



Leptomeningeal Carcinomatosis: Challenges in Diagnosis and Treatment

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Abstract

Leptomeningeal carcinomatosis occurs in approximately 3% to 5% of all cancer patients. Leptomeningeal metastasis from primary breast cancer is the most common etiology for all leptomeningeal diseases. Triple-negative breast cancer has significantly higher metastasis rates and a poorer prognosis compared to hormone-positive breast cancer. Leptomeningeal carcinomatosis is often difficult to diagnosis and can affect any level of the central nervous system. Imaging and CSF analysis often allows for the diagnosis of leptomeningeal diseases. However, once leptomeningeal metastasis is confirmed prognosis is often poor and treatment options remain limited. This case report and literature review is meant to highlight an uncommon late-stage complication of breast cancer because early diagnosis and treatment significantly impacts morbidity and mortality.

Keywords: Leptomeningeal carcinomatosis; Leptomeningeal metastasis; Triple-negative breast cancer

Abbreviations

TNBC: Triple-Negative Breast Cancer; IHC: Immunohistochemical; CK7: Cytokeratin 7; CK5/6: Cytokeratin 5/6; GCDFP-15: Gross Cystic Disease Fluid Protein 15; GATA-3: GATA Binding Protein 3; ER: Estrogen Receptor; PR: Progesterone Receptor; Her2/neu: Human Epidermal Growth Factor Receptor 2/neu; GFAP: Glial Fibrillary Acidic Protein; IT MTX: Intrathecal Methotrexate; CTLA-4: Cytotoxic T-Lymphocyte Associated Protein 4; PD1: Programmed Cell Death Protein 1

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Introduction

Leptomeningeal Carcinomatosis (LC) is an uncommon complication of malignant tumors that metastasize to the Cerebrospinal Fluid (CSF) and leptomeninges [1]. The presentation of LC varies based on its ability to affect any level of the Central Nervous System (CNS). Furthermore, symptoms may be isolated or subtle. The most commonly reported symptoms on initial presentation include migraines, confusion, and cerebellar signs [2]. Breast cancer is the most common primary site to metastasize to the leptomeninges, followed by Non-Small-Cell Lung Cancer (NSCLC) and melanoma [1,3]. Also, adenocarcinomas, regardless of the origin, most commonly metastasize to the CSF [3].

Improved neuroimaging methods such as Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) are more ubiquitous in the initial workup process allowing for earlier detection and diagnosis of LC [3]. Also, prolonged survival is associated with a higher prevalence of LC, which suggests non-CNS primary tumors are allowed more time to develop CNS metastases. Lastly, trends in the use of systemic anti-cancer agents that do not cross the Blood-Brain Barrier (BBB) may have a vital role, such as trastuzumab in HER2/neu positive breast cancer, doxorubicin, and paclitaxel for Triple-Negative Breast Cancer (TNBC), and gefitinib or erlotinib in NSCLC. Use of these agents with limited CNS penetration may control systemic disease, but allow leptomeningeal diseases to remain untreated and cloaked behind the BBB [4].

This report presents an uncommon case of leptomeningeal metastasis from breast cancer. When patients with a history of breast cancer complain of neurological symptoms, we should consider leptomeningeal metastasis from breast cancer.

Case Presentation

A 55-year-old female with a past medical history of right breast triple-negative adenocarcinoma

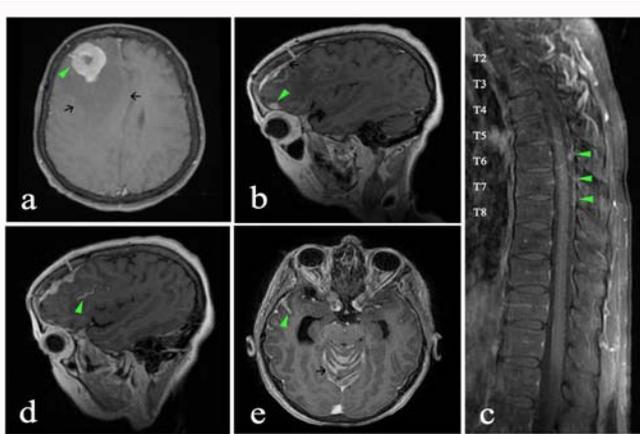


Figure 1: MRI with contrast demonstrated metastatic brain and leptomeningeal disease. (a) On initial presentation, axial images showed a large avidly enhancing lesion in the right anterior frontal lobe with central hemorrhagic necrosis (arrowhead; 4 cm anterior-posterior × 2.8 cm transverse × 3 cm craniocaudal) and extensive edema throughout the right frontal and parietal lobes (arrow) resulting in right to left midline shift (arrow). (b) Three months after craniotomy, image showed a T1 hyperintense focus (arrowhead) in the sagittal view representing lesion enhancement in the inferior right frontal lobe near the orbital gyrus. Expected, right frontal post-craniotomy changes were noted (arrow). (c) Three months following craniotomy, sagittal images revealed meningeal enhancement posterior to the spinal cord from segments T6-8 (arrowheads). (d) The patient’s metastatic leptomeningeal disease was refractory to intrathecal methotrexate, represented by sagittal images showing abnormal serpiginous T1 hyperintensity (arrowhead) in the inferior right frontal sulcus with leptomeningeal enhancement. (e) Axial views revealed leptomeningeal enhancement surrounding the folia of the superior aspect of the cerebellum (arrow) and along the anterior superior aspect of the right temporal lobe (arrowhead) representing metastatic disease.

time. Follow-up full body CT scans revealed a new 2 cm left breast mass that was concerning for metastatic disease. Tumor resection by craniotomy was performed. The brain tumor was immunoreactive for CK7, CK5/6, pancytokeratin, GCDPF-15, and GATA-3. In contrast, the malignant brain tissue was negative for ER, PR, HER2/neu, and GFAP. The pathology and IHC staining profile supported a poorly differentiated metastatic triple-negative breast adenocarcinoma.

One month after completing stereotactic radiosurgery to prevent brain tumor regrowth she developed severe headaches. Brain and whole-spine MRI with contrast was obtained, which showed new abnormal enhancement in the brain and spinal T6-8 meningeal enhancement (Figure 1b-1c). Large atypical cells resembling metastatic adenocarcinoma were noted in CSF fluid after lumbar puncture. Imaging and CSF analysis allowed for the diagnosis of LC. Intrathecal methotrexate was started. However, subsequent MRIs of the brain showed new metastatic brain disease to inferior right frontal, temporal, and cerebellar regions (Figure 1d-1e). She continued to deteriorate, IT MTX was stopped, and the patient was transitioned to comfort care.

Discussion

LC is recognized clinically in up to 8% in all cancer patients [3,5]. Increased clinical awareness of LC allows for earlier detection and treatment, maintains the quality of life, and prolongs survival [1]. Since LC can involve any level of the CNS, brain and whole spine imaging with contrast is recommended during the initial workup process [6]. Diagnosis of metastatic leptomeningeal disease is typically done with lumbar puncture and cytological examination for malignant cells in the CSF [7]. A high sensitivity ranging from 75% to 90% makes CSF analysis the gold standard for LC diagnosis [8]. Serial CSF sampling is recommended due to significant false-negative rates associated with CSF sampling [4]. Additionally, biomarker analysis of CSF for angiogenesis markers such as VEGF has shown good predictive value in detecting leptomeningeal disease [9].

Neurological imaging has proven to be very valuable in the

treated neoadjuvant chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel) followed right breast-conserving surgery by lumpectomy and postoperative radiation two years prior presented to the hospital with left hemiparesis. Initial MRI of the brain showed a large 4 cm right frontal lobe lesion (Figure 1a). Whole-spine MRI was not obtained. CSF sampling and analysis was not performed at this

Table 1: Intra-CSF drug therapies.

| Author, year | Primary Cancer | Treatment | † Survival, months |
|--------------------------|-------------------|------------------------|--------------------|
| Wasserstrom et al. [7] | Breast, lung | IV MTX | 5.8 |
| O. de Visser et al. [34] | Breast | IV / IT MTX | IV: 6, IT: 2 |
| Hitchens et al. [35] | Breast, SCLC | IV MTX | 2 |
| Levin et al. [36] | Various, leukemia | IV / IT ACNU | Phase 1 trial |
| Fizazi et al. [37] | Breast | IT MTX | LD: 1.8, HD: 3.5 |
| Chamberlain et al. [38] | NSCLC | IV MTX | 5 |
| Laufman et al. [39] | Breast (HER-2+) | IV Herceptin | Phase 1 trial |
| Blaney et al. [40] | Various, leukemia | IV / IT MTX, Topotecan | Phase 1 trial |
| Blaney et al. [41] | CNS embryonal | IV / IT Mafosfamide | Phase 1 trial |
| Gururangen et al. [42] | Primary brain | IV / IT Busulfan | Phase 1 trial |
| Bernardi et al. [43] | Various, leukemia | IV / IT Gemcitabine | Phase 1 trial |
| Waki et al. [44] | Breast, lung | IT MTX | 4.8 |
| Gauthier et al. [21] | Breast | IV MTX | 4.5 |
| Gwak et al. [33] | NSCLC | IV MTX | 3 |

†The predominate tumor(s) evaluated by a particular study represented by the number of cases. ‡Survival denotes median overall survival in months. Survival data not consistently based on Phase 1 trial design evaluating safety and efficacy
 IV: Intraventricular; IT: Intrathecal; LD: Low Dose; HD: High Dose; MTX: Methotrexate; ACNU: Nimustine Hydrochloride; CNS: Central Nervous System; SCLC: Small Cell Lung Cancer

diagnosis of LC. Contrast-enhanced MRI of the brain and spine is considered the standard imaging modality for cancer patients with clinically suggestive LC due to its excellent contrast resolution, safety profile, and multiplanar abilities [10]. A wide range of diagnostic sensitivity has been reported with MRI, ranging from 20% to 91% [11-13]. The large range in sensitivity is believed to be due to differences in detecting hematological malignancies vs. solid tumors [14]. Advancements in MRI technology such as the development of postcontrast Fluid Attenuated Inversion Recovery (FLAIR) and 3-dimensional T1 weighted sequences have led to a recent increase in sensitivity rates [15,16]. One MRI finding that is highly suggestive of LC is diffuse leptomeningeal enhancement in the brain or spine [17]. This finding is often referred to as “sugar coating” or *zuckerguss* (German for sugar icing), in reference to the appearance of diffuse sheet-like leptomeningeal contrast enhancement on imaging [14,18]. Other common findings on MRI include subarachnoid enhancing nodules, ependymal enhancement, sulcal enhancement, and nerve root enhancement [19]. If there are contraindications to MRI, a CT myelogram is the second line imaging technique to evaluate the spine and has additional benefit of performing CSF sampling during the same time as the study [14]. Head CT is not recommended in the diagnosis of LC due to low estimated 23% to 38% sensitivity of scan [20-21]. Ultimately, no modality is perfect, but when used together and in conjunction with a patient’s suggestive clinical picture, they are sufficient for the diagnosing LC [4-6,22].

TNBC cannot be treated adequately with targeted endocrine therapies. However, anthracyclines and taxanes, as well as combination anthracycline-cyclophosphamide-based chemotherapy regimens have good clinical and pathological response rates [23]. Thus, these classes are indicated as first-line treatment of TNBC [24]. Historically, doxorubicin, cyclophosphamide, and paclitaxel have been not used routinely for primary and metastatic TNBC, or for other solid tumors [25]. Cyclophosphamide is thought to cross the BBB with ease. In contrast, doxorubicin and paclitaxel only do so negligibly based on mechanisms that are not understood fully [26]. The clinical use of doxorubicin is limited by its toxicities and inherent BBB protein pumps that decrease penetration of the drug [27]. Newly developed liposomal delivery systems limit the toxicity of doxorubicin and potentially reverse drug-resistance [28]. Similar efforts have been made to promote improved delivery of paclitaxel, with the addition of nanoparticles [29].

There are no standard treatment guidelines for LC [30]. Historically, the treatment regimen for LC has been IT MTX, plus systemic chemotherapy with or without localized radiation therapy [3]. These treatment modalities have comparatively lower rates of adverse events, and improved the median survival following the diagnosis of LC from one month to 3-6 months. Radiotherapy can be a useful treatment for bulky leptomeningeal disease [31]. IT chemotherapy with MTX has been extensively examined in literature for patients with LC and been shown to increase overall survival when compared to patients that went untreated [32]. In addition to IT MTX, several other intra-CSF chemotherapeutic agents have been introduced in the treatment of LC (Table 1) [7,21,32-43]. IT administration of Mafosfomide, Gemcitabine, Busulfan, and ACNU have more recently been explored in phase 1 trials as potential treatment options with varying results [33]. IT MTX and thiotepa have been studied as a potential therapeutic option, but survival was not shown to be improved significantly by this intervention [44]. Similar outcomes have been published for combination

intraventricular therapies [45,46]. IT topotecan has been determined to be non-superior to other standard IT chemotherapeutic options [33]. IT trastuzumab for HER2-positive disease has been shown to be effective [47,48]. Besides toxicity, IT chemotherapy efficacy is CSF flow-dependent [49]. This is important to consider due to the prevalence of patients with leptomeningeal diseases having evidence of CSF flow obstruction. Ultimately, no current treatment modality has been shown to improve overall survival [50,31].

While surgery, radiation, and chemotherapy are central in the treatment of LC, recent literature has investigated molecular targeted therapy and immunotherapy as possible adjuvants to standard care. Application of molecular targeted drugs in patients with mutations in the EGFR or ALK gene in lung tumors, as well as positivity of CD20 in B cell lymphoma have all shown to promising clinical results [18]. LC patients with an EGFR mutation that received EGFR tyrosine kinase inhibitor therapy showed a longer overall survival of 10.9 months compared to 2.3 months for patients without the mutation [51]. Patients with NSCLC with ALK gene rearrangement can be treated with ALK inhibitors [52]. Second generation ALK inhibitors such as Ceritinib have shown great efficacy against LC with patients showing significant clinical and radiological improvements [53,54]. In patients with diffuse large B cell lymphoma, an anti-CD20 monoclonal antibody such as Rituximab has shown efficacy [55-57]. The large size of the monoclonal antibody has led ongoing studies to examine the efficacy of intrathecal administration of Rituximab [56]. Immunotherapy has also emerged as a promising new direction in the treatment of LC. Toll-like receptor 9 agonists have shown antineoplastic activity as well as the ability to increase the innate and adaptive immune system [58]. Immune checkpoint inhibitors such as antibodies against CTLA-4 and PD1 have shown significant activity against various solid tumor types [59]. Currently, there is limited data available on the specific use of these antibodies in patients with LC. Future studies are needed to assess the efficacy of the antibodies alone or in combination with other therapies for treatment of LC [59-60].

Treatment options for patients who develop metastatic CNS disease and LC include surgical resection, brain radiation, systemic chemotherapy, or supportive care [50]. Options are based not only on the malignant tumors location, number, and response to prior treatments, but also the patient’s other comorbidities. Due to the infrequent nature of leptomeningeal diseases, clinical trial data are difficult to gather on the subject to guide therapy. Patients with metastatic CNS disease until recently have been excluded from most clinical trials. As a result, response guidelines initially developed for non-CNS cancer patients have been modified in the past for CNS cancer patients enrolled in clinical trials. Novel and hypothetical trial designs for patients with leptomeningeal disease have been discussed in the literature. However, the majority of current clinical trial data are products of retrospective series designs, which limit evidence quality regarding the optimal treatment of LC [31]. Ultimately, patients need better treatment options and clinicians need a better understanding why certain patients are at higher risk for developing leptomeningeal disease. While there is no cure for leptomeningeal diseases, clinical trial researchers hope to learn how to predict when and if a patient will develop leptomeningeal disease. These studies will likely pave the way for earlier diagnosis and treatment [61].

Conclusion

This report presented a rare case of leptomeningeal carcinomatosis secondary to primary triple-negative breast adenocarcinoma, despite

the patient receiving prior breast cancer treatment. When patients present with neurological complaints and have a history of breast cancer, we should consider leptomeningeal carcinomatosis. Although a thorough history and physical exam are vital, MRI and CSF analysis are paramount for solidifying the diagnosis of LC. Despite advancements in chemotherapeutic agents and radiation therapies, treatment options are limited and median survival times are short. Further research is needed to elucidate additional therapies.

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