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Multimodal Treatment in Severe Breast Cancer Leptomeningeal Metastasis: A Rare Case of Prolonged Clinical Benefit

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Abstract

We report the case of a 44-year-old woman with previously treated hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2 (HER2)-negative breast cancer who developed a late metastatic recurrence with extensive leptomeningeal metastasis (LM), intracranial hypertension, and symptomatic hydrocephalus. Rapid neurological deterioration resulted in an Eastern Cooperative Oncology Group performance status (ECOG PS) of 4. Placement of a programmable ventriculoperitoneal shunt controlled hydrocephalus and resulted in marked neurological and functional recovery to ECOG PS 1, enabling treatment with intrathecal methotrexate and systemic letrozole and ribociclib. An ovarian metastasis identified during systemic staging was subsequently resected. Treatment was associated with a reduction in malignant cells in the cerebrospinal fluid (CSF), normalization of serum tumor markers, and sustained extracranial disease control. Intrathecal methotrexate was discontinued following the development of radiological leukoencephalopathy and persistent/progressive spinal leptomeningeal involvement. Despite persistent radiological and cytological evidence of LM, the patient remains clinically stable, functionally independent, and professionally active, with an ECOG-PS of 1 and sustained extracranial disease control, 15 months after LM diagnosis.

This case highlights the potential for prolonged clinical benefit from an individualized multimodal strategy in severe breast cancer LM. Effective management of hydrocephalus was critical in restoring performance status and enabling subsequent intrathecal and systemic treatment.

Categories: Neurology, Oncology, Neurosurgery
Keywords: breast cancer, hydrocephalus, intrathecal methotrexate, leptomeningeal metastasis, multimodal treatment, ventriculoperitoneal shunt

Introduction

Breast cancer is one of the most frequently diagnosed malignancies among women worldwide and remains a leading cause of cancer-related mortality [1]. Despite substantial improvements in outcomes, hormone receptor-positive (HR-positive), human epidermal growth factor receptor 2 (HER2)-negative breast cancer remains associated with a prolonged risk of recurrence, with distant recurrences continuing to occur up to 20 years after the initial diagnosis [2]. Central nervous system (CNS) involvement may occur later in the metastatic course, presenting as parenchymal disease or, less frequently, as leptomeningeal metastasis (LM) [3-5].

LM results from the dissemination of malignant cells within the leptomeninges and cerebrospinal fluid (CSF), potentially affecting multiple levels of the neuraxis. Its clinical presentation is heterogeneous and may include headache, nausea and vomiting, cranial nerve dysfunction, visual disturbances, gait impairment, and radicular symptoms. Diagnosis relies on the integration of neurological findings, contrast-enhanced magnetic resonance imaging of the entire neuraxis, and CSF analysis [6]. Despite therapeutic advances, LM remains associated with substantial neurological morbidity and a poor prognosis, with median survival generally limited to a few months [6].

The management of LM is largely palliative and aims to stabilize neurological function, preserve quality of life, and prolong survival. Treatment decisions are individualized according to performance status, tumor subtype, extent of systemic disease, and the radiological pattern of leptomeningeal involvement [6]. Systemic therapy is the backbone of treatment, ideally with agents that can reach the CNS. In HR-positive, HER2-negative breast cancer, this includes endocrine therapy, with or without cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, and chemotherapy agents such as capecitabine or high-dose methotrexate [6]. Intrathecal therapy, most commonly with methotrexate, cytarabine, or thiotepa, allows direct drug delivery into the CSF and is preferably administered through an intraventricular reservoir. Its benefit appears greatest in patients with linear (non-nodular) disease and preserved CSF flow [6,7]. Radiotherapy is mainly used for symptomatic or bulky nodular disease and for areas obstructing CSF flow. Proton craniospinal

irradiation has emerged as a promising option for selected patients [6,8].

Disruption of CSF circulation is a common finding in LM and may lead to intracranial hypertension and hydrocephalus, further contributing to neurological and functional deterioration [9]. Ventriculoperitoneal shunting can effectively restore CSF drainage and provide symptomatic relief; however, continuous diversion represents a challenge when intrathecal therapy is considered, as it may reduce drug exposure within the CSF compartment [6,10]. To overcome this limitation, programmable shunt systems can allow temporary adjustment of the valve opening pressure during intrathecal drug administration [6,10]. This approach enables CSF diversion and intrathecal therapy to be incorporated into a multimodal treatment strategy.

Case Presentation

A 44-year-old premenopausal woman was initially diagnosed with a locally advanced, grade 2, invasive lobular carcinoma of the left breast with a luminal B-like phenotype (HR-positive, HER2-negative score 0, Ki-67 20%), clinically staged as cT3mN1M0 (55-mm primary tumor with multiple synchronous tumor foci, two involved ipsilateral axillary lymph nodes, and no evidence of distant metastasis), stage IIIA (American Joint Committee on Cancer (AJCC) Eighth Edition) [11].

She underwent neoadjuvant treatment with four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2), administered every three weeks, followed by 12 weekly administrations of paclitaxel (80 mg/m^2). A left modified radical mastectomy was subsequently performed, achieving a partial pathological response (ypT1cN0 - residual invasive tumor with 1.1 cm, with no regional lymph node metastases). Adjuvant treatment consisted of chest wall radiotherapy (50 Gy in 25 fractions, over three weeks) and endocrine therapy with tamoxifen (20 mg once daily) plus ovarian function suppression with goserelin (3.6 mg every 28 days), for five years. No evidence of disease recurrence was observed during subsequent follow-up.

Seven years after surgery, the patient developed progressively persistent headaches, followed by vomiting and visual disturbances. Fundoscopy showed right-sided papilloedema (Figure *1A*).



FIGURE 1: Serial fundoscopic findings

Panel A: Initial fundoscopy demonstrating right-sided papilloedema. Panel B: Follow-up fundoscopy demonstrating resolution of papilloedema with bilateral optic disc pallor.

Initial contrast-enhanced cranioencephalic computed tomography (CT) showed progressive ventricular enlargement, with no intracranial mass lesions, midline shift, or effacement of the basal cisterns, findings suggestive of communicating hydrocephalus (Figure *2*). Lumbar puncture was reported as compatible with intracranial hypertension, and initial CSF findings are summarized in Table *1*. Neuroaxis contrast-enhanced magnetic resonance imaging (MRI) demonstrated hydrocephalus and leptomeningeal involvement, with abnormal enhancement of multiple cranial nerves and cervical spinal meninges (Figures *3A*, *3B*).

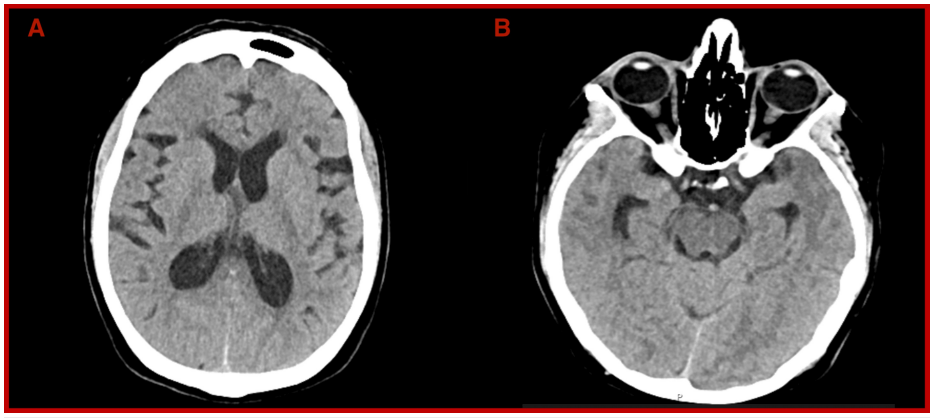


FIGURE 2: Contrast-enhanced cranioencephalic computed tomography (CT)

Panel A: Axial image demonstrating enlargement of the lateral ventricles. Panel B: Axial image at the level of the basal cisterns, without evidence of intracranial metastatic lesions.

Time Point	Clinical Status	ECOG PS	RBC (/mm³)	WBC (/mm³)	Atypical/Non-hematopoietic Cells	Protein (mg/dL)	Glucose (mg/dL)	LDH (U/L)	Cytology/Relevant Findings
At diagnosis	Headache, nausea and vomiting, visual impairment, right-sided papilledema; rapid neurological deterioration	4	58	4	34% CD45-negative cells*	72	54	—	Malignant cells identified, with immunocytochemistry supporting breast origin
~3 months after starting IT MTX	Resolution of headache, nausea, and vomiting; sustained neurological improvement	1	—	—	Rare suspicious cells	75.3	—	—	Rare cells with cytomorphological features suspicious for neoplastic epithelial cells
At IT MTX discontinuation	Mild attention and memory deficits; otherwise neurologically stable and independent in activities of daily living	1	—	—	Rare suspicious cells	116.9	—	—	Rare cells with cytomorphological features suspicious for neoplastic epithelial cells
~2 months after IT MTX discontinuation	Neurologically stable, without residual deficits; returned to work and regular physical exercise	1	—	—	Scant malignant epithelial cells	259.9	—	—	Scant malignant epithelial cells, compatible with the known breast primary

TABLE 1: Serial CSF findings in relation to clinical status and performance status

*The percentage of CD45-negative cells was obtained by immunophenotyping and is not directly comparable with subsequent morphological cell counts.

Abbreviations: CSF, cerebrospinal fluid; ECOG PS, Eastern Cooperative Oncology Group performance status; IT, intrathecal; LDH, lactate dehydrogenase; MTX, methotrexate; RBC, red blood cells; WBC, white blood cells.

Reference values: RBC, 0/mm³; WBC, 0–5/mm³; atypical/non-hematopoietic cells, absent; protein, 15–60 mg/dL; glucose, 50–80 mg/dL; LDH, <40 U/L. Reference ranges may vary according to the laboratory and analytical method.

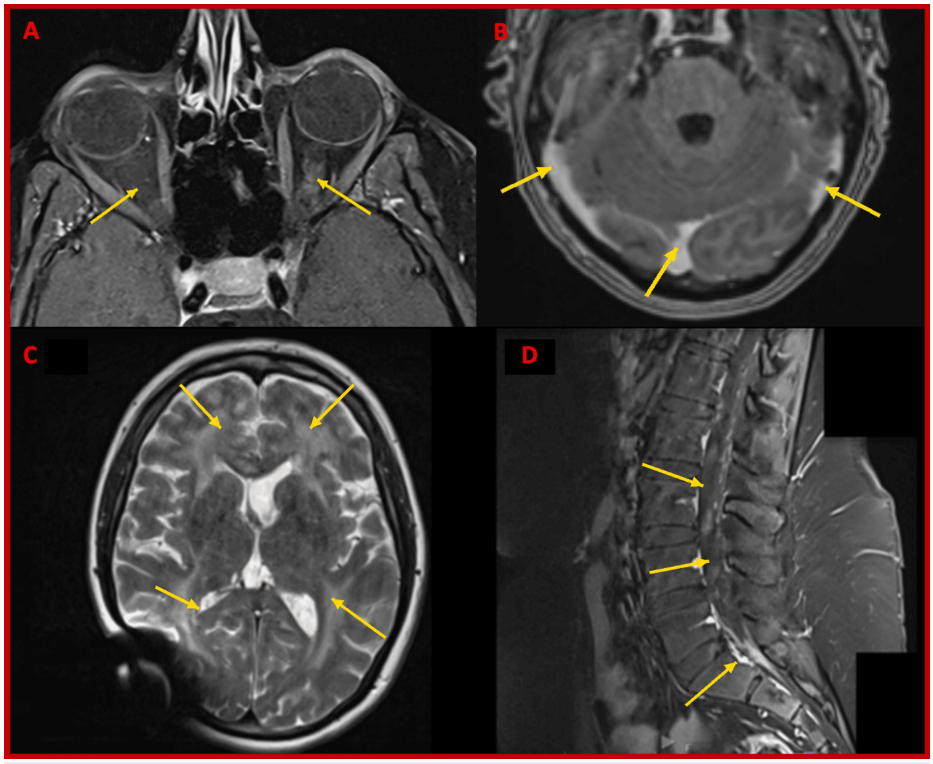


FIGURE 3: Serial neuroaxis magnetic resonance imaging (MRI) findings

Panel A: Initial MRI, obtained at diagnosis (prior to ventriculoperitoneal shunt placement): axial contrast-enhanced, fat-suppressed T1-weighted orbital MRI demonstrating optic nerve involvement (arrows), compatible with leptomeningeal dissemination. Panel B: Initial MRI, obtained at diagnosis (prior to ventriculoperitoneal shunt placement): axial contrast-enhanced T1-weighted MRI of the posterior fossa demonstrating leptomeningeal enhancement along the cerebellar surface (arrows). Panel C: Follow-up MRI, performed after the final administration of intrathecal methotrexate (with ventriculoperitoneal shunt in place): axial T2-weighted brain MRI demonstrating new diffuse, bilateral white-matter hyperintensity consistent with leukoencephalopathy (arrows), with resolution of hydrocephalus. The rounded artifact in the right posterior parietal region corresponds to the programmable shunt valve. Panel D: Follow-up MRI, performed after the final administration of intrathecal methotrexate: sagittal contrast-enhanced T1-weighted spinal MRI demonstrating persistent/progressive linear leptomeningeal enhancement along the conus medullaris and cauda equina, with micronodular involvement (arrows).

Neurological symptoms progressed rapidly within one week of symptom onset, with persistent nausea and vomiting, worsening visual impairment, and marked functional decline, reaching an Eastern Cooperative Oncology Group performance status (ECOG PS) of 4 [12]. CSF cytological examination demonstrated malignant epithelial cells compatible with breast origin, supported by immunocytochemical expression of epithelial markers and GATA3 (Figure *4*). Together with the clinical and radiological findings, these results established the diagnosis of leptomeningeal recurrence of breast cancer.

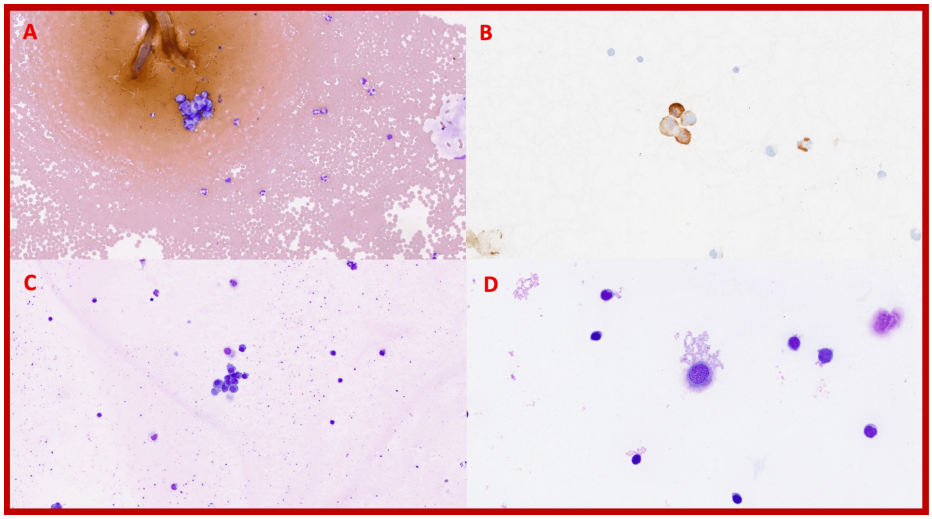


FIGURE 4: Cytological and immunocytochemical findings in cerebrospinal fluid

Panel A: Cluster of atypical epithelial cells with enlarged, hyperchromatic nuclei. Panel B: Immunocytochemical staining demonstrating positive GATA3 expression in epithelial cells. Panel C: Cluster of malignant epithelial cells exhibiting nuclear enlargement and pleomorphism. Panel D: Isolated atypical cell with an enlarged nucleus and nuclear atypia.

The severity of intracranial hypertension, with persistent symptoms and impaired oral intake refractory to medical treatment with corticosteroids and acetazolamide, required repeated therapeutic lumbar punctures for CSF drainage as a temporizing measure, under close neurological monitoring, ultimately necessitating urgent CSF diversion. Two weeks after symptom onset, a programmable ventriculoperitoneal shunt with a coupled Rickham reservoir (Sophysa Polaris®, Orsay, France) was implanted. Following transient symptoms of CSF overdrainage requiring valve adjustment, control of hydrocephalus was achieved, with substantial improvement in headache, nausea, and vomiting. This was accompanied by marked neurological and functional recovery, with improvement from ECOG PS 4 to ECOG PS 1, providing the clinical conditions required to proceed with active oncological treatment.

Systemic staging with 18F-fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) demonstrated a 5.1×4.2 cm hypermetabolic left adnexal lesion (maximum standardized uptake value (SUVmax) 9.6), with no other unequivocal sites of metabolically active extracranial disease (Figure *5A*). Histopathological assessment of the ovarian lesion confirmed metastatic breast carcinoma with a lobular phenotype, with immunohistochemistry showing estrogen receptor expression (80%), progesterone receptor expression (30%), and a HER2 score of 0.

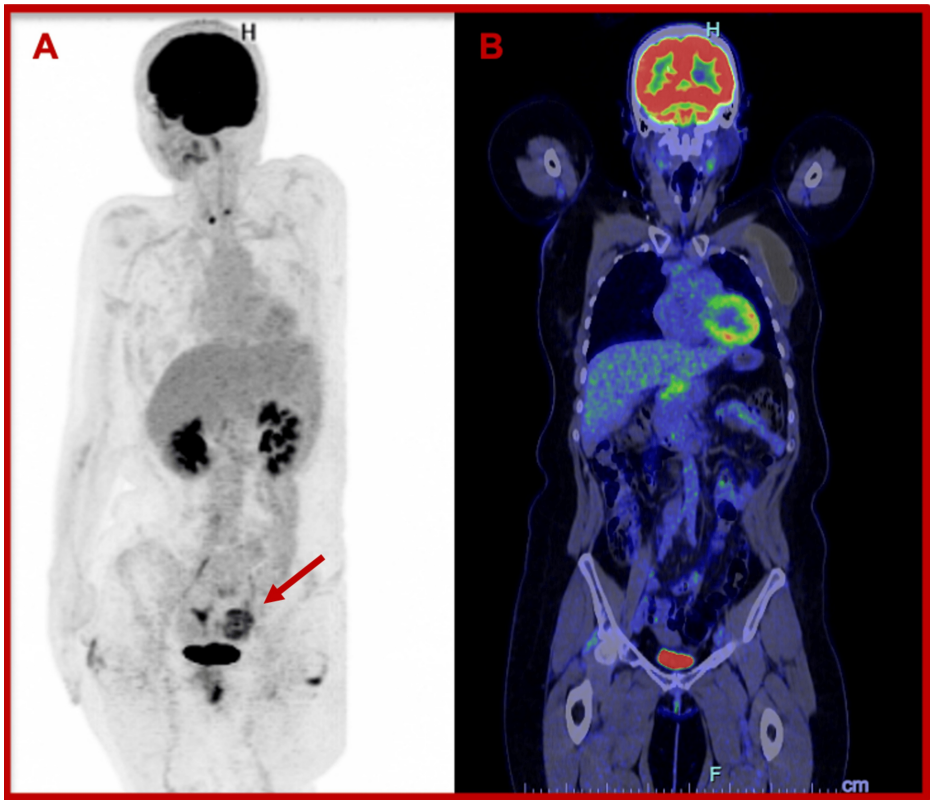


FIGURE 5: Serial 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) findings

Panel A: Initial PET/CT: Staging examination demonstrating a hypermetabolic left adnexal/ovarian lesion (arrow), subsequently confirmed as metastatic lobular breast carcinoma. Panel B: Follow-up PET/CT: restaging examination demonstrating no metabolically active extracranial disease.

Note: The PET/CT examinations were performed at different institutions, using different equipment and image-processing software; therefore, color scales differ between panels and are not directly comparable.

Given the substantial clinical and functional improvement, a multimodal treatment strategy combining intrathecal and systemic therapy was initiated. Intrathecal methotrexate (10 mg) was initially administered bi-weekly, followed by weekly and then monthly maintenance. During each administration, the programmable shunt was temporarily closed to restrict CSF drainage and optimize intrathecal drug exposure and reopened after six hours of bed rest.

Systemic treatment was subsequently initiated with ovarian function suppression using goserelin (3.6 mg every 28 days) and letrozole (2.5 mg once daily), followed by the addition of ribociclib (400 mg once daily, on days 1-21 of each 28-day cycle due to concomitant intrathecal therapy). Serial CSF examinations demonstrated a progressive reduction in malignant cells, with subsequent samples showing only rare suspicious or neoplastic epithelial cells (Table *1*).

This cytological response was accompanied by sustained neurological improvement and normalization of serum tumor markers (Table *2*).

Time point	Clinical status	ECOG PS	CEA (ng/mL)	CA 15-3 (U/mL)
At diagnosis/baseline	Headache, nausea and vomiting, visual impairment, right-sided papilledema; rapid neurological deterioration	4	4.09	73.52
~3 months after starting IT MTX	Resolution of headache, nausea, and vomiting; sustained neurological improvement	1	2.26	34.42
At IT MTX discontinuation	Mild attention and memory deficits; otherwise neurologically stable and independent in activities of daily living	1	1.5	20.79
~2 months after IT MTX discontinuation	Neurologically stable, without residual deficits; returned to work and regular physical exercise	1	2.12	18.02
Latest assessment (15 months after LM diagnosis)	Clinically stable, normal gait, functionally independent, professionally active; no clinically significant neurological symptoms	1	2.45	17.9

TABLE 2: Serial serum tumor marker levels during treatment

Reference ranges: CEA ≤5.00 ng/mL; CA 15-3 ≤35.00 U/mL.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CEA, carcinoembryonic antigen; IT, intrathecal; MTX, methotrexate; LM, leptomeningeal metastasis

Approximately two months after treatment initiation, given the sustained clinical benefit and preserved performance status, the patient underwent bilateral adnexectomy with complete macroscopic resection of an approximately 6-cm left ovarian mass. Histopathological examination confirmed the metastatic breast origin and lobular phenotype previously identified on biopsy.

The clinical response was sustained over time, with persistent control of neurological symptoms and progressive recovery of independence in activities of daily living. During follow-up, the patient returned to work and resumed regular physical exercise. The sustained clinical response was accompanied by normalization of serum tumor markers, which remained within the reference range.

After seven months of intrathecal methotrexate, the six-month protocol response assessment neuroaxis MRI was performed. It showed resolution of hydrocephalus but newly developed diffuse white-matter changes consistent with leukoencephalopathy, considered most likely related to intrathecal methotrexate (Figure *3C*). Additionally, persistent and progressive linear leptomeningeal involvement of the spinal cord was observed, with micronodularity of the cauda equina (Figure *3D*). At this time, the patient presented with mild attention and memory deficits, attributed to leukoencephalopathy, with no symptoms related to the progression of leptomeningeal disease. Given the evidence of treatment-related neurotoxicity and radiological disease progression, intrathecal methotrexate was discontinued after a total of 13 administrations, while systemic treatment with letrozole and ribociclib was maintained.

Two months after the follow-up MRI, CSF analysis demonstrated marked protein elevation and sparse malignant epithelial cells compatible with the known breast primary (Table *1*). Despite these findings, the patient remained neurologically stable, with no residual deficits, no recurrent manifestations of intracranial hypertension, resolution of papilledema with bilateral disk pallor (Figure *1B*), and preserved functional independence. She remains professionally active, exercises regularly, and reports no headache, nausea, vomiting, radicular pain, visual or sensory disturbances, or motor deficits.

The most recent FDG PET/CT, performed 14 months after the diagnosis of LM to assess extracranial disease status and the response to systemic therapy, showed no evidence of metabolically active extracranial disease (Figure *5B*), and serum tumor markers remained within normal limits. At the most recent clinical assessment, 15 months after the diagnosis of LM and six months after discontinuation of intrathecal methotrexate, the patient remained clinically stable, with an ECOG PS of 1, normal gait, preserved functional independence, and continued professional activity. She reported no clinically significant neurological symptoms attributable to hydrocephalus or leptomeningeal disease. Despite persistent malignant cells in the CSF and radiological evidence of leptomeningeal dissemination, the absence of meaningful clinical deterioration, together with sustained extracranial disease control, supported continuation of systemic treatment without additional therapeutic interventions.

Discussion

LM remains a severe complication of metastatic breast cancer, associated with substantial neurological morbidity and limited survival [5,6,13]. Outcomes are heterogeneous and are influenced by several factors, including breast cancer subtype, performance status, disease burden, and receipt of active oncological treatment [14]. In the present case, extensive LM complicated by intracranial hypertension and hydrocephalus resulted in rapid neurological deterioration and an ECOG PS of 4. Despite this initial presentation, the patient remained clinically stable 15 months after LM diagnosis, substantially exceeding the median overall survival of 4.2 months reported for patients with HR-positive/HER2-negative breast cancer and LM [5].

Management of hydrocephalus was central to the subsequent therapeutic strategy. Ventriculoperitoneal shunting controlled intracranial hypertension and resulted in substantial neurological and functional improvement, which made active oncological treatment possible. In selected patients with LM, CSF diversion may therefore extend beyond symptomatic relief by reversing a potentially treatable cause of functional deterioration and enabling further oncological treatment [15]. The programmable shunt also allowed temporary restriction of CSF drainage during intrathecal methotrexate administration, an approach previously reported as feasible and safe with on-off or programmable valves, although experience remains limited [10,16-18].

The prolonged clinical course likely reflects the contribution of several therapeutic interventions rather than a single treatment. Intrathecal methotrexate was associated with a reduction in malignant cells in the CSF, while endocrine therapy combined with CDK4/6 inhibition achieved sustained extracranial disease control. Recovery of performance status also enabled surgical resection of the ovarian metastasis. The subsequent absence of metabolically active extracranial disease, despite persistent leptomeningeal involvement, further illustrates that disease in the systemic and CNS compartments may follow different courses.

Evidence for the treatment of LM in HR-positive, HER2-negative breast cancer is limited and mostly retrospective, with receipt of systemic therapy associated with improved survival [19]. Durable responses have been reported with endocrine therapy, alone or combined with CDK4/6 inhibition, integrated with CNS-directed treatment [20], consistent with the course observed in the present case.

Beyond systemic and intrathecal therapy, radiotherapy is the other main treatment modality for LM and was also considered in this patient. It is mainly indicated for symptomatic or bulky nodular disease and for CSF flow obstruction, and proton craniospinal irradiation has recently shown promising results [6,8]. In this patient, radiotherapy was not used because the disease was predominantly linear, CSF flow was restored by shunting, spinal progression was asymptomatic, and its combination with intrathecal methotrexate would have increased the risk of leukoencephalopathy [6].

A particularly relevant aspect of this case was the discordance between clinical, radiological, and cytological findings, as described in the case presentation. Intrathecal methotrexate was discontinued following the development of radiological leukoencephalopathy, accompanied by mild attention and memory deficits, and persistent/progressive spinal leptomeningeal involvement without related symptoms. Alternative causes of diffuse white-matter changes were considered unlikely. The patient had never received cranial irradiation, her previous radiotherapy having been limited to the chest wall. Transependymal CSF edema was not supported by the imaging, as hydrocephalus had resolved, and the changes showed no contrast enhancement suggestive of parenchymal tumor infiltration. The temporal association with intrathecal methotrexate therefore supported a treatment-related etiology. Subsequent CSF analysis continued to demonstrate sparse malignant cells. Nevertheless, neurological and functional stability was maintained after treatment discontinuation. Current recommendations emphasize integrating neurological examination, neuroimaging, and CSF findings when assessing LM [21]. In this patient, persistent objective evidence of leptomeningeal disease had to be balanced against sustained clinical stability and treatment-related neurotoxicity. This supported continuation of systemic therapy without further intrathecal treatment, under close clinical and radiological surveillance.

As an individual case report, no causal relationship can be established between any single intervention and the prolonged clinical course, and these findings cannot be generalized to all patients with LM. Nevertheless, this case illustrates how treatment of a reversible neurological condition may restore performance status and enable active multimodal therapy in selected patients with severe LM.

Conclusions

Breast cancer LM is associated with an aggressive course and poor prognosis, making the prolonged clinical benefit observed in this patient particularly uncommon. The integration of CSF diversion, intrathecal therapy, and systemic treatment enabled sustained neurological and functional stability, highlighting the potential value of an individualized multimodal strategy in selected patients with severe LM.

This experience further underscores the importance of identifying and treating reversible complications such as hydrocephalus when they substantially contribute to neurological and functional deterioration.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Gonçalo Cunha, Luís G. Santos, Sofia Broco, Cláudia Lima

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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