Peer Review File
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Reviewer A

Comments to the Author

This case report presented a patient with leptomeningeal carcinomatosis (LMC) from pancreatic cancer. This article is meaningful because the development of LMC from pancreatic cancer is rare, and no specific treatments have been reported. However, this report has several problems.

Major comments

Comment 1: Not a few cases of LMC from pancreatic cancer were previously reported. Therefore, not only the rarity but also the novelty is necessary for forward reports. However, the novel findings were unclear in this report. Please describe the novelty of the case.

Reply 1: We acknowledge that this case in particular was not necessarily novel, but we believe that it was important to report this case because it pancreatic cancer progressing to leptomeningeal carcinomatosis is still rare. In the past, pancreatic cancer patient prognosis was poor enough that they would not have lived long enough to reach this diagnosis. For that reason, we believed that this case would be an important contribution to the literature.

Comment 2: LMC from pancreatic cancer is not extremely rare, over 30 cases were reported so far. The author's literature research is insufficient. Please add at least the following reports to the references. In addition, literature research should be performed again.

Rebischung C, Hoffmann D, Stefani L, et al. First human treat- ment of resistant neoplastic meningitis by intrathecal administration of MTX plus 125IUdR. Int J Radiat Biol 84: 1123-1129, 2008.

Blows SJ, Morgan R, Dhariwal U, Petts G, Roncaroli F. Pancre- atic adenocarcinoma presenting with sudden onset bilateral deaf- ness secondary to metastatic leptomeningeal infiltration. Age Age- ing 41: 818-819, 2012.

Anne M, Ahmad N, Lee P, Aziz M, Lebowicz Y. An unusual presentation of isolated leptomeningeal disease in carcinoma of un- known primary with pancreatic features. J Investig Med High Im- pact Case Rep 1: 2324709613494830, 2013.

Naqvi SA, Ahmed I. Carcinomatous meningitis: a rare complica- tion of pancreatic adenocarcinoma. J Coll Physicians Surg Pak 25: 458-459, 2015.

Trinh VT, Medina-Flores R, Chohan MO. Leptomeningeal carcinomatosis as primary manifestation of pancreatic cancer. J Clin Neurosci 30: 124-127, 2016.

Johnson WR, Theeler BJ, Van Echo D, Young P, Kwok M. Treatment of leptomeningeal carcinomatosis in a patient with metastatic pancreatic cancer: a case report and review of the literature. Case Rep Oncol 11: 281-288, 2018.

Ikeda Y, Yoshida M, Ishikawa K, et al. Pancreatic cancer with leptomeningeal carcinomatosis: case report and literature review. Int Cancer Conf J 9: 96-100, 2020.

Ceccon G, Wollring M, Brunn A, et al. Leptomeningeal carcino- matosis in a patient with pancreatic cancer responding to nab- paclitaxel plus gemcitabine. Case Rep Oncol 13: 35-42, 2020.

Iwatsuka K, et al. Treatment Outcome of Nab-paclitaxel Plus Gemcitabine for Leptomeningeal Carcinomatosis from Pancreatic Ductal Adenocarcinoma: An Autopsy Case Report. Internal Medicine: 4456-20, 19 Jun 2021.

Reply 2: Thank you for bringing these reports to our attention. We have updated our literature review and summary table(s) accordingly. (see updated citations in lines 142-149, Table 1, and References list)

Comment 3: Although the MRI findings support LMC diagnosis, LMC is definitively diagnosed by cerebrospinal fluid cytology via a lumbar puncture, or autopsy. Are there any histological or cytological evidences of LMC? Otherwise, this patient is not definitively diagnosed with LMC.

Reply 3: We acknowledge that LMC is often definitively diagnosed by CSF cytology; however, a lumbar puncture was deferred given the severity of the patient's pain and discomfort at the time of suspected LMC and the sheer extent of metastases and leptomeningeal involvement evident on imaging alone. It has been shown that multiple lumbar punctures are sometimes needed because of the low sensitivity of CSF cytology for malignant cells (see reference #34). Furthermore, even patients with clear LMC on MRI may have negative cytology (see reference #1). Given our high suspicion of LMC, we prioritized initiating treatment and controlling the patient's pain over subjecting the patient to multiple LPs for the sake of definitive diagnosis. Our clinical rationale is now included within the manuscript (see lines 112-115, 158-163, in red).

Minor comments

Comment 1: Stage of the pancreatic cancer is unclear. Details of the pancreatic cancer according to TNM classification should be added.

Reply 1: Per review of previous oncology and radiology notes, our patient's pancreatic cancer TNM classification at the time of diagnosis was the following: T4N0M0 (see line 95, in red)

Comment 2: The cause of death was not described (e.g., progression of primary lesion, progression of LMC, and other cause). In previous reports, not a few patients died from LMC progression although systemic chemotherapy was effective for primary pancreatic lesion. Systemic chemotherapy is generally regarded as ineffective for LMC because of it's poor intracerebral fluid transferability. Therefore, the cause of death is important.

Comment 2: Unfortunately, there is scant documentation available for review past the point where the patient was transitioned to hospice care. The patient had expressed a desire to pass away peacefully in his home country within Eastern Europe, hence why we lost him to follow-up at about 6 months after diagnosis of LMC. This information is now reflected in the main body of the text (see lines 121-126, in red).

Reviewer B

Comment 1: This is an important case representation and helps with the current body of literature available on the subject matter.

Please provide further information about patients case, ie what were findings of ex-lap? what happened after it, resection? if not why not. also please provide initial information on how patient presented, his initial clinical staging. this area of case presentation needs a little bit more work.

Also histological information about grade, differentation, etc would be helpful to understanding biology of tumor.

it is important in the case description to clearly note that there was no evidence of other sites of metastases in the patient , if that is indeed the case if that is likely many other patients. It would be good to give some biological insight into why is it that some of these

If there is any information available on the NGS/sequencing of this patient and others from cited literature, would good to include

Reply 1: Thank you for your feedback. The patient's clinical course is described in much greater detail now (see lines 79-126, in red). Biopsy results are specified within this text (see lines 94-99, in red).