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Case Report

Carcinomatous Meningitis due to Ovarian and Gastric Cancers: Case Report and Literature Review on the Therapeutic Approach to this Rare Cancer Complication

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Abstract: Carcinomatous meningitis is a rare neuropathological entity in the routine oncology practice, with an estimated frequency of one case in ten metastatic cancers (10% or less). Lung cancer, breast cancer, melanoma, or primary brain tumors usually have the propensity to generate meningeal metastases according to the literature. We herein report unusual cases of Carcinomatous meningitis diagnosed in two young patients of 46 and 38 years old who were primarily followed up for metastatic ovarian cancer and metastatic gastric cancer respectively. Neurological symptoms were prominent at the time of diagnosis. The brain scan was non-contributory. The radiological diagnosis was made by injected brain magnetic resonance imaging (MRI) which showed metastatic meningeal lesions in both cases. Anatomopathological analysis of the cerebrospinal fluid (CSF) was decisive in revealing cancerous cells. The treatment consisted of a doublet of intrathecally (IT) Methotrexate-Depomedrol (patient with ovarian cancer) and a triplet of IT Methotrexate-cytarabine-Depomedrol (patient with gastric cancer). The evolution was marked by a clinical improvement without CSF sterilisation for the patient on the doublet treatment but died 5 months later on the occasion of a new progression. For the other patient on the triplet, the evolution was towards a rapid clinical deterioration with death within 2 months from diagnosis. Carcinomatous meningitis is therefore a serious complication that rapidly threatens the life of patients. Survival rarely exceeds 4 months.

Keywords: Carcinomatous meningitis, ovarian cancer, gastric cancer.

INTRODUCTION

In the routine oncological practice, the meninges and/or cerebrospinal fluid (CSF) are rarely cited as common sites of metastasis of solid cancers. In the literature, meningeal dissemination of cancers is rare, reported in small series or case reports, with an estimated frequency of less than 10% of patients with metastatic cancers [1]. Carcinomatous meningitis classically complicates some solid tumors primarily brain tumors, breast cancers, lung cancers, and melanoma [2, 3] . In all cases, the occurrence of Carcinomatous meningitis constitutes a very negative turning point in the cancerous disease. On the one hand, it most often

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complicates an already very advanced and progressive systemic cancer disease. On the other hand, their diagnosis is not easy and the treatment options are limited and disappointing in terms of outcome.

In this article, we will review the diagnostic and therapeutic approaches to Carcinomatous meningitis based on two cases of such disease complicating ovarian and gastric cancers that were followed in the medical oncology department of the Orleans Regional Hospital.

CASES PRESENTATION

CASE 1

A 46-year-old female patient with no notable history, followed since April 2019 for a high-grade serous ovarian carcinoma with a germline mutation of the BRCA 1 gene. At the time of diagnosis, her cancer was metastatic at the lymph node, pleural and peritoneal level, i.e. a FIGO stage IV classification. Until June 2021, the patient had already received three lines of chemotherapy, namely Paclitaxel plus carboplatin in the first line followed by Olaparib maintenance, then Gemcitabine plus carboplatin in the second line, and paclitaxel weekly in the third line. At the end of July 2021, the patient developed a headache in the helmet of increasing intensity with associated speech and balance disorders. She went to the emergency department where a brain scan performed was normal. Given the severity of the problem, she was admitted to the medical oncology department for further investigations. On admission, she was slightly improved by the analgesic treatment administered and her consciousness was normal (Glasgow score 15). However, there were still balance problems with the inability to stand up. The rest of the clinical examination was non-contributory. Biologically, the blood count, blood ionograms, liver function tests, renal function tests, and tumor markers (CA125, CA15-3) were normal. However, analysis of the cerebrospinal fluid (CSF) collected during a lumbar puncture performed revealed atypical hypercellularity (139/mm3) on cytological examination, hyperproteinorrachia at 1.47 g/l (for normal values of 0.15-0.40 g/l) and hypoglucorrachia at 1.1 mmol/l (for normal values 2.2-3.89 mmol/l). Radiologically, the brain MRI with gadolinium injection confirmed the presence of diffuse carcinomatous leptomeningitis predominating in the subtensorial region, with infiltration of the acoustic-facial bundles; there was also a discrete dilatation of the supra- tensorial ventricular cavities without CSF resorption disorders. The brain parenchyma was free of lesions. Evaluation of ovarian cancer disease by positron emission tomography (PET) scan showed a complete response at the lymph node level with the stability of other targets and meningeal metabolic fixation. Therapeutically, intrathecal chemotherapy with Methotrexate and Depomedrol was started (regimen: 15mg twice weekly for 4 weeks, then 15mg once weekly for 4 weeks - then 15mg monthly until progression with Depomedrol intrathecal 40mg at each Methotrexate injection). The multidisciplinary consultation meeting of oncology did not find any lesions indicating radiotherapy in the meninges and proposed to continue chemotherapy with weekly Paclitaxel. The evolution of the treatment was marked by an improvement in the patient's clinical symptoms and general condition after 8 weeks of IT Methotrexate plus dépomédrol with nevertheless a persistence of some neoplastic cells in the CSF analysed at each therapeutic lumbar puncture. However, five months later, the patient reconsulted the emergency service for a sudden onset of intracranial hypertension (ICHT) syndrome with severe headache, balance disorders, visual blur, and vomiting. The evolution was rapidly fatal.

CASE 2

38 years- old female patient with a family history of pancreatic cancer in her brother at the age of 38 years old, and breast cancer in her maternal cousin at the age of 55 years old. She has been followed up since January 2021 for a gastric adenocarcinoma which revealed itself by the appearance of melena and then haematemesis which were complicated by anaemia, all in the context of an evolving pregnancy of 32 weeks (a premature delivery will then be scheduled at 34 weeks). The abdominal MRI performed initially revealed the existence of a gastric mass with a thickening of the upper 1/3 of the stomach extending over a height of 8cm (confirmed by oesogastroduodenal fibroscopy (OGDF). Pathological study of the biopsy tissue confirmed the existence of a moderately differentiated adenocarcinoma, not overexpressing HER-2, and with stable microsatellites. An 18-FDG PET scan was performed to evaluate the extent of the disease, revealing multiple nodules of peritoneal carcinosis associated with a left latero-uterine mass. DPD phenotyping was normal. The patient was then treated with first-line chemotherapy such as FOLFOX. The PET scan performed after 3 months of FOLFOX concluded that the adnexal mass and peritoneal carcinosis had regressed. Biologically, tumor markers had decreased and the decision was made to continue chemotherapy. After the 12th cycle of chemotherapy, the patient developed incapacitating headaches resistant to the usual analgesics with nausea and vomiting, all in the context of an altered general condition. She was then admitted to the hospital for further investigations.

The emergency brain scan performed was normal. But, the brain MRI performed showed diffuse carcinomatous leptomeningitis, predominantly in the posterior fossa with an enhancement of the cranial pairs (III, V, VII, and VIII) in their cisternal portion. Absence of hydrocephalus with no associated intraparenchymal metastatic lesions. A lumbar puncture was then performed and CSF analysis showed carcinomatous hypercellularity on the pathological study, mild hyperproteinorrachia at 0.41 g/l (Normal values at: 0.15-0.40 g /l), and normoglycorrachia at 3mmol/l (Normal values: 2.2-3.89 mmol/l). An evaluation of the primary cancer disease by 18 FDG PET scan noted a progression of the disease with an increase in the size of the left adnexal mass and the appearance of medium to large ascites and a 10 mm nodule of the hepatic segment II. The second line of chemotherapy was decided (FOLFIRI) associated with IT administration of a therapeutic triplet of methotrexate plus cytarabine and Depomedrol, twice a week. The evolution under this treatment was marked by a significant deterioration of the patient's clinical condition leading to the discontinuation of all treatments after 4 intrathecal injections, followed by death, 2 months after the diagnosis.

DISCUSSION

Table 1: Summary of patient characteristics

Characteristics	Patient 1	Patient 2
Age at cancer diagnosis	46 years old	38 years old
Primary cancer location	Ovary	Gastric
Histological type of primary cancer	High grade serous carcinoma	Undifferentiated adenocarcinoma
Initial metastatic sites	Peritoneum, pleura, lymph node	peritoneum
Time between diagnosis of primary cancer and Carcinomatous meningitis	27months	8 months
Prior lines of chemotherapy before Carcinomatous meningitis	3(Paclitaxel-carboplatin, carboplatin-gemcitabine, weekly paclitaxel	1(FOLFOX)
Assessment of cancer disease at the time of Carcinomatous meningitis	stability	Progression
Symptoms of Carcinomatous meningitis	Headaches, balance disorders, speech disorders	Headaches, nausea, vomiting, altered general condition
Brain Scan work-up	Normal	Normal
Brain MRI work-up	Positive	Positive
CSF characteristics of Carcinomatous meningitis	Hypercellularity, hyperproteinorrachia and hypoglycorrhachia	Hypercellularity, hyperprotéinorrachia and normoglycorrhachia
Treatment received for Carcinomatous meningitis	Intrathecally Methotrexate and Depomedrol	Intrathecally Methotrexate-Cytarabine and Depomedrol
Clinical response to Intrathecally treatment	Clinical improvement	Clinical deterioration
CSF Biological response to Intrathecally treatment	No response	No response
Evolution	Death	Death
Time from diagnosis of Carcinomatous meningitis to death	5months	2 months

Carcinomatous meningitis or leptomeningeal metastases refers to meningeal invasion by cancerous cells from solid or haematological extra meningeal cancers [2, 4]. In general, carcinomatous meningitis is rare, complicating 5-10% of solid tumors [2, 3]. With advances in diagnostic imaging positioning brain MRI as the initial work-up for cancers with cerebral metastatic tropism or neurological signs, and with current therapeutic advances providing a continuum of care for cancer patients and improving survival, the incidence of carcinomatous meningitis is expected to continue to increase [2]. According to some available literature data, it is reasonable to assume that every solid tumour can give rise to leptomeningeal metastases, but breast, lung and melanoma cancers are responsible for the majority of the cases encountered [2, 3, 5]. However, as a matter of course, Carcinomatous meningitis complicating gastric or ovarian cancers, as in the case of our two patients, remains very rare routinely.

The physiopathological principle of leptomeningeal metastases follows the classical pattern of metastatic dissemination of cancers. Indeed, the cancer cells by disseminating by haematogenous, lymphatic, perineural, or anatomical contiguity routes reach the subarachnoid space from where they disseminate into the cerebrospinal fluid [3, 4, 6]. Meningeal spread may also be iatrogenic during neurosurgical procedures such as resection of brain metastases [5]**.** Involvement may be focal or diffuse in the CNS and periphery by migration of cancer cells via the CSF. This explains the wide range of clinical manifestations at the time of diagnosis, but also the risk of misdiagnosis due to the diverse clinical pictures.

The diagnosis is primarily suspected in the presence of a suggestive but non-specific clinical picture of acute neurological disorders. For our two patients, the diagnosis of Carcinomatous meningitis was first suspected on the basis of clinical signs that were essentially neurological and related to leptomeningeal invasion of the central nervous system (headache, speech, or walking disorders). This is in agreement with the literature which confirms headache as the main clinical manifestation to suspect Carcinomatous meningitis [4]. The mechanism of headache is related to a context of intracranial hypertension within the inextensible enclosure of the cranium, resulting from impeded CSF flow and a context of meningeal inflammation. However, the symptoms at diagnosis can be very diverse in the case of very extensive meningeal involvement or diffuse peri-medullary leptomeningeal involvement. This is in agreement with the data of Cochereau *et al.,* In a retrospective series of 41 patients followed up for carcinomatous leptomeningitis, they found that headache was indeed by far the most frequent symptom at diagnosis, but also that symptoms related to cranial pair involvement or medullary or radicular leptomeningeal involvement were also relevant and could be the sole indicators of Carcinomatous meningitis [7]. Thus, in current clinical practice, a meticulous neurological examination is essential and a hypothesis of Carcinomatous meningitis should systematically be evoked when neurological symptoms of all types (central or peripheral) appear in patients followed for cancers, and not only for cancers known to have the propensity to metastasise to the cerebral-meningeal level. Signs such as headache, nausea and vomiting, mental disorders, gait disorders, cranial nerve paralysis with diplopia, visual or auditory disorders, and radicular pain should raise questions in a cancer patient [1]. Moreover, differential diagnoses mimicking a similar clinical picture (infectious or inflammatory pathology, subarachnoid haemorrhage, etc.) must be systematically eliminated.

The median time between the diagnosis of primary cancer and the occurrence of Carcinomatous meningitis is variable, in the order of 1 to 2 years or less [5]. For our two patients, the disease occurred after delays of 27 months and 8 months respectively (Table 1). This delay was 8.1 months in the series of Rouviere D. *et al.,* with exclusively pulmonary primary cancers [8]. Cochereau *et al.,* found a delay of 7.1 months with extremes ranging from 10 days to 34 months after the diagnosis of breast cancer [7]. However, rare cases of inaugural Carcinomatous meningitis are also described in the literature

In the presence of a clinical situation suggestive of Carcinomatous meningitis, an imaging work-up is useful and should be performed as a matter of urgency. The brain scan proved to be insufficient for the detection of such metastases in our two patients. Some literature data suggest that brain MRI is superior to brain CT with an estimated specificity of 66-98%. This means that with a normal brain MRI, the diagnosis of Carcinomatous meningitis is unlikely [1, 9]. The brain scan should be reserved for contraindications or the unavailability of an MRI.

After the clinical and radiological arguments, a lumbar puncture should be performed for CSF analysis as part of the diagnostic work-up for Carcinomatous meningitis or to discriminate from other differential diagnoses such as infectious meningitis or other inflammatory meningeal pathologies. As in our two patients, in the case of Carcinomatous meningitis, the main characteristics of the CSF are an increase in the number of leukocytes, hyperproteinorrachia or hypoglycorrachia, and the presence of cancerous cells [1].

The management of Carcinomatous meningitis is multidisciplinary, but medical oncological treatment is always at the forefront. However, the prognosis remains very poor due to both the evolution of the systemic disease and the very low chemosensitivity of the leptomeningeal metastases. As the molecules used cannot cross the blood-brain barrier to be given intravenously, chemotherapy is administered either intrathecally (IT) or intraventricularly (IV) in combination with intrathecal and/or systemic corticosteroid therapy. The therapeutic arsenal is practically limited to 3 products: Methotrexate, cytarabine, and Thiotepa. Several other products are being tried but none has

done better to date [1]. However, none of the chemotherapy drugs used has really established itself as a therapeutic standard and this results in very low median survival rates [1]. A randomised trial comparing intrathecal chemotherapy versus systemic chemotherapy for Carcinomatous meningitis was negative. Indeed, on an intention-to-treat basis, Boogerd W *et al.,* showed that intrathecal chemotherapy did not improve either progression-free survival or overall survival and was associated with increased neurotoxicity compared to systemic chemotherapy [10]. In their review of treatments for Carcinomatous meningitis published in 2010, Beauchesne *et al.,* found that several drugs could be used routinely in this indication by IT route. These are Methotrexate, cytarabine, thiotepa, Topotecan, and Etoposide. In the same review, they report data from the literature showing similar benefits to the use of IT Methotrexate (10-15mg twice weekly for 4 weeks; then 10-15mg once weekly for 4 weeks then 10-15mg once monthly until progression or toxicity) or liposomal cytarabine (25-100mg three times weekly for 4 weeks, then 25-100mg once weekly for 4 weeks, then 25-100mg once monthly until progression or toxicity) in terms of clinical-biological response(p=0. 76), duration of response(p=0.31) and 1-year survival (p=0.43) [2]. Other studies have evaluated the efficacy of combined regimens combining these two most commonly used molecules. Dae-Young Kim *et al.,* randomised 55 patients with Carcinomatous meningitis to one of two arms: Methotrexate alone in IT (n=29) or triplet Methotrexate plus cytarabine plus Hydrocortisone in IT (n=26). Results were significantly better with the triplet than with monotherapy in terms of CSF biologic response rate (38.5 vs 13.8%, P = 0.036) and median survival improvement (18.6 weeks vs 10.4 weeks, P = 0.029). Treatment was well tolerated in both arms [11].

Radiotherapy is also listed as a treatment option in the literature. However, its benefit remains to be demonstrated. Its effects on neurological deficits are less. It can have an analgesic effect and help to manage radicular pain or the symptoms of meningoencephalitis. When recourse to it becomes essential, its focus is on sites of CSF flow blockage or on macroscopic meningeal sites responsible for clinical symptoms [1]. Our patients were treated with the doublet (IT methotrexate plus Depomedrol) for Carcinomatous meningitis of ovarian origin, and with the triplet (methotrexate plus liposomal cytarabine plus Depomedrol) for Carcinomatous meningitis of gastric origin. The clinical responses to treatment were different, with an improvement in symptoms but no biological response in the CSF with the Doublet (Methotrexate + Depomedrol) and a worsening of the clinical condition with the Triplet (Methotrexate + Cytarabine + Depomedrol). There were no irradiables sites on MRI for both patients. In addition to the treatment, our patients received psychological support as well as appropriate supportive care, mainly for pain relief. CSF analysis was performed at each IT chemotherapy injection. The lack of clinical response led to death 2 months after diagnosis. For the patient with a clinical response, the disease progressed rapidly and fatally in the 5th month.

The prognosis for Carcinomatous meningitis is generally poor with survival rarely exceeding 4 months. In their series of 41 patients who developed Carcinomatous meningitis in breast cancer, Cochereau *et al.,* found that patients had a median survival of 4 months after treatment with intrathecal methotrexate [7]. Similar results were found by Boogerd *et al.,* who found a median survival of 18.3 weeks with intrathecal methotrexate and 30.3 weeks with non-intrathecal methotrexate [10]. Beauchesne's review of the literature found a median survival of 105 days (for patients treated with liposomal Cytarabine) or 78 days (for patients treated with IT Methotrexate) [2].

CONCLUSION

Carcinomatous meningitis is a rare complication with a very poor prognosis that is rapidly life-threatening. It is nevertheless accessible to medical treatment, mainly administered by IT. Despite this treatment, the prognosis remains appalling with a median survival rarely exceeding 4 months. Diagnosis is initially clinical, with neurological symptoms in the foreground, and characteristic abnormalities on brain MRI. Cerebral CT is often normal and therefore not recommended in the first instance. CSF analysis is essential to confirm the diagnosis by demonstrating cancer cells and biochemical abnormalities, which together rule out other differential diagnoses. All in all, it remains a therapeutic emergency because it rapidly engages the patient's vital prognosis.

Conflicts of Interest: None declared.

By Way of Consent

We carried out this work when the patients concerned had already died. We certify that we have obtained the agreement of the department to carry out this work. We have also undertaken to maintain the strict anonymity of the patients concerned.

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