Case Report

Pancreatic cancer with leptomeningeal carcinomatosis: case report and review of the literature

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Background: Leptomeningeal carcinomatosis (LMC) is a complication of advanced malignancy that is characterized by metastatic spread of a primary cancer to the pia mater, arachnoid mater, and subarachnoid space. Lung, breast, melanoma, acute lymphoblastic leukemia, and non-Hodgkin lymphoma are the most common cancers that give rise to LMC. In contrast, LMC secondary to pancreatic cancer is exceedingly rare, and there is a paucity of evidence in the literature describing the best evaluation and management strategies for such cases.

Case Description: We describe the case of a 72-year-old man with LMC secondary to pancreatic cancer with parenchymal brain involvement of the brain and cervical cord. We also conducted a literature review, through which we identified 23 reports describing only 25 distinct cases of LMC in pancreatic cancer. Notably, factors including age, sex, and initial pancreatic cancer staging among patients who progress to LMC are highly variable. Interestingly, most patients had no known metastases prior to LMC diagnosis.

Conclusions: More accurate diagnoses and improved cancer therapeutics will likely serve to increase the incidence of LMC and/or brain parenchymal involvement among patients with pancreatic cancer. This report is one of only several in the world to describe the characteristics of this insidious and dangerous disease.

Keywords: Leptomeningeal carcinomatosis (LMC); pancreatic cancer; neuro-oncology; case report

Received: 15 August 2023; Accepted: 09 October 2023; Published online: 28 November 2023.
doi: 10.21037/apc-23-7
View this article at: https://dx.doi.org/10.21037/apc-23-7

Introduction

Leptomeningeal carcinomatosis (LMC) is a complication of advanced malignancy that describes the metastatic spread of a primary cancer to the pia mater, arachnoid mater, and subarachnoid space (1). An estimated 5–8% of solid tumors and 5–15% of hematological cancers are eventually complicated by LMC (2,3). With the greater sensitivity of newer diagnostic modalities and improved efficacy of oncologic treatments over time, LMC has become increasingly prevalent across all primary tumor types (4).

At present, lung, breast, melanoma, acute lymphoblastic leukemia, and non-Hodgkin lymphoma are the most common cancers that give rise to LMC (5). Current management strategies often involve a combination of intra-cerebrospinal fluid (CSF) chemotherapy, systemic therapy, radiotherapy, and supportive measures (6). The prognosis for cancer patients who develop LMC remains

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poor, however, regardless of tumor type. LMC secondary to pancreatic cancer is exceedingly rare, and there is a paucity of evidence in the literature describing the best evaluation and management strategies for such cases.

In this report, we describe the case of a patient with LMC secondary to pancreatic cancer as well as a systematic review of the relevant literature regarding LMC secondary to pancreatic cancers. We performed a comprehensive literature review using Google Scholar, PubMed, and Ovid Web with the following search terms: 'leptomeningeal (LM) carcinomatosis', 'LM metastasis', 'LM disease', and 'LM spread' combined with 'pancreatic cancer' or' 'tumor'. We included all reports in which an abstract or full manuscript was published in English.

Case presentation

A 72-year-old otherwise healthy Eastern European man presented to the Emergency Department (ED) for several episodes of vomiting and abdominal pain that were initially attributed to gastritis. His symptoms failed to improve with a couple weeks of histamine blockers. One month after his initial presentation, he underwent a comprehensive work-up by gastroenterology, including an esophagogastroduodenoscopy (EGD) which showed excessive fluid in the stomach and moderate extrinsic deformity in the first part of the duodenum and endoscopic ultrasound (EUS) that revealed diffuse enlargement of the pancreatic head. At that time, fine needle aspirate (FNA) taken from the pancreatic head was negative for malignancy.

Due to the inconclusive yet concerning nature of his gastrointestinal (GI) work-up, the patient subsequently underwent exploratory laparotomy, cholecystectomy, Roux-en-Y choledochojejunostomy, gastrojejunostomy, and transduodenal core biopsy of the enlarged pancreatic head approximately 1 month later. In the operating room, the patient was found to have a locally advanced, unresectable pancreatic head mass with involvement of the duodenum and direct extension onto the surface of the gallbladder, as well as encasement of the superior mesenteric vein and portal confluence. Core biopsies revealed poorly differentiated pancreatic ductal adenocarcinoma (T4N0M0) with tumor cells staining positive for CK7, but negative for CK20 and CDX2 markers. Duodenal biopsy showed poorly differentiated carcinoma, and gallbladder showed metastatic poorly differentiated carcinoma involving the gallbladder serosa and surrounding soft tissue.

Soon after the diagnosis of pancreatic adenocarcinoma was confirmed by biopsy, he was started on FOLFIRINOX, but his regimen was complicated by febrile neutropenia, thus precipitating a switch to capecitabine. Approximately 3 months later, he was started on neoadjuvant capecitabine and radiotherapy treatments for 5 weeks. Two months following the conclusion of the capecitabine and radiotherapy treatments, the pancreatic mass appeared to have decreased in size, at which point a Whipple procedure was attempted; however, the mass was again found to be unresectable.

Six months after his last treatment, the patient presented to the ED with severe headache, ataxia, dizziness, and vision changes. Magnetic resonance imaging (MRI) brain showed a right cerebellar contrast-enhancing lesion with extensive surrounding edema (*Figure 1*). MRI spine showed multi-level, diffuse leptomeningeal changes consistent with advanced metastasis and thus LMC. At this point, given our high suspicion of LMC and the patient's severe discomfort, we prioritized initiating treatment and controlling the patient's pain over subjecting the patient to multiple lumbar punctures for the sake of definitive diagnosis.

After extensive discussion over goals of care with the patient and his daughter (who acted as an interpreter and medical decision-maker), whole brain radiation therapy (WBRT) was initiated with the aim of maintaining functional independence. He was also started on a steroid regimen of 4 mg dexamethasone every 6 hours with gradual improvement of his neurologic symptoms.

Following treatment, the patient remained ambulatory.

Highlight box

Key findings

- Patient with leptomeningeal carcinomatosis (LMC) with cervical cord and parenchymal brain involvement secondary to pancreatic cancer.
- Systematic literature review of 25 similar cases.

What is known and what is new?

- LMC in pancreatic cancer is rare but may become more common as patient survival increases.
- Clinical symptoms and imaging characteristics of this patient population as provided by our case report and literature review.

What is the implication, and what should change now?

- As treatments and prognosis improve, the incidence of LMC secondary to pancreatic cancer may rise. Clinicians should be aware of this trend and the developing diagnostic criteria for this rare disease.

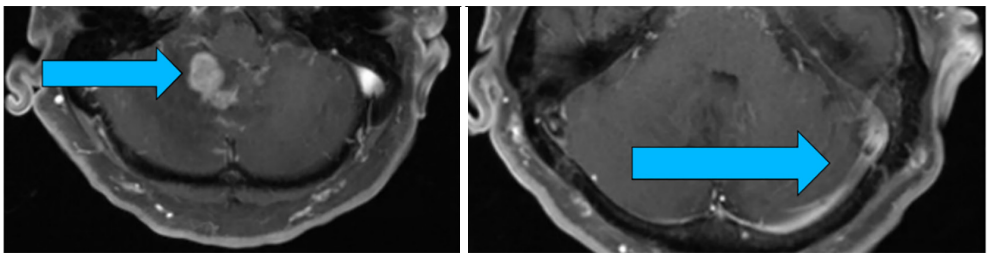

Figure 1 Axial view of T1-weighted post-contrast MRI brain showing an enhancing intracerebellar lesion (left, denoted by blue arrow) with increased enhancement of the cerebellar leptomeninges (right, denoted by blue arrow). MRI, magnetic resonance imaging.

However, his clinical course was complicated by bowel perforation requiring endoscopic drain and gastro-jejunal tube placement. He was then referred to hospice care. Oncology continued to follow the patient till about 6 months after the diagnosis of LMC, when his daughter explained by phone that her father's pain was well-controlled and that he wished to pass peacefully in his home country within Eastern Europe.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Clinical reports of LMC are scarce. This is especially the case with pancreatic cancer. While it is known that LMC occurs more frequently with certain types of tumors, the risk factors that may predispose a patient to developing LMC are not always apparent. Furthermore, with few cases to compare to, clinicians may be unsure of when to initiate diagnostic work-up for the disease. In this case report, we described one case of a male patient who developed LMC in the setting of pancreatic cancer.

This case report represents a valuable contribution to the literature, especially when considering the findings of our literature review. Overall, we identified 23 reports describing only 25 distinct cases of LMC in pancreatic cancer (*Table 1*) (7-29). Among these reports, analysis of the studies published by Yagi *et al.* and Hirota *et al.* were limited since the abstracts were written in English, while the manuscripts were written in Japanese (7,8). One report was completely excluded from review because the data was limited to the abstract and was written completely in Italian (9). The age range of patients included was wide (36–80 years old) and the majority were male (7,10-17,20,24,25,27,29). Interestingly, many patients had no known metastases prior to their diagnosis of LMC (7,13,14,16-22). Like our patient, several patients endorsed headache (7,10,11,15,16,18-26), gait ataxia (14,27,28), and nausea with vomiting (7,15,19,22). Six patients did not receive any treatment whatsoever after diagnosis (16,17,19,29); however, like our patient, 9 different patients underwent WBRT (8,10-12,18,22,25,30) and 7 patients began a steroid regimen (10,13,21,22,27,28,30). Finally, all but 3 (8,25,26) of these patients were deceased by 6 months following LMC diagnosis.

Based on our literature review alone, the age, sex, and initial pancreatic cancer staging among patients who progress to LMC are highly variable. It is also alarming to note that most patients had no known metastases prior to LMC diagnosis. One previously identified risk factor for eventual LMC has been defined as piecemeal resection of posterior fossa metastases (31,32); however, this finding is limited to patients who had diagnosed brain metastases prior to LMC, and it is not specific to those with primary pancreatic cancer.

Current diagnostic and treatment methods for LMC in general are also scarce. It is generally held that the gold standard of LMC diagnosis is CSF cytology, but the diagnosis is often made in modern practice with the use of MRI (1). Even patients with clear LMC on MRI may have negative cytology, and multiple lumbar punctures are sometimes necessary to solidify diagnosis given the low sensitivity of CSF cytology for malignant cells (33). In a 2020 review article on leptomeningeal metastasis from solid tumors, Thakkar *et al.* proposed an algorithm for treatment strategies based on risk stratification at the time of diagnosis

Table 1 Summary of literature review describing 25 distinct cases of LMC in the setting of pancreatic cancer

Publication [year]	Age, years/sex	Initial cancer staging	Known metastases prior to diagnosis	Symptoms upon diagnosis of LMC	LMC treatment modalities	Survival following LMC diagnosis (months)
Iwatsuka *et al.* [2021]	57/F	T3N1M1	None	Seizure, headache, nausea, limb numbness, hearing loss	Dexamethasone, nab-PTX + GEM, WBRT	5
Ceccon *et al.* [2020]	51/M	T1NxM1	L kidney, spleen, lung	Headache, neck stiffness	Gemcitabine + erlotinib, FOLFIRINOX, nab-PTX + GEM	3
Ikeda *et al.* [2020]	59/M	T2NxM1	Liver	Neck stiffness, lower extremity weakness, dysarthria	None (modified FOLFIRINOX and nab-PTX + GEM prior to dx)	<1
Johnson *et al.* [2018]	53/M	T1NxM1	Liver	Occipital headaches, dysarthria, word-finding difficulty	WBRT, intrathecal topotecan, CAPIRI, bevacizumab	>12
Trinh *et al.* [2016]	58/M	None—diagnosed at autopsy	None	Worsening headache, paraparesis, unilateral CNVII palsy	Erroneously treated for TB meningitis given absence of cancer cells in repeat LP	1
Amico *et al.* [2016]	42/F	T3N0M1	Liver	Headache, neck pain	Steroids, WBRT	1
Amico *et al.* [2016]	57/M	T3N1M1	Liver, retroperitoneal LN, lungs	Headache, back pain	WBRT	4
Yoo *et al.* [2015]	80/M	T4NxM1	Liver	Headache, seizure, weight loss	WBRT with palliative intent	Lost to follow-up
Naqvi *et al.* [2015]	58/F	T1NxM0	None	Confusion, agitation	Dexamethasone	<1
Hong *et al.* [2014]	72/F	T3NxM1	Liver	Headache, slurred speech, ataxia	Palliative dexamethasone	8.5
Anne *et al.* [2013]	45/F	Unclear; dx was “metastatic adenocarcinoma of unknown primary with pancreatic features”	Various peritoneal implants	Headache, slurred speech, agitation	Palliative care	Lost to follow-up
Rao *et al.* [2013]	57/M	Poorly differentiated, T3NxM1	Bone	Seizure, R leg weakness, neck stiffness, photophobia, urinary incontinence	WBRT, palliative RT (spine, R shoulder), FOLFIRINOX[†]	Transitioned to hospice after 2 cycles of chemotherapy, lost to follow-up
Blows *et al.* [2012]	72/M	T3N2M1	Liver, multiple LN	Sudden onset hearing loss, gait ataxia	dexamethasone	<1
Minchom *et al.* [2010]	59/M	T2N0M1	None	Left leg weakness, intermittent seizures	Intrathecal methotrexate, cytarabine, hydrocortisone	<1

Table 1 (*continued*)

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Publication [year]	Age, years/sex	Initial cancer staging	Known metastases prior to diagnosis	Symptoms upon diagnosis of LMC	LMC treatment modalities	Survival following LMC diagnosis (months)
Hirota *et al.* [2008]	64/M	T3NxMx	None	Vague left-sided pain	WBRT, gemcitabine + S-1 (tegafur, CDHP, Oxo)	42
Rebischung *et al.* [2008]	44/F	T1N1M1	Superior mesenteric vein	Headache, static instability	methotrexate, thiotepa, MTX-^{125}IUdR	8
Grira *et al.* [2007]	55/M	TxNxM1	None	Vision loss, vertigo, ataxia	None	1.5
Yagi *et al.* [2006]	64/M	T4NxM1	None	Fever, vomiting, and headache	Gemcitabine, RT	Lost to follow-up after 20 months of symptom onset
Giglio *et al.* [2005]	53/F	T3N1M1	None	Headache, visual complaints	WBRT, doxorubicin, cytoxan	15
Ferreira Filho *et al.* [2001]	49/M	T2N1M1	Ribs, supraclavicular LN	Headache, vomiting	Intrathecal methotrexate, cytarabine, thiotepa	1.5
Kurzaj *et al.* [1980]	36/M	Acinar cell carcinoma, T3N1M1	None	Subdural hemorrhage, progressive headache, papilledema, abdominal pain	None—diagnosed at autopsy	0.5
Little *et al.* [1974]	42/M	TxNxM1	None	Diagnosis established at autopsy	None—diagnosed at autopsy	Unspecified, ranged from 2 weeks to 8 months (average 2 months)
Olson *et al.* [1974]	46/F	TxNxM1	Bone	Right hemiparesis, followed by progressive numbness, drowsiness, abnormal behavior, short attention span	Prednisone, WBRT	1.75
McCormack *et al.* [1953]	60/F	T3NxM1	None	Nausea, vomiting, occipital headaches, hazy vision	None	<2 months of symptom onset
McCormack *et al.* [1953]	43/F	Undifferentiated, T3N1M1	None	Back pain, neck pain, L arm numbness, and confusion; then headaches, vomiting, flaccid paralysis, deafness, and blindness	None	1.25

Case reports by Galatioto *et al.* [1975] and Hirota *et al.* [2008] were not included in this review because the abstracts were not publicly available for review and both studies were written entirely in either Italian or Japanese, respectively. †, Yagi *et al.* [2016]—in Japanese, information limited to abstract. LMC, leptomeningeal carcinomatosis; F, female; nab-PTX, nanoparticular albumin-bound paclitaxel; GEM, gemcitabine; WBRT, whole brain radiation therapy; M, male; L, left; FOLFIRINOX, 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin; CAPIRI, capecitabine and irinotecan; CNVII, Cranial Nerve 7; TB, tuberculosis; LP, lumbar puncture; LN, lymph nodes; dx, diagnosis; R, right; RT, radiation therapy.

and clinical presentation. For instance, it is suggested that low risk symptomatic and asymptomatic individuals could benefit from systemic therapy; however, due to the poor prognosis that accompanies leptomeningeal disease, many patients could reasonably pursue symptomatic treatment, along with palliative and comfort care, even at the time of initial diagnosis (34).

This case report and the accompanying literature review are a valuable addition to the literature on this exceedingly rare diagnosis. In fact, the one significant limitation to this study was the sheer lack of existing reports describing LMC in pancreatic cancer. At present, the outlook may seem grim for those diagnosed with LMC. Even so, we suggest that neurologists and neuroradiologists familiarize themselves with the known characteristics of this disease, such that they remain vigilant for new cases.

Conclusions

At present, pancreatic cancer associated LMC is extremely rare, but advancements in the treatment of pancreatic cancer with longer survival rates, and more accurate diagnosis of LMC, will likely lead to a higher incidence of LMC and/or parenchymal involvement for this tumor type. To date, as with LMC associated with other solid tumors, survival is poor.

Acknowledgments

Funding: None.

Footnote

Peer Review File: Available at https://apc.amegroups.com/article/view/10.21037/apc-23-7/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apc.amegroups.com/article/view/10.21037/apc-23-7/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/apc-23-7
Cite this article as: Seu M, Perilla ASP, Melian E, Schneck MJ. Pancreatic cancer with leptomeningeal carcinomatosis: case report and review of the literature. Ann Pancreat Cancer 2023;6:12.

