Case Reports in Oncology

Case Rep Oncol 2019;12:311–316

DOI: 10.1159/000499761
Published online: April 10, 2019

Case Report

A Case of Leptomeningeal Carcinomatosis from Aggressive Metastatic Prostate Cancer

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Keywords
Leptomeningeal · Carcinomatosis · Prostate cancer

Abstract
Leptomeningeal carcinomatosis (LC) is a rare leptomeningeal spread of diffusely metastatic tumors. It occurs more commonly with hematologic tumors, less commonly with solid tumors, and is exceedingly rare in prostate cancer. Due to its scarcity, it has traditionally been difficult to diagnose LC but advancement of MRI has helped considerably. However, even with technological improvements, pre-mortem diagnosis of LC remains difficult and controversial. Our case is a 71-year-old male with prostate cancer with bone metastases who presented to our facility with altered mental status (AMS), lower extremity weakness, and worsening diarrhea. The diarrhea was responsive to antibiotic therapy, but his AMS did not resolve. A head CT without contrast was negative but follow-up brain MRI revealed leptomeningeal enhancement highly suggestive of LC. Cerebrospinal fluid (CSF) cytology results were negative and other CSF studies were inconclusive. Although further studies were planned, the patient continued to deteriorate, and the family elected to withdraw care. He passed away without beginning treatment for the LC. Despite advances in cancer therapies, LC remains difficult to diagnose and treat. Imaging may be suggestive of the condition but the confirmatory tests such as repeated CSF cytology or meningeal biopsy are not only invasive but also usually occur postmortem.

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Additional methods of CSF testing have been studied to evaluate their role in accurately diagnosing LC but low specificity for LC has somewhat limited their use. Although treatment options are mainly palliative in nature, prompt recognition and early treatment could grant valuable time for patients and families.

Introduction

Leptomeningeal carcinomatosis is a rare complication of malignancy defined as metastasis of cancer to the leptomeninges. Leptomeningeal spread of cancerous cells occurs more commonly with hematologic tumors such as leukemia with an incidence of 10–15% and less often with solid tumors – breast cancer, lung cancer, and melanoma being most common- at an incidence of 1–5%. Spread of hematologic malignancies to the leptomeninges is commonly referred to as lymphomatous meningitis while spread of solid tumors is referred to as leptomeningeal carcinomatosis (LC) [1, 2].

Typically, LC is a late complication of cancer at its more advanced stages. However, it can occasionally present as the initial diagnosis, especially in insidious cancers that remain asymptomatic for a long time. Presenting symptoms of LC most commonly include a headache, AMS, nausea, and vomiting along with cranial nerve palsies which can be attributed to obstruction of CSF flow and direct invasion of nerve tissues, respectively [1, 3].

Although extremely rare with only a handful of cases reported in the medical literature, LC can arise from metastatic prostate cancer. Due to the scarcity of this particular condition and the lack of sensitivity of CSF cytological testing, it was traditionally difficult to diagnose. The recent advancements in MRI studies have considerably increased the accuracy of diagnosis process; however, pre-mortem diagnosis of this condition without a direct biopsy continues to remain difficult and controversial.

Case Presentation

This report presents a case of a 71-year-old Caucasian male admitted to the ICU with AMS, lower extremity weakness, and worsening diarrhea. The patient had aggressive, castration-resistant prostate cancer with a Gleason score of 4 + 4 and known metastases to the bones, bone marrow, and bladder. The patient was being treated with leuprolide and denosumab at the time of admission, and his previous treatment regimen included leuprolide, bicalutamide, abiraterone, and prednisone. During the patient's hospital course, consent for discussion and report of findings related to his care was obtained from family members.

The patient suffered from diarrhea for two weeks prior which resolved after seven days of metronidazole; however, his diarrheal condition resurfaced and worsened when he was given additional antibiotics for suspected UTI. The family reported that in the week prior to admission the patient's mental status had slowly worsened, his lower extremities became increasingly weak which rendered him unable to walk independently, and his overall functional status deteriorated. The family reported that these represented significant decline when compared to his previous condition. Of note, at time of presentation, his measured serum PSA was 5.82 ng/mL.

In order to further evaluate his AMS, a CT scan of the head without contrast and a follow-up MRI scan were ordered. Although the CT scan was negative, the follow-up MRI of the brain revealed a diffuse enhancement of the meninges which was highly suggestive of LC (Fig. 1, 2).

MRI of the cervical and lumbosacral spine showed evidence of diffuse osseous metastatic disease without a bulky focus of meningeal disease.

The CSF cytology obtained through a lumbar puncture showed no malignant cells and further studies of the CSF revealed glucose <1 mg/dL, protein 8 mg/dL, 0 white blood cells/mm^3, 1 red blood cell/mm^3, PSA 0.64 ng/mL, negative ACE, negative VDRL, and negative PCR testing and cultures for routine bacterial, viral, and fungal pathogens.

The patient was diagnosed with LC from malignant prostate cancer based on the known history of the aggressive disease, clinical presentation, and highly suggestive MRI findings despite CSF studies which were largely unrevealing. The results, further diagnostic options including repeat CSF studies, and prognosis were discussed with his family as the patient's mental status continued to decline. Although further diagnostic and subsequent treatment options were offered, the family collectively elected to withdraw care.

Discussion

LC is a rare complication of advanced-stage malignancies. The clinical diagnostic criteria and methods for LC remain controversial. The advancement of MRI has enhanced pre-mortem diagnosis of LC, and specific MRI findings are considered highly suggestive. However, a definitive diagnosis requires a pathologic confirmation by diagnostic tests such as repeated CSF cytology or meningeal biopsy which is usually performed only post-mortem. It is important to note that the false-negative rate for CSF cytology for all types of tumors is 50% with a single lumbar tap, 20% with two, and 10% with three [4]. Even with multiple lumbar taps, studies have reported that about 26 to 50% of cases show persistently negative cytology in patients with later confirmed leptomeningeal disease via a more definitive method such as biopsy.

This prompts further investigation to determine the better diagnostic method of LC: a diagnosis made only after CSF sampling or direct biopsy provides cytological confirmation or a more clinically based diagnosis with MRI findings serving as confirmatory tests. Due to the invasive nature of the cytological confirmatory tests, it is important for clinicians to consider whether these tests are absolutely necessary when diagnostic images are consistent with LC in addition to clinical suspicion based on history and physical findings.

As mentioned, one of the confirmatory tests is repeated CSF evaluation which has variable sensitivity with many factors playing a role in its utility. One study has shown that the false negative rate of CSF studies in leptomeningeal disease from all causes can be less than 3% when the volume of analyzed CSF fluid is at least 10.5 mL [4]. Another strategy to increase the accuracy of CSF studies is to selectively sample CSF from sites closer to suspected foci of disease when possible with image-guided procedures providing increasingly sophisticated methods of sampling from precise locations. Sampling CSF from a device such as an intraventricular drain when LC is cranial or sampling via lumbar tap when LC is spinal has shown to increase sensitivity of testing when compared to sampling at more distant locations from the location of disease [4]. It is also recommended to evaluate CSF samples promptly since a delay of just 48 hours even with appropriate preservation techniques significantly decreased the sensitivity [4].

Although diagnosing LC with negative cytology results continues to remain difficult, some CSF studies have shown promising results in predicting the presence of LC. CSF fibronectin and beta-glucuronidase levels, when elevated in a clinically appropriate situation, can be indicators of leptomeningeal disease. However, these markers are nonspecific and can also be elevated in infectious conditions. Other clues to indicate possible leptomeningeal disease

when cytology is negative include opening pressure >150 mm H_2O, glucose <40 mg/dL, protein >50 mg/dL, and white blood cell count >5 cells per mm^3 [5]. A newer technique called random cell capture technology (RCCT) has been developed and tested to be used as a more sensitive test for LC of any origin. This method aims to capture circulating tumor cells within the CSF using targeted cell adhesion molecules. Using this method, a cutoff of 1 circulating tumor cell captured per 1 milliliter of CSF analyzed provided a sensitivity of 93% and a specificity of 95% [6].

Specifically for LC with suspected origin from the prostate, one study demonstrated that CSF evaluation of PSA level may play a significant role in the confirmation of LC and the authors reported that an elevated CSF PSA in addition to suggestive MRI findings may be enough to make the diagnosis without further testing [7]. These findings could justify empiric treatment for leptomeningeal diseases, which, in cases of adenocarcinoma of the prostate, has included liposomal cytarabine or intrathecal methotrexate. Other treatments reported in the literature include radiation and a combination of radiation and corticosteroids, but the effectiveness of these methods has not been reported. Due to the exceedingly low number of reported cases of LC from prostate cancer, a standard therapy has not been established but reported therapies include those listed along with surgical debulking of any subdural mass when applicable. For many patients, treatment options can best be determined by their functional status at the time of diagnosis of LC and their willingness to undergo potentially highly toxic therapies including intense chemotherapy or extensive radiation treatments.

Overall, the prognosis of LC is grim. Unfortunately, at this time no treatment has been discovered that has shown long-term efficacy in the management of leptomeningeal disease of any origin. Nayar et al. published a review in 2017 which documented attempted treatments for LC of multiple different origins with all reported trials providing palliation at best. At this time, strategies to provide tumor-specific intrathecal therapies represent the main goal of treatment. However, due to toxicities and the aggressiveness of tumors that have invaded the meninges and epidural space, much work remains to be done to provide treatment for these conditions [8, 9]. Major prognostic indicators include Karnofsky scale scores where a score of 70 or greater represents an average survival of approximately nine months, and a score of 60 or lower represents a mean survival time of a little over one month [2]. As treatment options for prostate cancer continue to advance, lengthening of survival is likely to continue to improve; thus, increasing the incidence of LC originating from prostate cancer [5].

Conclusion

While LC treatment options remain palliative in nature, the potential benefits of successful diagnosis and initiation of early treatment must be considered. A successful palliation can be of tremendous benefit and importance to patients and their families. Early intervention has the potential to restore some function of affected nerves and to resolve mental status alterations, albeit temporarily. These measures can lengthen the valuable remaining time for patients while allowing families to spend time together in addition to allowing them to discuss plans for future care. Our case demonstrates an example of a leptomeningeal disease with negative CSF studies where the question of whether to begin treatment without cytological confirmation holds great importance. With the low sensitivity of CSF testing and the expected increase in the incidence of the leptomeningeal spread of all cancers as treatments improve, this question warrants further consideration and study.

Statement of Ethics

Informed consent was obtained from the patient's family for the presentation of the patient's case along with the associated medical imaging.

Disclosure Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Sources

The authors received no financial support for the research, authorship, and/or publication of this article.

Author Contributions

Ryan Carroll participated directly in care of the patient, performed literature review, and assisted in drafting of the components of the case report.

Cindy Leigh performed literature review, assisted in drafting of the components of the case report, and assisted in formatting the presented material.

Zachary Curtis, Anthony Thorpe, and Jason Ballengee assisted in literature review.

Toni Pacioles served as faculty advisor in the development of the case report and all presented materials.

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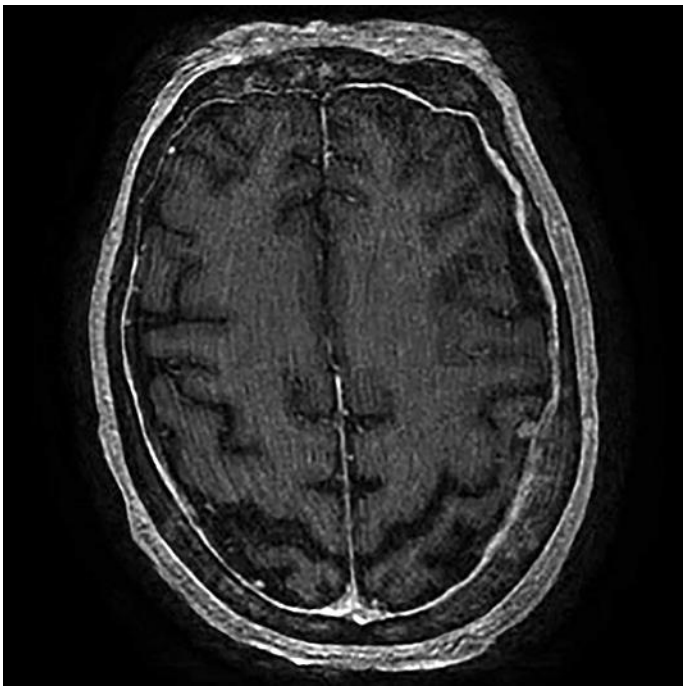

Fig. 1. Diffuse meningeal enhancement on MRI of the brain – transverse view.

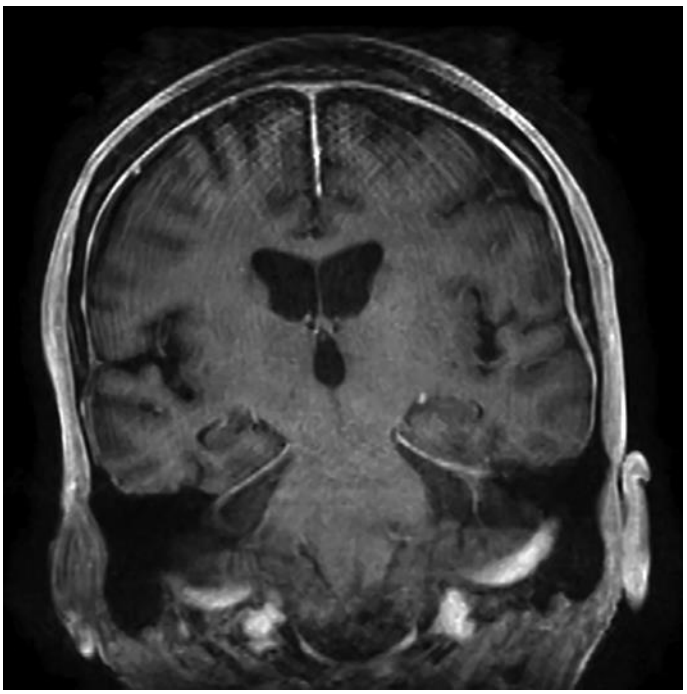

Fig. 2. Diffuse meningeal enhancement on MRI of the brain – coronal view.