1. Introduction

Leptomeningeal carcinomatosis (LC) refers to the infiltration of the leptomeninges by metastatic carcinoma. Its most common etiology is breast carcinoma, although LC is relatively uncommon in women with breast cancer, and concurrent brain metastases, serving as either a late-stage prognostic complication or the initial evidence of metastasis. Prognosis for LC remains poor, with survival rates ranging from 4 weeks without treatment to 4 months for patients undergoing treatment.

Several primary variables have been associated with survival in LC, including performance status at diagnosis, cerebrospinal fluid (CSF) protein levels, and the presence of the triple-negative subtype. LC is primarily diagnosed through CSF cytological analysis and/or magnetic resonance imaging (MRI). Current management strategies for LC encompass a combination of intra-CSF chemotherapy, systemic therapy, radiotherapy, and best supportive care. Methotrexate remains the drug of choice for intra-CSF chemotherapy.

In this case report, we describe a case of a female patient who initially presented with leptomeningeal metastasis (LM) as the first sign of breast cancer. Remarkably, she achieved a prolonged survival of 18 months following intrathecal therapy in conjunction with systemic therapy, making this particular case rare.
2. Case presentation

A 59-year-old female patient with a history of left breast carcinoma since 2000 was admitted to the hospital with newly diagnosed right breast type I lobular carcinoma, staged as T2N2Mx, pathological stage IIIa. She had a previous history of a cerebral vascular accident (CVA) and was on a medication regimen that included Plavix 75 (clopidogrel) and Avas 10 (a statin) tablet. She underwent a mastectomy with axillary clearance and received only six cycles of adjuvant CNF combination therapy (cyclophosphamide, mitoxantrone, and 5-fluorouracil).

Immunohistochemical staining assays revealed positive results for both estrogen receptor (ER) with a total score of 7/8 and progesterone receptor (PR) with a total score of 6/8, while human epidermal growth factor receptor 2 (HER-2) expression was negative (+1). All her complete blood count (CBC) results, as well as chest and brain computed tomography (CT) scans were normal. In addition, her renal and liver function tests yielded normal results. Abdominal ultrasound showed no abnormalities, but abdominal CT revealed ascites with a nonenhancing wall cyst measuring 15 × 15 mm in segment 4. A small amount of liver fluid was also observed in the peritoneal cavity. Surgical histopathology reported findings consistent with right mastectomy with axillary clearance. Gross fatty breast tissue with overlying skin, nipple, and areola measured 20 × 12 × 10 cm. There were no skin scars or ulcers. Serial cross sections revealed a mass in a central quadrant, measuring 2.7 cm.

Microscopic examination revealed invasive lobular carcinoma of the classic type, Grade II, infiltrating the breast parenchyma in an Indian file pattern, involving fatty tissue with desmoplastic stromal reaction, perineural invasion, and foci of lymphatic vessel permeation, with an invasive ductal carcinoma component comprising 4%. Surrounding breast tissue showed adenosis with epithelial foci, but there was no skin involvement or Paget’s disease. Furthermore, surgical resection margins, both deep and circumferential, were clear. Of the 14 axillary lymph nodes examined, seven showed metastases with focal infiltration of the axillary fatty tissue. The CA-125 test result yielded a measurement of 212, and CA 15/3 was elevated above 300. After 1 month, CA-125 increased to 322.5, while CA 15/3 was 299.3. Abdominal ultrasound revealed a liver simple cyst measuring 1.5 cm, along with a bulky uterus measuring 7 × 6 × 5 cm. Cervical spine MRI showed degenerative changes at C4−5, C5−6, C6−7, along with disc bulge and osteophytes. MRI of the dorsal and lumbosacral spine illustrated central diffuse bony metastasis involving all dorsal, lumbar, and sacrococcygeal regions (both bodies and posterior elements), along with multiple degenerated disc changes at L2−3, L3−4, and L4−5 intervertebral discs. Treatment began with vinorelbine 40 mg intravenous (IV) on days 1 and 8, along with zoledronic acid injection.

In this known case of metastatic carcinoma involving both breasts, a recent comparative positron emission tomography (PET) CT scan revealed no evidence of hypermetabolic local recurrence in the bilateral postoperative mammary regions. Metabolically inactive extensive metastatic lesions were stable. Resolution of hypermetabolic ground-glass opacities in the lungs confirmed their infectious origin. The previously noted metabolic portacaval node, which had recovered from an inflammatory etiology in a previous scan, recurred. There was no evidence of other metabolically active disease elsewhere in the body. These overall findings suggested an ongoing metabolic remission in the context of breast carcinoma.

PET scan results from 2019 indicated the absence of skeleton-related metabolic lesions, with localized recurrent metabolic inactivity. However, hypermetabolic infiltration persisted in both lungs (indicative of stable infectious disease). MRI of the dorso-lumbo-sacral spine revealed diffuse abnormal heterogeneous signal intensity in the bone marrow, with heterogeneous enhancement following contrast administration. Scattered focal lesions were observed in the vertebral bodies and neural arches. Chronic degenerative changes included decreased height and hydration of L2/3, L3/4, L4/5 intervertebral discs, along with circumferential bulging causing pressure on the thecal sac. Neural foraminal narrowing was mild and did not significantly impinge on the nerve roots, and there were no space-occupying lesions (SOL).

In 2020, the patient started having lower limb weakness. There was a presence of diffuse linear sheet-like leptomeningeal enhancement observed throughout the visualized spinal cord, accompanied by nerve root enhancement, reminiscent of leptomeningeal involvement. Mild enhancement was also noted surrounding the Schmorl’s nodes, accompanied by mild
edema.

On T2 STIR scans of the iliac and sacral bones, only a few areas exhibited high signal intensity, which necessitated further analysis and could potentially indicate secondary deposits. The most prominent diffuse degenerative changes observed in the lumbar intervertebral discs were as follows: a circumferential disc bulge at L2–L3, ligamentum flavum hypertrophy, and facet arthropathy, all of which were abutting the bilateral lateral recesses and causing a subsequent mild bilateral neural foraminal narrowing affecting the descending L3 nerve roots. Notably, there was no evidence of neural impingement or spinal canal stenosis. Similar findings were identified at the L3–L4 and L4–L5 levels, and an approximately 10-mm subcutaneous cyst was identified within the dorsal subcutaneous tissue, possibly related to a small epidermal inclusion cyst.

Brain contrast-enhanced MRI (CE-MRI) revealed a focal area of gliosis in the left frontoparietal region, associated with mild edema and atrophic brain changes that had caused enlargement of the left lateral ventricle due to an old cerebrovascular lesion. However, no enhancing focal brain lesions were identified. Ventricles and CSF spaces were within normal limits. The basal ganglia and thalamus exhibited no abnormalities, and the brainstem and cerebellum appeared unremarkable, with no lesions observed in the cerebellopontine angle (CPA) on both sides. There was no evidence of brain metastasis. Progressive limb and knee nerve conduction study (NCS) showed degenerative changes in the lower extremities, along with mild axonal neuropathy.

In 2020, repeat PET scan and brain MRI yielded findings consistent with previous examinations. Dorso-lumbo-spine MRI confirmed bone marrow infiltration and leptomeningeal infiltration. Bilateral deep vein thrombosis (DVT) necessitated the insertion of an IVC filter. Subsequent spinal MRI revealed multiple discs with severe spinal stenosis. CSF examination showed the presence of lymphocytes, as well as a few large basophils with abundant cytoplasm, primarily of nonhemopoietic origin, indicating secondary metastasis involvement. Whole-spine MRI indicated leptomeningeal infiltration and multiple bone metastases.

At the end of 2020, a bone MRI revealed widespread bone metastases, accompanied by subtle leptomeningeal infiltration. Analysis of CSF showed a few red blood cells (RBCs), lymphocytes, macrophages, and a small number of large mononuclear cells. By 2021, the patient had developed severe osteoporosis along with continued bone metastasis. A summary of the patient’s therapeutic interventions is presented in Table 1.

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<table>
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<th>Table 1: A summary of the patient therapy.</th>
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<tr>
<td><strong>Systemic chemotherapy</strong></td>
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<td>Gemcitabine plus carboplatin</td>
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<td>Vinorelbine (Navelbine)</td>
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<td>Taxol weekly for four doses</td>
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<td><strong>Intrathecal chemotherapy</strong></td>
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<td>Methotrexate 12.5 mg plus hydrocortisone 50 mg intra-thecal by interlumbar route with frequent positive and negative cytology</td>
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3. Discussion

LM is a relatively rare but well-recognized late-stage complication of breast cancer that has become increasingly prevalent[16]. Heightened clinical awareness of LC facilitates earlier detection and treatment, thereby preserving patients’ quality of life and extending survival[16]. Radiologically, metastatic lesions in the leptomeninges are typically more conspicuous at the base of the brain, along the dorsal spinal cord, and within the cauda equina[3].

In contrast to our case, brain metastases are more commonly observed (10%) among young adults (20–39 years old), with a higher prevalence in African American patients compared to white patients (7.4% vs. 4.6%)[16].

Similar to our patient, individuals with hormone receptor-negative breast cancer are four times more likely to develop central nervous system (CNS) metastases than those with hormone receptor-positive tumors[11]. This receptor-positive breast cancer case aligns with previous studies that have associated receptor-positive breast cancer with longer median overall survival following the onset of distant metastases compared to triple-negative breast cancer[12].

Once LC is confirmed, the initiation of treatment, although essential, often shortens survival time[13], improving it from 1 month to 3–6 months[9]. Studies showed that breast cancer LM can occur as an isolated CNS metastatic site or in conjunction with concurrent brain metastasis at variable frequencies (37%–63%)[14, 15]. Concurrent active cancer outside CNS is documented in 60%–80% of cases at the time of LM diagnosis[15, 16].

Patients frequently present with spinal symptoms, particularly leg weakness and paresthesia[13]. The definitive method for diagnosing LM involves the demonstration of malignant cells in CSF through a lumbar puncture[17]. In our case, as in others, metastasis was readily diagnosed through MRI and CSF analysis.
The standard treatment for LC typically involves a combination of intrathecal methotrexate and systemic chemotherapy, often with the option of localized radiation therapy. However, the efficacy of intrathecal chemotherapy is dependent on CSF flow. Approximately 50% of patients with leptomeningeal disease exhibit signs of CSF flow obstruction, highlighting the importance of intracranial pressure measurements before treatment administration. Despite various treatment approaches, there is currently no established modality that has been shown to significantly improve overall survival.

Given the limited number of chemotherapeutic agents believed to penetrate the blood–brain barrier (BBB), current treatments for LM primarily involve radiotherapy targeted at symptomatic or bulky sites, intrathecal chemotherapy, or a combination of both. In a randomized clinical trial comparing intrathecal DepoCyt R (a slow-release formulation of cytarabine) with intrathecal methotrexate in patients with neoplastic meningitis due to breast cancer, similar response rates were observed, but there was a significantly greater time to neurological progression in the DepoCyt R group (58 vs. 30 days).

The main advantage of IV chemotherapy is that it does not cause chemical meningitis and has a lower risk of leukoencephalopathy compared to intrathecal treatment. However, IV methotrexate may lead to systemic side effects such as mucositis, bone marrow suppression, and nephrotoxicity. Leukoencephalopathy (observed in 7.5% of cases in case series) and bacterial meningitis (occurring in 3.75% of cases in case series) associated with the use of an intraventricular reservoir are two additional rare events that were previously considered major toxicities of intrathecal treatment.

Molecular therapeutic strategies are expected to play an increasingly significant role in the management of breast cancer LM. Individual case reports demonstrated potential activity of intrathecal trastuzumab in patients with HER-2–positive breast cancer LM, with indications of good tolerability. Response to treatment following capecitabine or lapatinib has also been reported in a limited number of breast cancer LM.

4. Conclusion

LC is a relatively uncommon yet well-recognized oncological condition, signifying a terminal complication of breast cancer. Clinical suspicion should remain high in patients with a positive breast cancer history who present with focal neurological signs despite a history of previous breast cancer treatment. In spite of an increased incidence of breast cancer LM, overall survival with current treatments remains limited to less than 6 months on average.

Advancements in our comprehension of the mechanisms underlying CNS metastasis, coupled with the development of more effective screening and early detection methods, are poised to pave the way for improved therapies. These developments are likely to usher in innovative treatments for LM and result in more informed therapeutic decisions, ultimately extending survival times in this challenging scenario.

Conflict of Interest

The author declares no conflict of interest.

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Ethical Statement

Written consent for publication of the clinical details was obtained from the patient.

References


