CASE REPORT

Treatment Outcome of Nab-paclitaxel Plus Gemcitabine for Leptomeningeal Carcinomatosis from Pancreatic Ductal Adenocarcinoma: An Autopsy Case Report

Kunio Iwatsuka¹, Daiichiro Kikuta¹, Hitoshi Shibuya¹, Masahiro Ogawa¹, Takuji Gotoda¹, Mitsuhiko Moriyama¹, Hiroshi Nakagawara², Akihiro Hemmi³ and Kenji Yamao⁴

Abstract:
A 57-year-old woman with a sudden-onset seizure was hospitalized. Brain magnetic resonance imaging findings led to a suspicion of leptomeningeal carcinomatosis (LMC) without a brain parenchymal tumor, and abdominal computed tomography showed a tumor in the pancreatic tail. Endoscopic ultrasonography-guided fine needle aspiration of the pancreatic mass revealed adenocarcinoma. Therefore, LMC from pancreatic ductal adenocarcinoma was strongly suspected. She received three courses of nab-paclitaxel plus gemcitabine and whole-brain radiation. Shortly thereafter, she developed a severe consciousness impediment and died. A pathological autopsy showed adenocarcinoma in a wide area of the leptomeninges.

Key words: leptomeningeal carcinomatosis, pancreatic ductal adenocarcinoma, chemotherapy, radiation therapy

(Intern Med 60: 3743-3748, 2021) (DOI: 10.2169/internalmedicine.4456-20)

Introduction

Metastatic leptomeningeal carcinomatosis (LMC) is defined as infiltration of the leptomeninges by malignant cells and it is a fatal complication of cancer (1-5). LMC is estimated to occur in from 3% to 8% of patients with solid cancers (6) and it is a devastating complication of such cancers; the median survival time is less than 2 months without treatment (7). In patients with pancreatic ductal adenocarcinoma (PDAC), metastasis to the central nervous system (CNS) is generally rare (occurring in approximately 0.3% of all cases) (8). In particular, the development of LMC metastasis is quite rare: only 17 cases of LMC from PDAC have been reported to date (9-25). LMC is a serious complication of PDAC with an extremely poor prognosis and limited treatment options. Few articles to date have described the treatment approach for LMC from PDAC (11, 13-15, 18, 19, 23, 25). In this report, we present an autopsy case of LMC from PDAC in a patient who was treated with nab-paclitaxel plus gemcitabine (nab-PTX+GEM).

Case Report

A 57-year-old woman without any notable medical history was transferred to our hospital by ambulance because of a sudden-onset seizure. The seizure was stopped by the intravenous injection of diazepam. However, her severe consciousness impediment did not improve. Symptoms of meningeal irritation (stiff neck, Brudzinski’s sign, and Kernig’s sign) were not present. Magnetic resonance imaging (MRI) of the brain revealed edematous cerebral parenchyma of the right frontal lobe (Fig. 1A) and leptomeningeal enhancement around the right to left cerebral folia (Fig. 1B). Although leptomeningeal metastasis was suspected, a brain parenchymal tumorous lesion was noticeably absent. Abdominal computed tomography (CT) showed a tumor in the tail of the pancreas, and the tumor was invading the splenic...
admistered as neurogenic symptomatic therapy. Her consciousness gradually improved: her Japan Coma Scale score on the first, second, and fourth days after admission was III-200, II-10, and I-1, respectively. Beside the consciousness impairment, headache, nausea, and limb numbness were seen. These neurogenic symptoms also suggested that LMC had caused intracranial hypertension.

On the 12th day after admission, endoscopic ultrasonography-guided fine needle aspiration of the pancreatic mass lesion was performed, and ductal adenocarcinoma was identified. As a result, the patient was clinically diagnosed with PDAC (cT3N1M1 Stage IV). In general, LMC is definitively diagnosed by cerebrospinal fluid (CSF) cytology via a lumbar puncture. However, multiple lumbar punctures are sometimes needed because of the low sensitivity of CSF cytology for malignant cells (26). The patient refused lumbar puncture because of the period of time required to achieve a definitive diagnosis and the possible complications of lumbar puncture. Therefore, we prioritized treatment for PDAC, and systemic chemotherapy was begun 19 days after admission.

We chose the combination of nab-PTX+GEM, which was the first-line regimen for unresectable PDAC at that time in Japan. The regimen comprised nab-PTX (125 mg/m\(^2\)) followed by GEM (1,000 mg/m\(^2\)) administered on days 1, 8, and 15 every 4 weeks (one cycle). Shortly after chemotherapy administration, the patient developed an exacerbation of her headache and a left hearing impairment associated with LMC. Thus, a total of 20 Gy of whole-brain radiation therapy (WBRT) was performed as symptomatic therapy, and her symptoms were gradually relieved. The patient then developed two episodes of neutropenia associated with chemo-
therapy. Therefore, the dosages of nab-PTX and GEM were reduced to 80% and 60%, respectively, from the second dose in the first cycle and first dose in the third cycle.

After three courses of chemotherapy, abdominal CT showed a slightly reduced mass volume of the PDAC (Fig. 3). However, brain MRI revealed widespread LMC from the right to left cerebral folia (Fig. 4). The carbohydrate antigen 19-9 level after the first, second, and third course of chemotherapy was 1,080 U/mL, 623 U/mL, and 1,613 U/mL, respectively. After the third course, the patient developed a consciousness impediment and left hearing impairment (Japan Coma Scale score of I-3) and was readmitted on an emergency basis (108 days after the first visit). Although neurogenic symptomatic therapy was promptly administered, the patient’s consciousness level worsened, and she finally died 161 days after the first visit. A pathological autopsy revealed well-differentiated adenocarcinoma throughout a wide area of the bilateral leptomeninges. Brain parenchymal involvement was not detected (Fig. 5). Cancer tissue was not detected in the spinal pia mater. Well-differentiated tubular adenocarcinoma measuring 4 cm in size was identified in the pancreatic tail (Fig. 6).
damage of cancer cells or nests, which is regarded as a treatment effect, was not seen in either the primary PDAC lesion or leptomeninges. Additionally, several metastatic lymph nodules were detected, including the para-aorta lymph nodules, and a single liver metastasis with a diameter of 1 cm was detected in liver segment 4. Despite the inability to confirm the definitive diagnosis before treatment, LMC from PDAC was still suspected.

Discussion

Symptoms of LMC may include generalized findings such as headache and nausea, or patients may exhibit focal neurologic deficits that reflect the location of the involved leptomeninges, cranial neuropathies, and focal motor deficits (7). Symptomatic therapy is occasionally required for patients with LMC, and WBRT is commonly used. WBRT promptly provides significant palliation for neurogenic symptoms associated with CNS metastasis (7). The diagnosis of LMC is confirmed by neuropathological examination of contrast-enhanced brain MRI and CSF analysis. Brain MRI shows leptomeningeal contrast enhancement, subependymal deposits, nodular enhancement, and hydrocephalus; these findings support the diagnosis (7). The definitive diagnosis is difficult in most patients because it requires the detection of malignant cells on CSF cytology obtained via lumbar puncture. Malignant cells are detected in the initial CSF sample in only 50% of patients with LMC (26). Thus, multiple lumbar punctures are sometimes required. Occasionally, the diagnosis must be confirmed comprehensively (e.g., MRI findings, existence of advanced cancer, and elevated tumor markers) if malignant cells are not detected.

Systemic chemotherapy is a common treatment for unresectable PDAC but it is generally regarded as ineffective for LMC because only a limited number of anticancer drugs have shown good intracerebral fluid transferability (29). Although the effectiveness of intrathecal chemotherapy for brain metastasis has been reported, the evidence level remains insufficient: only small case series have so far been published (30). Thus, systemic chemotherapy with good intracerebral fluid transferability is reasonable for the treatment of LMC from PDAC in daily clinical practice. Nevertheless, most patients with PDAC have already undergone several treatment regimens when LMC develops, and the available regimens are generally limited.

The combination of nab-PTX+GEM is widely used as the first-line regimen for unresectable PDAC (31). However, only one report has focused on the treatment outcomes for LMC from PDAC. In this report, Ceccen et al. (25) described a 51-year-old man with LMC from PDAC that responded to nab-PTX+GEM in terms of elimination of tumor cells from the CSF and concurrent long-term clinical improvement (3 months after diagnosis of LMC). The patient finally developed neurogenic disorders associated with LMC progression (palsies of cranial nerves, gait disorder, and severe consciousness impediment) and soon died.

In our case, the primary PDAC lesion decreased in size as it responded to nab-PTX+GEM. However, the LMC lesion spread widely throughout the cerebral folia. Although the patient finally died of LMC progression, her survival time exceeded that of most patients with LMC described to date (Table). This result might indicate that nab-PTX+GEM can provide a longer survival period than other regimens (e.g., thiotepa+methotrexate+cytarabine, methotrexate+cytarabine+gemcitabine, and pelareorep+carboplatin+paclitaxel) (11, 15, 19). However, nab-PTX+GEM seems to be
The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Angela Morben, DVM, ELS, for editing a draft of this manuscript.

References

1. Rudnicka H, Niwinska A, Grusfeld A, Pienkowski T. Diagnosis and treatment of carcinoid meningitis: a challenge to the neurologist and oncologist. Pol J Neurosurg 37: 811-824, 2003.
2. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastasis: a retrospective case series. J Neurooncol 109: 143-148, 2012.
3. Chamberlain MC, Sando AD, Press GA. Leptomeningeal metastasis: a comparison of gadolinium-enhanced MR and contrast-enhanced CT of the brain. Neurology 40: 435-438, 1990.
4. Groves MD, Glantz MJ, Chamberlain MC, et al. A multicenter phase II trial of intrathecal topotecan in patients with meningeal malignancies. Neuro Oncol 10: 208-215, 2008.
5. Niwitska A, Rudnicka H, Murawska M. Breast cancer leptomeningeal metastasis: propensity of breast cancer subtypes for leptomeninges and the analysis of factors influencing survival. Med Oncol 30: 408, 2013.
6. Lee JL, Kang YK, Kim TW, et al. Leptomeningeal carcinomatosis in gastric cancer. J Neuro Oncol 66: 167-174, 2004.
7. Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: leptomeningeal metastases in solid tumors. Surg Neurol Int 30: S265-S288, 2013.
8. Park KS, Kim M, Park SH, Lee KW. Nervous system involvement by pancreatic cancer. J Neuro Oncol 63: 313-316, 2003.
9. Galatiero S, Savetieri G. Meningeal carcinomatosis secondary to a primary pancreatic tumour. Acta Neurol (Napoli) 30: 359-367, 1975 (in Italian).
10. Kurzaj E, Kopczynski S, Barowska Lehman J, Ludwickzak R. Subdural haematoma associated with dural carcinomatosis in a patient with primary carcinoma of the pancreas. Neurochirurgia (Stuttg) 23: 13-17, 1980.
11. Ferreira Filho AF, Cardoso F, Di Leo A, et al. Carcinomatous meningitis as a clinical manifestation of pancreatic carcinoma.
Ann Oncol 12: 1757-1759, 2001.
12. Grira MT, Ben Jemaa HM, Lamnouchi TM, Benammou SA. Meningitis revealing pancreatic carcinoma. Neurosciences (Riyadh) 12: 256-258, 2007.
13. Hirota M, Yagi Y, Yamashita K, Okamoto K, Sato T, Ichihara T. A long survival case of unresectable pancreatic cancer by chemoradiotherapy with gemcitabine as the key drug. Gann To Kagaku Ryoho 35: 2413-2416, 2008 (in Japanese, Abstract in English).
14. Rebischung C, Hoffmann D, Stefani L, et al. First human treatment of resistant neoplastic meningitis by intrathecal administration of MTX plus 125I UdR. Int J Radiat Biol 84: 1123-1129, 2008.
15. Minchom A, Chan S, Melia W, Shah R. An unusual case of pancreatic cancer with leptomeningeal infiltration. J Gastrointest Cancer 41: 107-109, 2010.
16. Blows SJ, Morgan R, Dharwul U, Petts G, Roncaroli F. Pancreatic adenocarcinoma presenting with sudden onset bilateral deafness secondary to metastatic leptomeningeal infiltration. Age Ageing 41: 818-819, 2012.
17. Anne M, Ahmad N, Lee P, Aziz M, Lebowicz Y. An unusual presentation of isolated leptomeningeal disease in carcinoma of unknown primary with pancreatic features. J Investig Med High Impact Case Rep 1: 2324709613494830, 2013.
18. Rao R, Sadashiv SK, Goday S, Monga D. An extremely rare case of pancreatic cancer presenting with leptomeningeal carcinomatosis and synchronous intraparenchymal brain metastasis. Gastrointest Cancer Res 7: 90-92, 2013.
19. Hong CS, Kurt H, Elder JB. Asynchronous leptomeningeal carcinomatosis from pancreatic cancer: a case report and review of the literature. Clin J Gastroenterol 7: 434-440, 2014.
20. Naqvi SA, Ahmed I. Carcinomatous meningitis: a rare complication of pancreatic adenocarcinoma. J Coll Physicians Surg Pak 25: 458-459, 2015.
21. Yoo IK, Lee HS, Kim CD, et al. Rare case of pancreatic cancer with leptomeningeal carcinomatosis. World J Gastroenterol 21: 1020-1023, 2015.
22. Trinh VT, Medina-Flores R, Chohan MO. Leptomeningeal carcinomatosis as primary manifestation of pancreatic cancer. J Clin Neurosci 30: 124-127, 2016.
23. 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.
24. 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.
25. Ceccon G, Wollring M, Brunn A, et al. Leptomeningeal carcinomatosis in a patient with pancreatic cancer responding to nab-paclitaxel plus gemcitabine. Case Rep Oncol 13: 35-42, 2020.
26. Kesari S, Batchelor TT. Leptomeningeal metastases. Neuror Clin 21: 25-66, 2003.
27. Chang EL, Maor MH. Standard and novel radiotherapeutic approaches to neoplastic meningitis. Current Oncol Rep 5: 24-28, 2003.
28. Lai R, Abrey LE, Rosenblum MK, DeAngelis LM. Treatment-induced leukoencephalopathy in primary CNS lymphoma: a clinical and autopsy study. Neurology 62: 451-456, 2004.
29. Bhowmik A, Khan R, Ghosh MK. Blood brain barrier: a challenge for effectual therapy of brain tumors. Biomed Res Int 2015: 320941, 2015.
30. Lee DW, Lee KH, Kim JW, Keam B. Molecular targeted therapies for the treatment of leptomeningeal carcinomatosis: current evidence and future directions. Int J Med Sci 17: 1074-1085, 2016.
31. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369: 1691-1703, 2013.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).