present a variety of cases with different forms of nervous system involvement, each less common than the previous to point that although rare [18], CNS involvement can occur and has been reported sporadically [18–23] and should be considered a possibility given the right clinical picture.

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Fig. 1.

Morphologic and molecular features of brain metastases. Shown are high-powered views of the primary carcinoma and matched brain metastasis that developed in this patient 1 year later. Both the primary and brain metastasis show strong positive nuclear labeling for TP53, indicating a genetic mutation in the *TP53* gene, whereas labeling for SMAD4 is intact indicating the *SMAD4* gene is wild type. All images, $\times 200$

Fig. 2.
High right parasagittal parietal likely intra-axial enhancing mass, with moderate surrounding vasogenic edema. This image is of patient 2

Fig. 3.
Mass located along the anterior margin of vermis herniating into the fourth ventricle. Patient 6

Fig. 4.
Ring enhancing mass at the right caudate head with trace vasogenic edema. The image is of patient 6