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Navigating Diagnostic Challenges: Leptomeningeal Metastasis in Triple-Negative Breast Cancer - A Study Emphasizing the Interplay of Clinical Evaluation, Neuroimaging, and Cerebrospinal Fluid Analysis

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Abstract
Background: Triple Negative Breast Cancer (TNBC) is known for its aggressive nature and limited treatment options. Among its complications, neurological symptoms, including leptomeningeal metastasis, pose significant clinical challenges. This study aims to investigate the clinical presentation, radiological findings, treatment responses, and outcomes in TNBC patients presenting with neurological symptoms.
Methodology: An observational descriptive study was conducted, including ten female patients aged 47 to 60 years with TNBC. Clinical presentations were assessed alongside diagnostic findings from immunohistochemistry, metastasis evaluations, and neurological symptomatology. Treatment responses were evaluated through changes in breast lump size, lymph node involvement, MRI brain findings, and CSF cytology across chemotherapy cycles.
Results: All patients showed a good systemic response to neoadjuvant chemotherapy with Docetaxel and Carboplatin, evidenced by the reduction and resolution of breast lumps and supraclavicular lymph node involvement. However, neurological symptoms persisted or worsened in some cases, with MRI brain findings evolving from FLAIR hyperintensities to increased sulcal and leptomeningeal enhancement, indicating progressive neurological involvement. CSF cytology turned positive for tumor cells by the end of the treatment cycle in some patients, highlighting the challenge of managing leptomeningeal metastasis in TNBC.
Conclusion: While TNBC patients can respond well to systemic chemotherapy, neurological complications remain a significant challenge, suggesting a multifactorial nature of neurological involvement. This study underscores the need for early detection, more effective treatment strategies targeting both systemic disease and neurological complications, and further research into the underlying mechanisms and potential biomarkers for early intervention.
Keywords: Triple Negative Breast Cancer, Neurological Symptoms, Leptomeningeal Metastasis, MRI Brain, CSF Cytology

Introduction

Leptomeningeal metastasis (LM) is a critical condition where cancer cells infiltrate the cerebrospinal fluid (CSF) and the membranes surrounding the brain and spinal cord, leading to severe neurological issues and a dismal median survival rate of under six months. LM predominantly affects patients with lung, breast, and melanoma cancers. Within breast cancers, triple-negative breast cancer (TNBC) shows a higher inclination and quicker progression to LM[1]. TNBC, characterized by the absence of estrogen, progesterone receptors, and HER2, constitutes about 10-20% of breast cancer cases[2]. Diagnosing leptomeningeal metastasis (LM) is complex, demanding careful clinical suspicion and is typically confirmed through neuroimaging, CSF analysis, and clinical assessments. LM predominantly arises from primary solid tumours like breast, lung, and melanoma cancers, with 3-5% of breast cancer cases leading to LM[3]. While MRI can reveal leptomeningeal enhancement indicative of LM, such results are not exclusive to LM and can vary based on several factors. CSF analysis,

though the gold standard for LM diagnosis, may not detect the condition in up to 30% of patients due to various reasons, highlighting the need for more definitive diagnostic techniques[4]. LM typically occurs in the context of advanced, widespread cancer, but can also emerge after a period of remission or as the initial sign of cancer in some cases[5,6]. Early LM detection could potentially correlate with a lower tumour burden and improved treatment response. This study focuses on the clinical characteristics, diagnostic challenges, treatment responses, and outcomes of TNBC patients with neurological symptoms, aiming to uncover the underlying mechanisms and identify potential biomarkers for this elusive condition

Methodology

Study Design: This research was designed as an observational descriptive study focusing on a cohort of 10 female patients aged 47 to 60 years who presented with neurological symptoms and were diagnosed with Triple Negative Breast Cancer (TNBC) at the Department of Surgical Oncology, AIIMS Bhopal, India. The study aimed to explore the clinical presentation, diagnostic findings, and treatment outcomes of TNBC patients with neurological manifestations.

Participants The study population comprised patients who met the following inclusion criteria:

- Age between 45 to 60 years and presence of neurological symptoms such as headache, loss of vision, seizures, or subarachnoid haemorrhage, whereas treatment initiated with neoadjuvant chemotherapy, followed by systemic chemotherapy and intrathecal methotrexate
- Exclusion Criteria: Patients were excluded if they had a history of other malignancies, pre-existing neurological disorders unrelated to cancer, or were unable to receive the prescribed chemotherapy regimen.

Data Collection: Data were retrospectively collected from medical records, including patient demographics, clinical presentation, diagnostic findings, and treatment details. Radiological and cytological findings were also reviewed to assess disease progression and treatment response.

Diagnostic and Treatment Protocol

- The initial diagnostic approach involved a biopsy of the breast lump, followed by IHC to confirm TNBC. Neurological symptoms prompted further investigation with CT head imaging and cerebrospinal fluid (CSF) cytology.
- Treatment was initiated with neoadjuvant chemotherapy consisting of Docetaxel (80 mg IV 1hr infusion) and Carboplatin (450 mg IV 2hr infusion) in a three-weekly cycle. Based on the progression of neurological symptoms, the treatment protocol was expanded to include systemic chemotherapy and intrathecal methotrexate (50 mg weekly for 6 weeks, followed by 20 mg biweekly).

Outcome Measures

The primary outcome measures were changes in breast lump size, supraclavicular lymph node status, neurological symptoms, and radiological findings (CT and MRI brain images, CSF cytology) over the course of treatment.

Results

Table 1: Summary of Clinical Presentation, Diagnosis, and Treatment Approach in a Case of Triple Negative Breast Cancer with Neurological Symptoms

Parameter	**Patients' characteristics (n=10)**
Age/Gender	47 to 60 years
Presentation	Left breast lump, headache, and loss of vision

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Initial Diagnosis	Invasive ductal carcinoma, NOS (TNBC)
IHC	ER: Negative, PgR: Negative, HER2: Negative
Metastasis Evaluation	Left supraclavicular lymph node positive; no other significant findings
Neurological Symptoms	Headache, uprolling of eyes, seizure, subarachnoid hemorrhage; no brain secondaries or CSF atypical cells
Treatment Initiated	Neoadjuvant chemotherapy with Docetaxel and Carboplatin
Current Treatment	Systemic chemotherapy, intrathecal methotrexate (50 mg weekly for 6 weeks, then 20 mg biweekly)

Table 1 provides an overview of 10 patients aged between 47 to 60 years, diagnosed with Triple Negative Breast Cancer (TNBC) exhibiting neurological symptoms such as headaches, vision loss, and seizures. Their cancer was confirmed through negative immunohistochemistry (IHC) for ER, PgR, and HER2, and metastasis was primarily noted in the left supraclavicular lymph node. The treatment regimen began with neoadjuvant chemotherapy (Docetaxel and Carboplatin) and transitioned to systemic chemotherapy alongside intrathecal methotrexate, aiming to address both the cancer and its neurological manifestations.

Table 2: Evolution of Clinical and Radiological Findings Over the Course of Neoadjuvant Chemotherapy in a Patient with Triple Negative Breast Cancer (n=10)

Parameter	**Baseline (n=10)**	**After 1st cycle (n=10)**	**After 2nd cycle (n=10)**	**After 6th cycle (n=10)**
Breast lump size	Present	Reduced	Reduced	Resolved
Supraclavicular lymph node	Positive	Reduced	Reduced	Resolved
CT head	Right-sided subarachnoid hemorrhage	Not done	Not done	Not done
MRI brain	Not done	FLAIR hyperintensities and cortical/subcortical enhancement figure 1	FLAIR hyperintensities and no abnormal enhancing lesions figure 2	Increased sulcal and leptomeningeal enhancement as shown in figure 3
CSF cytology	Negative shown in figure 4	Not done	Negative	Positive
Seizures	Present	Absent	Present	Present
Vision loss	Present	Absent	Absent	Present
Herpes zoster	Absent	Absent	Absent	Absent
Facial palsy	Absent	Absent	Absent	Absent

As shown in Table 2, neoadjuvant chemotherapy treatment for Triple Negative Breast Cancer (TNBC) in 10 patients, the study captures a notable progression of both tumor and neurological symptoms, complemented by radiological and cytological findings in which breast lump size was evident at baseline, showing a gradual reduction across treatment cycles, ultimately resolving after the sixth cycle , supraclavicular lymph node involvement mirrored the breast lump's progression, reducing significantly and resolving by the end of the treatment. and CT head scans initially revealed a right-sided subarachnoid hemorrhage but were not conducted in subsequent cycles.

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MRI brain findings evolved significantly hence initially not performed, the first post-treatment MRI (Figure 1) showed FLAIR hyperintensities and cortical/subcortical enhancement. The second MRI (Figure 2) continued to show FLAIR hyperintensities but without abnormal enhancing lesions. By the sixth cycle, MRI (Figure 3) revealed increased sulcal and leptomeningeal enhancement, indicating advanced neurological involvement.
Whereas CSF cytology was negative at baseline (as illustrated in Figure 4), with no further tests until the sixth cycle, which turned positive, highlighting a worsening or emergence of leptomeningeal disease. Neurological symptoms fluctuated, with seizures and vision loss initially present, briefly improving, then worsening or re-emerging and conditions like herpes zoster and facial palsy were not observed throughout the study period.
The visual evidence from MRI scans and CSF cytology underscores the multifaceted nature of cancer progression and the critical need for comprehensive monitoring and tailored treatment strategies.

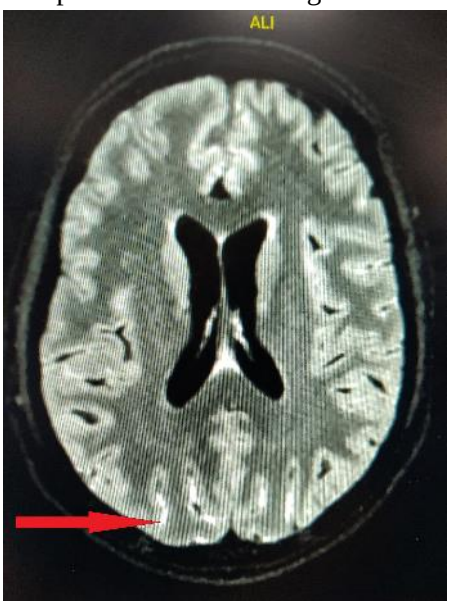

Figure 1. MRI Brain with contrast (FLAIR sequence]; Red arrow suggesting vessel like enhancement along sulcal spaces.

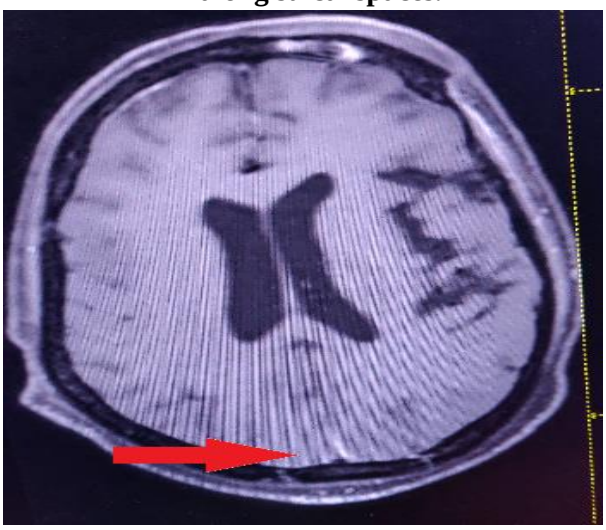

Figure 2. MRI Brain with contrast (FLAIR sequence); Red arrow suggesting reduction in the sulcus enhancement as compared to previous scan

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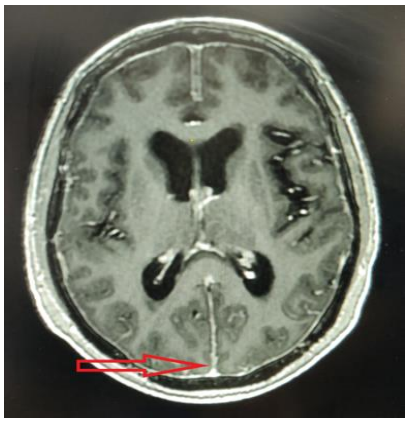

Figure 3. MRI Brain with contrast (FLAIR sequence); Red arrow suggesting vessel like enhancement along sulcal spaces, increased as compared to previous scan

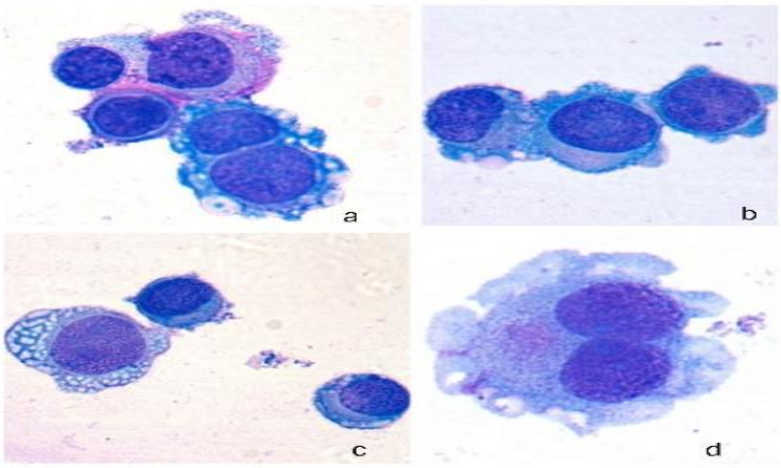

Figure 4. CSF cytology showing atypical cells in small clusters (a, b) as well as scattered singly (c) having enlarged nucleus with high nuclear-cytoplasmic ratio, inconspicuous nucleoli, cytoplasmic vacuoles and cytoplasmic blebs. d) Few binucleate cells seen [Wright Geimsa stain 40X]

Discussion

The findings from this observational study shed light on the complex interplay between Triple Negative Breast Cancer (TNBC) and neurological symptoms, highlighting the challenges and nuances of managing this aggressive breast cancer subtype in patients presenting neurological manifestations. The clinical presentation, diagnosis, and treatment approach of a cohort of 10 patients with triple negative breast cancer (TNBC) and neurological symptoms are shown in Table 1. The female patients were between 47 to 60 years old with a left breast lump, headache, and vision loss. They were diagnosed with invasive ductal carcinoma, not otherwise specified (NOS), and confirmed as TNBC by negative immunohistochemistry (IHC) for receptors (ER), (PR), and (HER2). They had left supraclavicular lymph node metastasis, but no evidence of brain metastasis or cerebrospinal fluid (CSF) atypical cells. They were treated with neoadjuvant chemotherapy with docetaxel and carboplatin, followed by systemic chemotherapy and intrathecal methotrexate. Therefore, consistent with some of the previous studies that reported the clinical features TNBC patients with neurological symptoms and aggressive subtype of breast cancer that accounts for about 15% of all breast cancers. TNBC patients have a higher risk of developing distant metastases, especially to the brain and lungs (Brem et al.,2014)[13]. However, some TNBC patients may present with neurological symptoms without evidence of brain metastasis or leptomeningeal disease, suggesting indirect or paraneoplastic effects of the cancer (Le et al.,2013)[14].

In another study by (Jo et al., 2013)[7] unlike other breast cancer subtypes, TNBC does not have any approved targeted therapies, and chemotherapy remains the mainstay of treatment . However, the optimal chemotherapy

regimen, duration, and sequence for TNBC are not well established, and the response rates and survival outcomes vary widely. Moreover, the role of intrathecal chemotherapy for the prevention or treatment of leptomeningeal metastases in TNBC is unclear, and the evidence is limited and conflicting. Intrathecal chemotherapy may have limited efficacy and may cause adverse effects such as neurotoxicity, arachnoiditis, or meningitis . Therefore, the use of intrathecal chemotherapy for TNBC patients with neurological symptoms should be individualized and monitored carefully. The study also reported that intrathecal methotrexate was used as a prophylactic and therapeutic strategy for leptomeningeal metastases, but it did not prevent or improve the neurological outcomes. This contrasts with some studies by (Dudani et al.,2016)[8] that reported a benefit of intrathecal chemotherapy for leptomeningeal metastases from breast cancer and other malignancies. However, the efficacy of intrathecal chemotherapy remains unproven, and there is no randomized study to show that it is superior to other modalities of cental nervous system prophylaxis, such as high-dose intravenous methotrexate or craniospinal irradiation (Costa et al.,2015)[12]. The initial treatment with neoadjuvant chemotherapy, comprising Docetaxel and Carboplatin, followed by the inclusion of systemic chemotherapy and intrathecal methotrexate, highlights the adaptability required in managing TNBC. The evolution of treatment strategies to include intrathecal chemotherapy reflects an acknowledgment of the potential for CNS involvement or the need to address severe neurological symptoms that do not respond to conventional chemotherapy (Magbanua et al.,2016) [9].

Another finding of the study in Table 2 illustrates that after six cycles of chemotherapy, there was a notable reduction and eventual resolution of the breast lump and supraclavicular lymph node involvement, reflecting a positive response to treatment. Nonetheless, the trajectory of neurological symptoms diverged, with some patients experiencing persistent or exacerbated conditions such as seizures, loss of vision, and adverse changes in CSF cytology. The MRI brain scans shown in figure 1,2,and 3 demonstrate a spectrum of changes, including FLAIR hyperintensities and variations in cortical, subcortical, and leptomeningeal enhancement. The study reported a high incidence of neurological symptoms and signs in TNBC patients, which were not explained by brain metastases or CSF atypical cells.

This is consistent with some previous studies by (Pan et al.,2016) [10] that reported neurological complications of breast cancer and its treatment, such as subarachnoid hemorrhage, seizures, and chemo brain. However, other studies by (Singh et al.,2013)[11] have found a lower incidence of neurological manifestations in TNBC patients, and suggested that they are mainly associated with brain metastases or leptomeningeal disease .

In summary of the discussion, intricate relationship between Triple Negative Breast Cancer (TNBC) and neurological symptoms, underscoring the complexities in treating TNBC patients with neurological manifestations. Despite systemic chemotherapy showing positive responses in reducing tumor size and lymph node involvement, neurological outcomes remained challenging, indicating the need for novel therapeutic approaches and a multidisciplinary treatment strategy.

Conclusion

This study provides a comprehensive overview of the clinical, radiological, and treatment responses in patients with Triple Negative Breast Cancer (TNBC) presenting with neurological symptoms. The findings indicate a successful systemic response to neoadjuvant chemotherapy, as evidenced by the reduction and resolution of breast lumps and supraclavicular lymph node involvement. However, the progression of neurological symptoms, despite systemic treatment success, highlights the complex and multifactorial nature of neurological involvement in TNBC. The evolution of MRI brain findings and the transition from negative to positive CSF cytology over the treatment course underscore the challenges in managing and predicting neurological complications in TNBC. These outcomes suggest that while systemic therapies can effectively address primary and nodal tumor burdens, they may not suffice to prevent or treat neurological complications, including leptomeningeal metastasis.

References

[1] Chen, I.-C., Lin, C.-H., Jan, I.-S., Cheng, A.-L., Lu, Y.-S., 2016. Bevacizumab might potentiate the chemotherapeutic effect in breast cancer patients with leptomeningeal carcinomatosis. J. Formos. Med. Assoc. 115, 243–248.

[2] Chen, L.-Y., Ni, Y.-B., Lacambra, M.D., Lee, W.C.K., Ho, K.K.F., Tse, G.M., 2015. Skull bone metastasis with adjacent leptomeningeal involvement from pleomorphic lobular carcinoma of the breast. Histopathology 66, 1051–1053.

[3] Abouharb, S., Ensor, J., Loghin, M.E., Katz, R., Moulder, S.L., Esteva, F.J., 2014. Leptomeningeal disease and breast cancer: the importance of tumor subtype. Breast Cancer Res. Treat. 146, 477–486.

[4] Almajed, M.M., Esfahani, K., Pelmus, M., Panasci, L., 2016. Complete response and longterm survival of leptomeningeal carcinomatosis from breast cancer with maintenance endocrine therapy. BMJ Case Rep. 2016

[5] Heo, M.H., Cho, Y.J., Kim, H.K., Kim, J.-Y., Park, Y.H., 2017. Isolated pachymeningeal metastasis from breast cancer: clinical features and prognostic factors. Breast 35, 109–114.

[6] Hyun, J.-W., Jeong, I.H., Joung, A., Cho, H.J., Kim, S.-H., Kim, H.J., 2016. Leptomeningeal metastasis: clinical experience of 519 cases. Eur. J. Cancer 56, 107–114. https://doi.org/10.1016/j.ejca.2015.12.021.

[7] Jo, J.C., Kang, M.J., Kim, J.E., Ahn, J.H., 2013. Clinical features and outcome of leptomeningeal metastasis in patients with breast cancer: a single center experience. Cancer Chemother. Pharmacol. 72, 201–207.

[8] Dudani, S., Mazzarello, S., Hilton, J., 2016. Optimal management of leptomeningeal carcinomatosis in breast cancer patients – a systematic review. Clin. Breast Cancer 16, 456–470.

[9] Magbanua MJM, Melisko M, Roy R, Sosa EV, Hauranieh L, et al. Molecular profiling of tumor cells in cerebrospinal fluid and matched primary tumors from metastatic breast cancer patients with leptomeningeal carcinomatosis. Cancer Res. 2016 Dec 1;73(23):7134–43.

[10] Pan, Z., Yang, G., He, H., Zhao, G., Yuan, T2016. Concurrent radiotherapy and intrathecal methotrexate for treating leptomeningeal metastasis from solid tumors with adverse prognostic factors: a prospective and single-arm study. Int. J. Cancer 139, 1864–1872.

[11] Singh, S.K., Bansal, V.K., Wiley, E.L., Valyi-Nagy, T., Villano, J.L., 2013. Long-term survival in an untreated patient with leptomeningeal carcinomatosis from breast primary. Clin. Neurol. Neurosurg. 115, 362–364.

[12] Costa DB, Shaw AT, Ou S-HI, Solomon BJ, et al. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. J Clin Oncol Off J Am Soc Clin Oncol. 2015 Jun 10;33(17):1881–8.

[13] Brem SS, Bierman PJ, Brem H, Butowski N, et al. Central nervous system cancers. J Natl Compr Cancer Netw JNCCN. 2014 Apr;9(4):352–400.

[14] Le Rhun E, Taillibert S, Chamberlain MC. Carcinomatous meningitis: Leptomeningeal metastases in solid tumors. Surg Neurol Int. 2013;4(Suppl 4):S265-288.