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Leptomeningeal Carcinomatosis as a Presentation of Relapse in Adenocarcinoma of Colon: A Case Report and Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors RS and Ashish Manne equally credited for working on gathering the literature data and writing the manuscript. Authors Ankit Madan and RKP coordinated to obtain case related information, reviewed and edited final draft and submitted for the publication.

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ABSTRACT

The incidence of leptomeningeal carcinomatosis (LC) has been increasing, due to advances in the cancer and the improved overall survival of cancer patients. Breast and lung cancer are the most frequently reported causes of LC among solid tumors. LC occurs very rarely in patients with colon cancer. Leptomeningeal carcinomatosis is characterized by multifocal seeding of the leptomeninges by malignant cells that originate from a solid tumor. The median survival of untreated patients is 4 to 6 weeks. Although the diagnosis may be challenging, an early treatment before the setting of neurological deficits is required in order to improve the clinical outcomes. The treatment requires a multidisciplinary approach by a combination of chemotherapy and targeted therapies administrated systemically or via intra-cerebrospinal fluid route, surgery and radiotherapy. Here, we describe a case of leptomeningeal carcinomatosis in which the primary tumor was colon cancer that has progressed to LC but responded significantly to our treatment strategy. Also, we review the literature on carcinomatosis in solid tumors.

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1. CASE REPORT

A 59-year-old male was diagnosed with sigmoid colon adenocarcinoma during routine colonoscopy and underwent sigmoidectomy. He was staged as T2N0 (Stage II) and had been on active surveillance for 4.5 years until he presented with left lower lobe pulmonary nodule 2.4 x 1.9 cm size. It was hypermetabolic (SUV =8.5) on PET scan and therefore underwent left lower lobe lobectomy. Pathology revealed metastatic adenocarcinoma with colon primary and KRAS was wild type. CEA elevated to 10 from normal baseline. He was then started on post-operative chemotherapy with modified FOLFOX. After three months while he was on treatment, he presented to local emergency department with sudden onset of a tonic-clonic seizure episode. He was afebrile, alert but disoriented. Examination of the cranial nerves was normal, sensory and motor examination was normal without ataxia or nuchal rigidity. Computerized tomography (CT scan) of brain was unremarkable for hemorrhage. Electroencephalogram, vitamin B12, thyroxin stimulation hormone, folic acid and ammonia level were unrevealing. A diagnostic lumber puncture (LP) was performed revealing an opening pressure of 12 cm water. Cerebrospinal fluid (CSF) analysis showed WBC, protein and glucose in normal limits. Cytological examination was negative for malignant cells. Repeat lumbar puncture is unremarkable. CSF microbiologic workup was negative. An enhanced magnetic resonance imaging (MRI) with gadolinium contrast showed diffuse leptomeningeal enhancement bilaterally throughout the cerebrum and in cerebellum consistent with leptomeningeal carcinomatosis. His functional status was assessed as ECOG 1. Upon discussion with Neuro-oncology a decision was made to change chemotherapy from 5-fluorouracil to capecitabine (1000 mg/m2 twice a day, per oral for two weeks in a 21 day cycle) to allow better penetration of blood brain barrier and bevacizumab (7.5 mg/kg, intravenous, once every 21 days) was added to control inflammation. No further seizures reported and patient's clinical status significantly improved over the course of 6 months. Repeat MRI at 3rd, 6th and 9th month showed resolution of leptomeningeal enhancement. Repeat staging assessments by CT scan of chest, abdomen and pelvis revealed no evidence of disease. He is currently continuing on same chemotherapeutic regimen.

2. DISCUSSION

Leptomeningeal carcinomatosis is estimated to occur in less than 5% of cases of solid tumors. The clinical manifestation usually involves neurological symptoms, including dizziness, headache, vomiting, nausea, and hemiparesis, symptoms similar to those of meningitis or brain tumors. Diagnostic methods for leptomeningeal carcinomatosis include brain magnetic resonance imaging and cerebrospinal fluid examination. Leptomeningeal Carcinomatosis (LC) in solid tumors patients confers a uniformly poor prognosis and decreased quality of life. Treatment options are limited and often ineffective, due in large part to limitations imposed by the blood–brain barrier and the very aggressive nature of this disease. The majority of studies investigating the treatment of LC are not specific to site of origin. Conducting randomized, disease-specific clinical trials in LC is challenging due to low rate of accrual and rapidly progressing disease. Optimal management of LC is challenging as the existing data on clinical outcomes is based on observational studies such as retrospective case series or case reports and has wide variety of tumor types, mainly breast cancer. The treatment decisions are made on a case by case basis requiring a multidisciplinary approach.

The rising incidence of LM in colorectal cancers has been attributed to increase in survival of patients with the discovery of newer therapeutic agents, and the poor penetration of these drugs into the CNS has likely to an increase in the number of cases of LC associated with colon adenocarcinoma. Our case is unique in that the patient initially presented with isolated recurrence in lung. While on adjuvant treatment with Fluorouracil, Oxaliplatin and Leucovorin (FOLFOX) the patient presented with seizure as the manifestation of recurrence of colon adenocarcinoma in the form of leptomeningeal metastasis. The treatment for our patient is made based on pharmacological dynamics of the drugs. Capecitabine was chosen due to better blood brain penetrance [1] and bevacizumab was chosen for anti-inflammatory properties in addition to vascular endothelial growth factor inhibition. This led to the prolonged disease

control beyond one year, even in the setting of guarded prognosis. There was no definitive evidence of intrathecal chemotherapy in the setting of solid tumors. Therefore it was reserved if our patient does not respond to the initial management strategy. The Fig. 1 depicts the pre and post treatment MRI changes.

The clinical presentation of LC is highly variable, as any level of the neuro-axis may be affected. The gold standard for diagnosis of LC is demonstration of malignant cells in cerebrospinal fluid (CSF), although the false negative rate may be substantial and improved sensitivity may rely on repeated sampling of the CSF [2]. One study reported that the sensitivity of a first lumbar puncture is about 45-55%, however, this can be increased up to 80% with a repeat CSF examination [3,4]. Also non-specific, elevated CSF protein was more sensitive in some studies [5,6], correlating with the diagnosis in 60–90% of cases. Other CSF biomarkers investigated include lactate dehydrogenase, carcinoembryonic antigen, lactate, oligoclonal bands, B-glucuronidase, beta-2 microglobulins, vascular endothelial growth factor, and cancer antigen 15-3 [6-8], but are not routinely used due to similarly suboptimal sensitivity and specificity. One retrospective review of LC patients showed that 53% of patients were diagnosed by imaging, 23% by cytology, and 24% by both [9]. Several studies have examined the diagnostic usefulness of other CSF measurements with mixed results. Hypoglycorrhachia (<50% of LC) [10-12], lymphocytic pleocytosis (25–64% of LC), and elevated opening pressures (50% of LC) are non-specific, but raise suspicion for LC in the proper clinical setting [11]. Neuroradiology criteria for the diagnosis of LC have played a growing role since the advent of MRI [13]. The characteristic finding on MRI is meningeal enhancement, best noted at the skull base between cerebellar folia, along cranial nerves, and around the spinal cord and nerve roots. MRI findings are abnormal in 75–90% of patients with cytology-positive CSF [11,14]. Most experts agree that typical MRI findings in conjunction with a consistent clinical picture fulfill diagnostic criteria for LC.

Overall survival for LC is very short with median overall survival of ranges from 4-5 weeks without treatment and 2-4 months with treatment [15,16]. Modalities used in patients with LC to date include radiation therapy (RT), systemic therapy, and intrathecal therapy. Radiotherapy(RT) has been tried however, remains controversial [17]. Craniospinal RT plays a role in the treatment of central nervous system (CNS) metastases because it addresses the entire CSF space. However, it is often associated with significant toxicity. A more focal approach is often employed to limit toxicity. Whole brain RT, alone or followed by chemotherapy, is used to treat a substantial portion of the CSF space, palliate symptoms, and improve quality of life [12]. Focal RT is frequently used to treat bulky disease as other treatment modalities may have limited effect on regions of large CSF tumor burden. Delivery of systemically administered treatments into CSF in

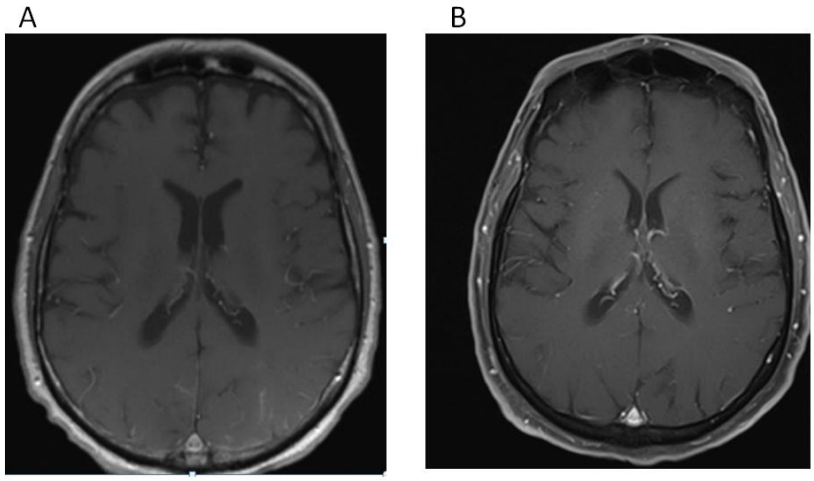

Fig. 1. MRI Brain with contrast

A. Baseline: The multiple areas of bright signal within the cortical sulci on FLAIR images mainly involving bilateral parieto-occipital sulci, right frontal lobe cortical sulci with enhancement consistent with leptomeningeal carcinomatosis. B: Post treatment (6 months): Significant improvement in the carcinomatosis

therapeutic concentrations is limited by the blood–brain barrier (BBB) and blood–CSF barriers. The barrier between the CNS and the rest of the body is a complicated and dynamic system limiting the ability of many molecules, particularly large hydrophilic ones, from reaching the CNS in therapeutic concentrations. Despite this, large non-lipophilic agents which would presumably inadequately cross the BBB have been show to lead to radiographic responses in the CNS [18]. While cases of LC responses in other solid tumors with temozolamide have been reported [19], there are no prospective trials and no case reports or case series specifically looking at temozolamide in colon cancer LC to our knowledge.

Intrathecal chemotherapy has served as a means to circumvent the BBB and blood–CSF barriers in LC. Four agents are currently approved by the United States FDA for direct injection into the intrathecal space: methotrexate, cytosine arabinoside (ara-c), liposomal cytarabine arabinoside, and thiotepa. These agents have been directly evaluated [10,20-22], studied in combination [2,23-26] and using different doses and schedules [5,27]. Responses were modest although complete response was noted in some patients, as defined by conversion of CSF cytology from positive to negative as well as absence of neurologic symptom progression [23,27,28]. Neurologic complications were higher in the patient group receiving intrathecal treatment [28].

3. CONCLUSIONS

Gastrointestinal cancers are responsible for 4% to 14% of cases of LC [29]. Colorectal carcinoma (CRC) spreading to the leptomeninges [30], is even a rarer occurrence. LC can be the first sign of relapse in colon cancer. Therapeutic options should be individualized based on the performance status of the affected patient. We reviewed the diagnosis, prognosis, and various therapeutic managements for colon cancer LC. Prognosis for LC is poor; however, patients with colon cancer appear to have better outcomes when compared to patients with LC due to other solid tumors. No definitive management paradigm exists for colon cancer LC patients and multiple treatment modalities are employed. Further studies are needed to determine the risk factors for LC in the contest of colorectal adenocarcinoma and to formulate an early diagnosis and more effective treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ekenel M, Hormigo AM, Peak S, Deangelis LM, Abrey LE. Capecitabine therapy of central nervous system metastases from breast cancer. Journal of Neuro-oncology. 2007;85(2):223-227. e-pub ahead of print 2007/07/06.
DOI: 10.1007/s11060-007-9409-0
2. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: Experience with 90 patients. Cancer. 1982;49(4):759-772.
DOI:10.1002/1097-0142(19820215)49:4<759::aid-cncr2820490427>3.0.co;2-7
3. Chamberlain MC. Leptomeningeal metastasis. Current Opinion in Oncology. 2010;22(6):627-635.
DOI: 10.1097/cco.0b013e32833de986
4. Chamberlain MC, Glantz M, Groves MD, Wilson WH. Diagnostic tools for neoplastic meningitis: detecting disease, identifying patient risk, and determining benefit of treatment. Seminars in Oncology. 2009;36: S35-S45.
DOI: 10.1053/j.seminoncol.2009.05.005
5. Fizazi K, Asselain B, Vincent-Salomon A, Jouve M, Dieras V, Palangie T, et al. Meningeal carcinomatosis in patients with breast carcinoma: Clinical features, prognostic factors, and results of a high-dose intrathecal methotrexate regimen. Cancer. 1996;77(7):1315-1323.
DOI:10.1002/(sici)1097-0142(19960401)77:7<1315::aid-cncr14>3.0.co;2-4
6. Twijnstra A, van Zanten AP, Nooyen WJ, Ongerboer de Visser BW. Sensitivity and specificity of single and combined tumour markers in the diagnosis of leptomeningeal metastasis from breast cancer. Journal of

Neurology, Neurosurgery & Psychiatry. 1986;49(11):1246-1250.
DOI: 10.1136/jnnp.49.11.1246

7. Groves MD, Hess KR, Puduvalli VK, Colman H, Conrad CA, Gilbert MR, et al. Biomarkers of disease: Cerebrospinal fluid vascular endothelial growth factor (VEGF) and stromal cell derived factor (SDF)-1 levels in patients with neoplastic meningitis (NM) due to breast cancer, lung cancer and melanoma. Journal of Neuro-oncology. 2009;94(2):229-234.
DOI: 10.1007/s11060-009-9819-2
8. Le Rhun E, Kramar A, Salingue S, Girot M, Rodrigues I, Mailliez A, et al. CSF CA 15-3 in breast cancer-related leptomeningeal metastases. Journal of Neuro-oncology. 2014;117(1):117-124.
DOI: 10.1007/s11060-014-1361-1
9. Clayton AJ, Danson S, Jolly S, Ryder WD, Burt PA, Stewart AL, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer. 2004;91(4):639-643. e-pub ahead of print 2004/07/22.
DOI: 10.1038/sj.bjc.6601970
10. Boogerd W, Hart AAM, van der Sande JJ, Engelsman E. Meningeal carcinomatosis in breast cancer. Prognostic factors and influence of treatment. Cancer. 1991;67(6): 1685-1695.
DOI:10.1002/1097-0142(19910315)67:6<1685::aid-cncr2820670635>3.0.co;2-m
11. de Azevedo CRAS, Cruz MRS, Chinen LTD, Peres SV, Peterlevitz MA, de Azevedo Pereira AE, et al. Meningeal carcinomatosis in breast cancer: Prognostic factors and outcome. Journal of Neuro-oncology. 2011;104(2):565-572.
DOI: 10.1007/s11060-010-0524-y
12. Rudnicka H, Niwińska A, Murawska M. Breast cancer leptomeningeal metastasis—the role of multimodality treatment. Journal of Neuro-oncology. 2007;84(1):57-62.
DOI: 10.1007/s11060-007-9340-4
13. Clarke JL, Perez HR, Jacks LM, Panageas KS, DeAngelis LM. Leptomeningeal metastases in the MRI era. Neurology. 2010;74(18):1449-1454.
DOI: 10.1212/wnl.0b013e3181dc1a69
14. Gomori JM, Heching N, Siegal T. Journal of Neuro-oncology. 1998;36(1):55-60.
DOI: 10.1023/a:1005783507544
15. Bruno MK, Raizer J. Leptomeningeal metastases from solid tumors (Meningeal Carcinomatosis). In: Cancer Treatment and Research: Springer Science + Business Media. 2005;125:31-52.
16. DeAngelis L, Boutros D. Leptomeningeal metastasis. Cancer Investigation. 2005; 23(2):145-154.
DOI: 10.1081/cnv-200050458
17. Mehta M, Bradley K. Radiation therapy for leptomeningeal cancer. In: Cancer Treatment and Research: Springer Science + Business Media. 2005;147-158.
18. Lukas RV, Lesniak MS, Salgia R. Brain metastases in non-small-cell lung cancer: Better outcomes through current therapies and utilization of molecularly targeted approaches. CNS Oncology. 2014;3(1):61-75.
DOI: 10.2217/cns.13.66
19. Hottinger AF, Favet L, Pache J-C, Martin J-B, Dietrich P-Y. Delayed but complete response following oral temozolomide treatment in melanoma leptomeningeal carcinomatosis. Case Reports in Oncology. 2011;4(1):211-215.
DOI: 10.1159/000327699
20. Hitchins RN, Bell DR, Woods RL, Levi JA. A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol. 1987;5(10):1655-1662. e-pub ahead of print 1987/10/01.
21. Gaviani P, Silvani A, Corsini E, Erbetta A, Salmaggi A. Neoplastic meningitis from breast carcinoma with complete response to liposomal cytarabine: Case report. Neurological Sciences. 2009;30(3):251-254.
DOI: 10.1007/s10072-009-0044-8
22. Glantz M, Phupanich S, Jaeckle K, Swinnen L, Campbell T, Maria B, et al. Treatment of carcinomatous meningiti (CM) with Intra-CFS sustained-release encapsulated cytarablne (DEPOCYT™) vs. Methotrexate (MTX). European Journal of Cancer. 1997;33:S199.
DOI: 10.1016/s0959-8049(97)85606-7
23. Orlando L, Curigliano G, Colleoni M, Fazio N, Nole F, Martinelli G, et al. Intrathecal chemotherapy in carcinomatous meningitis from breast cancer. Anticancer Research. 2002;22(5):3057-3059.
24. Lara-Medina F, Crismatt A, Villarreal-Garza C, Alvarado-Miranda A, Flores-

Hernández L, González-Pinedo M, et al. Clinical features and prognostic factors in patients with carcinomatous meningitis secondary to breast cancer. The Breast Journal. 2012;18(3):233-241.
DOI: 10.1111/j.1524-4741.2012.01228.x

25. Yoshida S, Morii K. Intrathecal chemotherapy for patients with meningeal carcinomatosis. Surgical Neurology. 2005;63(1):52-55.
DOI: 10.1016/j.surneu.2004.06.011

26. Yu H, Mitsumori M, Nagata Y, Katakura Y, Kokubo M, Oya N, et al. Meningeal carcinomatosis in patients with breast cancer: Report of 8 patients. Breast Cancer. 2001;8(1):74-78.
DOI: 10.1007/bf02967482

27. Jaeckle KA, Phuphanich S, Bent MJvd, Aiken R, Batchelor T, Campbell T, et al. Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine. Br J Cancer. 2001;84(2):157-163.
DOI: 10.1054/bjoc.2000.1574

28. Boogerd W, van den Bent MJ, Koehler PJ, Heimans JJ, van der Sande JJ, Aaronson NK, et al. The relevance of intraventricular chemotherapy for leptomeningeal metastasis in breast cancer: A randomised study. European Journal of Cancer. 2004;40(18):2726-2733.
DOI: 10.1016/j.ejca.2004.08.012

29. Chamberlain MC. Neoplastic meningitis: A guide to diagnosis and treatment. Current Opinion in Neurology. 2000;13(6):641-648. e-pub ahead of print 2001/01/10.

30. Kato H, Emura S, Takashima T, Ohmori K, Sunaga T. Gadolinium-enhanced magnetic resonance imaging of meningeal carcinomatosis in colon cancer. The Tohoku Journal of Experimental Medicine. 1995;176(2):121-126. e-pub ahead of print 1995/06/01.

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