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Case Report

Leptomeningeal Carcinomatosis in a Patient with Pancreatic Cancer Responding to Nab-Paclitaxel plus Gemcitabine

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Leptomeningeal metastasis · Carcinomatous meningitis · FOLFIRINOX · Blood-brain barrier

Abstract
Leptomeningeal carcinomatosis is an extremely rare, but devastating complication in pancreatic cancer patients with a poor prognosis despite multimodal treatment. We present a 51-year-old male patient with the very rare condition of leptomeningeal carcinomatosis originating from pancreatic cancer. He presented to our hospital with severe headache and neck stiffness 30 months after systemic chemotherapy. Cerebral and spinal MRI as well as cerebrospinal fluid examination confirmed the diagnosis of leptomeningeal carcinomatosis. The patient responded to gemcitabine plus nab-paclitaxel in terms of elimination of tumor cells from the CSF and concurrent clinical improvement for 3 months. The observed findings suggest that the combination of gemcitabine plus nab-paclitaxel is potentially effective in affected cerebrospinal fluid of pancreatic carcinoma patients.

Background

Leptomeningeal carcinomatosis (LC) is a very aggressive complication of solid tumors and hematologic malignancies and occurs in approximately 5–15% of all cancer patients [1–3]. Symptoms are unspecific and may vary according to the localization of the cancer cells in

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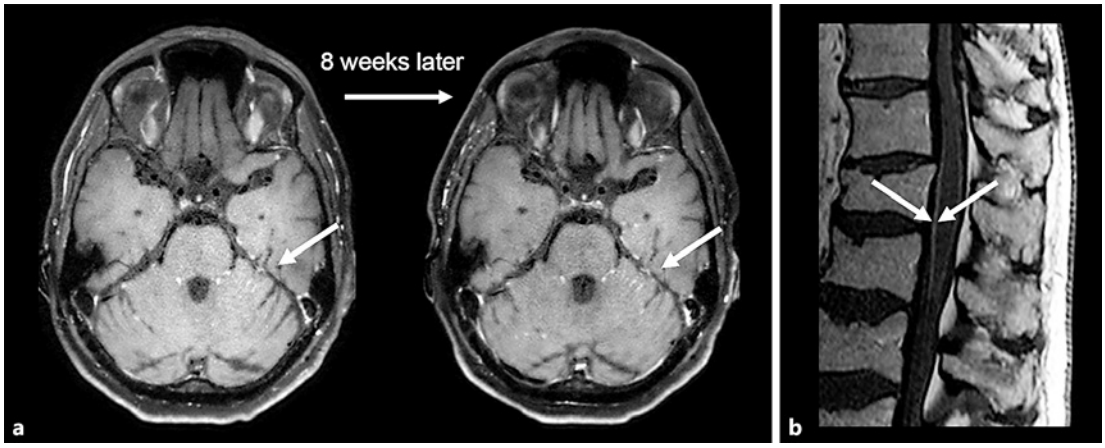

Fig. 1. a Contrast-enhanced cerebral MRI at baseline (left) with nodular and linear contrast enhancement in the cerebellum, consistent with leptomeningeal carcinomatosis. Follow-up MRI (right-hand side) shows a slight increase in contrast enhancement. **b** Contrast-enhanced spinal T1-weighted MRI of the spine (right) with leptomeningeal contrast enhancement.

the central nervous system. The most frequent clinical signs are headache, neck stiffness, changes in mental status, cranial nerve palsies, and spinal signs including dermatomal sensory loss, radicular pain, bowel and bladder dysfunction, and limb weakness [4, 5]. It predominantly occurs in breast and lung cancer as well as in melanoma [6]. Diagnosis is confirmed by the neuropathological examination of the cerebrospinal fluid (CSF) and contrast-enhanced MRI of the brain and spine. Usually, MRI shows leptomeningeal contrast enhancement [7, 8]. Subependymal deposits, nodular enhancement and hydrocephalus may also be seen. Most common CSF findings are pleocytosis of variable extent, high protein and lactate concentration, hypoglycorrhachia, elevated opening pressure, and, most importantly, presence of cancer cells [1, 4]. Not infrequently, to identify cancer cells, multiple lumbar punctures are required [9]. Despite aggressive treatment, prognosis remains dismal. Median survival is only within the range of weeks without treatment [6, 10, 11] and several months in patients undergoing multimodal treatment including systemic therapy, radiotherapy and intrathecal chemotherapy [12–16]. Thus, novel therapeutic options are urgently needed. Here, we present a patient with the extremely rare condition of LC secondary to pancreatic cancer who showed treatment response to nab-paclitaxel plus gemcitabine.

Case Description

A 51-year-old male patient with abdominal pain for several months was diagnosed with pancreatic cancer (Ca 19-9 and CK7 positive, CDX2 negative). At initial diagnosis, the left kidney and the spleen were already infiltrated by the tumor (UICC stadium IVB). Furthermore, X-ray examination of the thorax suggested multiple lung metastases. Due to the infiltration of the adjacent abdominal organs, complete surgical resection was not possible. Thus, first-line treatment consisted of gemcitabine plus erlotinib according to the RASH trial [17]. Thirteen months later, chemotherapy was changed to the FOLFIRINOX regimen (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin) due to local tumor progression. Following the second-line FOLFIRINOX regimen, the patient was stable for further 17 months. Thirty-two months after initial diagnosis of pancreatic cancer, the patient presented with severe headache. Neuro-

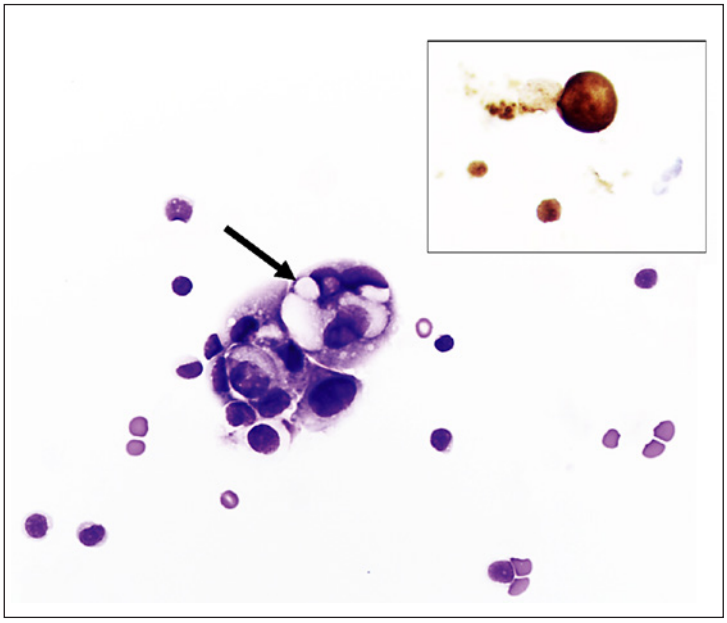

Fig. 2. CSF findings: clusters of epithelial tumor cells with enlarged, hyperchromatic nuclei and a small cytoplasm. Note prominent mucoid cytoplasmic vacuoles leading to signet ring cells (arrow). Pappenheim staining; original magnification ×400. Insert: the tumor cells express CK7. Immunohistochemistry with mouse anti-human cytokeratin 7 (DCS, Hamburg, Germany); original magnification ×500.

logical examination revealed neck stiffness without further neurological deficits. Cerebral and spinal contrast-enhanced MRI showed leptomeningeal enhancement (Fig. 1); lumbar puncture revealed elevated protein (0.52 g/dL), low glucose (42 mg/dL), increased lactate (3.9 mmol/L), and a mild pleocytosis (23 cells/μL). CSF cytology revealed clusters of enlarged, pleomorphic epithelial cells harboring large nuclei and prominent cytoplasmic vacuoles, frequently corresponding to "signet ring cells" (Fig. 2). The tumor cells were intermingled with reactive inflammatory cells consisting of lymphocytes and macrophages. Immunohistochemistry of the CSF detected CK7-positive cells, thus, yielding the diagnosis of LC due to an adenocarcinoma (Fig. 2).

However, the patient refused treatment escalation to radiotherapy and intrathecal chemotherapy. Instead, he consented to change the systemic treatment regimen to nab-paclitaxel plus gemcitabine. After a few weeks, the patient's condition improved substantially. Headache and neck stiffness vanished almost completely. In addition, CSF cell count had declined to 12 cells/μL and cancer cells were no longer detectable. However, follow-up cerebral MRI showed a slight increase in leptomeningeal contrast enhancement (Fig. 1).

Upon the patient's request, treatment was continued with nab-paclitaxel and gemcitabine, without applying intrathecal chemotherapy or adding radiotherapy. Notwithstanding, 3 months later, his condition deteriorated rapidly with palsies of cranial nerves III, IV, VI, and VII, gait disorder and, finally, disturbed consciousness despite systemic chemotherapy with nab-paclitaxel and gemcitabine. The patient died 35 months after the diagnosis of pancreatic cancer, and 3 months after diagnosis of LC.

Discussion and Conclusions

In our patient with unresectable pancreatic cancer, LC was diagnosed when systemic disease had been stable for 32 months following systemic chemotherapy. After initiation of treatment with gemcitabine plus nab-paclitaxel, the clinical symptoms and CSF findings improved substantially and the patient lived for further 3 months, although follow-up MRI

was slightly progressive. This case is remarkable in two ways. First, only 15 cases of LC in pancreatic cancer have been published so far [18–32]. Most of the patients described in these case reports were male and more than 50 years old, matching the characteristics of our patient. Nearly all of them rapidly deteriorated clinically and died soon after LC was diagnosed. However, in 2 cases, a longer survival has been reported. The patient reported by Hirota et al. [22] lived approximately 3.5 years after the diagnosis of LC. In that case, LC seemed to have completely dissolved following whole brain radiotherapy, and the patient finally died from progressive systemic disease. It remains unclear why whole brain radiotherapy was so efficient in this single patient. More recently, Johnson et al. [32] observed a patient in whom survival of approximately 10 months could be achieved using multimodal chemotherapy including capecitabine, irinotecan, intrathecal topotecan, and bevacizumab. These data underline the extreme rarity but also the severity of LC secondary to pancreatic cancer; patients usually do not survive more than a few weeks.

Second, a clear clinical response could be achieved following treatment with gemcitabine and nab-paclitaxel, which was also accompanied by an improvement of pleocytosis and removal of adenocarcinoma cells from the CSF. Treatment of LC with CSF involvement usually consists of radiotherapy of the brain and spine, accompanied by systemic chemotherapy and intrathecal application of chemotherapeutic agents. Frequently used drugs for intrathecal chemotherapy are methotrexate, cytarabine and thiotepa [12–14, 33]. However, due to possible severe side effects and the necessity of repeated hospitalization, the patient refused an aggressive treatment regimen. Thus, in the present case, treatment was changed to gemcitabine and nab-paclitaxel.

In the last few years, nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is increasingly being used in patients with breast cancer and non-small-cell lung cancer. In contrast to standard formulations of taxanes (e.g., paclitaxel and docetaxel), nab-paclitaxel is associated with fewer hypersensitivity reactions and with better penetration into cancer cells [34–39]. In addition to greater efficacy and a favorable safety profile compared to standard paclitaxel in these cancer types [37, 40], the use of gemcitabine plus nab-paclitaxel in patients with pancreatic cancer has also been reported to lead to an improved response rate as well as longer progression-free and overall survival when compared to gemcitabine monotherapy [41, 42]. The main reason for this superiority seems to be a better penetration of nab-paclitaxel into the tumor. One possible mechanism could be binding of albumin by SPARC (secreted protein acidic and rich in cysteine). This glycoprotein is often overexpressed in different types of tumors, leading to a better response to nab-paclitaxel by transferring the drug into the extravascular space [43, 44]. Other studies have discussed SPARC-independent ways such as the gp60 albumin receptor pathway. Binding of albumin to this glycoprotein seems to lead to the forming of transcytotic vesicles and delivering nab-paclitaxel into the cancer cells [45–48].

Many chemotherapeutic agents are considered ineffective for treating LC due to their limited ability to cross the blood-brain barrier (BBB). According to the literature, the combination of gemcitabine and nab-paclitaxel seems not very promising. For gemcitabine, data are ambiguous. One study showed that less than 10% penetrate into the central nervous system [49]. In a rat model, Apparaju et al. [50] observed a relative brain distribution coefficient of <0.1, indicating no relevant penetration of the BBB. However, considerably higher values were measured in the brain tumor relative to tumor-free regions of the brain in that study. This was attributed to a more permeable tumor vasculature. On the other hand, Sigmond et al. [51] administered gemcitabine to patients prior to brain biopsy, and, subsequently, detected relevant concentrations in the bioptic samples. Thus, it remains questionable whether gemcitabine reaches the central nervous system in a sufficient concentration. For nab-paclitaxel, data are even more scarce. While paclitaxel is known to have a poor BBB pene-

Table 1. Overview of reports addressing leptomeningeal carcinomatosis in pancreatic cancer

Study	Age, years	Gender	Chemotherapy	RT performed	Survival
Galatioto et al. [18], 1975	n.r.	n.r.	n.r.	n.r.	n.r.
Kurzaj et al. [19], 1980	36	M	No	No	Few weeks, not specified
Ferreira et al. [20], 2001	49	M	Thiotepa Methotrexate Cytarabine	No	8 weeks
Grira et al. [21], 2007	55	M	No	No	7 weeks
Hirota et al. [22], 2008	64	M	Gemcitabine	Yes	3.5 years
Rebischung et al. [23], 2008	44	F	Methotrexate and intrathecal ^{125}IUdR	No	6 months
Minchom et al. [24], 2010	59	M	Methotrexate Cytarabine Gemcitabine	No	6 weeks
Blows et al. [25], 2012	72	M	No	No	Few weeks, not specified
Anne et al. [26], 2013	45	F	No	No	Rapid death
Rao et al. [27], 2013	57	M	FOLFIRINOX	Yes	n.r.
Naqvi and Ahmed [29], 2015	58	F	No	No	7 days
Yoo et al. [30], 2015	80	M	No	Yes	n.r.
Trinh et al. [31], 2016	58	M	No	No	34 days
Hong et al. [28], 2014	72	F	Pelareorep Carboplatin Paclitaxel	No	8 weeks
Johnson et al. [32], 2018	53	M	Capecitabine Irinotecan Topotecan Bevacizumab	Yes	45 weeks

n.r., not reported; RT, radiotherapy; ^{125}IUdR, 5-iodo-2′-deoxyuridine labeled with 125-I; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin.

tration [52], only one study in a mouse model evaluated the uptake of nab-paclitaxel in the brain [53]. Here, nab-paclitaxel only accumulated at low levels in the brain indicating that it cannot cross the BBB. In conclusion, due to the limited ability to cross the BBB, the combination of gemcitabine and nab-paclitaxel seems to be ineffective for LC treatment.

Remarkably, despite the issues discussed concerning BBB crossing, our patient showed rapid clinical improvement when gemcitabine and nab-paclitaxel were administered. He lived for 3 months after the diagnosis of LC, which exceeds survival of most pancreatic cancer patients with LC published so far (Table 1). One possible explanation for treatment efficacy could be the local impairment of the BBB. In brain metastases secondary to breast cancer, Lockman et al. [54] could demonstrate partial permeability of the BBB, but the uptake of ^{14}C-doxorubicin and ^{14}C-paclitaxel into brain metastases were less than 15% compared to

other tissues. In LC, the same phenomenon has been described [55]. One might argue that the described improvements in our patient were not related to treatment. However, when looking at the devastating clinical courses of LC despite treatment – with a median survival of several weeks [6, 10, 11] – this seems very unlikely.

In conclusion, the present case suggests possible efficacy of gemcitabine plus nab-paclitaxel in a patient with LC secondary to pancreatic cancer. Further data are necessary to confirm our observations.

Statement of Ethics

Written informed consent for publication of this case report and associated images could not be obtained from the patient because of reduced consciousness. Informed written consent to publish data and images was obtained from the patient's wife.

Disclosure Statement

The authors declare that they have no competing interests.

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Author Contributions

G.C. and N.G. made the conception and design of the paper, interpretation of data, and drafted the manuscript. G.C., M.W., A.B., M.D., and D.W. made substantial contribution to the acquisition and analysis of data. G.R.F. was involved in critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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