Neoplastic Meningitis: A Study from a Tertiary Care Hospital from Coastal India

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Abstract

Introduction: Neoplastic involvement of cerebrospinal fluid (CSF) secondary to known or unknown primaries elsewhere is a poor prognostic factor and is equivalent to stage IV disease. Aim: The aim of the study is to analyse the cytological features of neoplastic meningitis in a tertiary care center. Materials and Methods: A retrospective study of 400 consecutive CSF samples was done in the cytology laboratory of our hospital. The fluid obtained by spinal tap was sent for microbiological, biochemical and cytological evaluation. Smears that showed the presence of malignant cells were included in this study. Results: Out of 400 cases, 36 (9%) showed neoplastic meningitis. Of which, 13 cases (36%) revealed leukemic infiltration, 2 (6%) lymphomatous infiltration and 21 (58%) carcinomatous meningitis. The leukemia cases included seven cases of acute lymphoblastic leukemia and six cases of acute myeloid leukemia. Among the carcinomatous meningitis cases, eight were metastasis from carcinoma breast, six from lung carcinoma and one each from malignancies of gallbladder, stomach and retinoblastoma. Four cases were metastatic adenocarcinoma from unknown primary. Pleocytosis was a significant finding seen in 58% cases (n = 21). Elevated protein and hypoglychorrhachia was noted in 68% cases (n = 18). Conclusion: A combined diagnostic approach including biochemical, microbiological and pathological evaluation was useful in eliminating infectious meningitis and confirming neoplastic meningitis in these cases. Cytology should be performed on cerebrospinal specimens from all patients with known or suspected malignancy with meningismus. Detection of malignant cells on cytological examination of CSF is the diagnostic gold standard for neoplastic meningitis.

Keywords: Cerebrospinal fluid, cytology, elevated protein, hypoglychorrhachia, neoplastic meningitis, pleocytosis

Introduction

Neoplastic meningitis (NM) is the result of seeding of the leptomeninges and cerebrospinal fluid (CSF) by malignant cells. It is an uncommon occurrence, with an increasing incidence due to longer survival of cancer patients and advances in adjuvant therapy. It results in significant morbidity, and short median survival duration despite therapy.[1,2] NM can be caused by metastasis from solid tumors, which is termed as carcinomatous meningitis or by infiltration from leukemias or lymphomas, which is termed as leukemic or lymphomatous meningitis, respectively. The latter is the most common cause of NM seen in 5–15% of patients with leukemias, followed by carcinomatous meningitis which is seen in 1–5% of cases with solid tumors. Rarely, meningeal seeding with CSF spillover of primary brain tumors (1–2%) is seen.[1,2] Adenocarcinoma is the most common type of carcinomatous meningitis. The commonest primaries to metastasize to the leptomeninges and/or CSF are breast, lung and melanoma. Although small cell lung cancer and melanoma have the highest rates of spread to the leptomeninges (11% and 20%, respectively) as compared to carcinoma breast (5%), the latter remains the major cause of NM because of its higher incidence. Carcinomatous meningitis from unknown primaries constitutes 1–7% of all cases.[1,2]

There have been only occasional case reports and a few case series of NM documented in medical literature from the Indian subcontinent. This study was done to analyse the clinical, biochemical and cytological features of CSF as well as spectrum of NM cases from our center.

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MATERIALS AND METHODS
This retrospective case study was done for a period of 4 years in our laboratory. The study was undertaken after the approval by institutional ethics committee. Smears made by cytocentrifugation and stained with Papanicolaou and Leishman stains. All the smears were reviewed by two experienced pathologists. Only those cases where the diagnosis of NM was established by CSF cytology were included in the study. A systematic screening of the in-patient records was done from the hospital database and the data were analysed with reference to clinical features, past history of primary malignancy and biochemical findings. The quantitative data were summarised as percentages, median and inter-quartile range (IQR).

RESULTS
The cytology laboratory received 400 CSF cytology samples during the study period. There were 36 cases (9%) which were diagnosed as NM. While, 21 cases (58.3%) were positive for leptomeningeal carcinomatosis, rest 15 cases (41.7%) were positive for leukemic (13 cases)/lymphomatous (2 cases) infiltration. Among the carcinomatous meningitis, eight cases (38.1%) were from breast carcinoma [Figure 1a–c], six (28.6%) from lung carcinoma [Figure 1d–f], one (4.7%) each from gallbladder carcinoma [Figure 1g–i] and gastric carcinoma. Four (19.04%) cases of metastatic adenocarcinoma of unknown origin were also noted [Figure 1j–l]. Among the 13 leukemic cases, seven were acute lymphoblastic leukemia [Figure 1m–o] and six acute myeloid leukemias (AML). The AML cases included one case each of AML-M1, -M2, -M3, and AML with aberrant lymphoid antigen expression, respectively. There were two cases of acute monocytic leukemia. The case of AML-M3 was further confirmed by demonstrating PML-RARα translocation. Two cases of non-Hodgkin's lymphoma (NHL) were also noted, of which one was metastasis from a diagnosed case of primary cutaneous large B-cell lymphoma-leg type (PCLBCL-leg). We found one case of trilateral retinoblastoma (TR) with metastasis to the CSF in a 5-year-old child [Figure 1p–r]. In the present study we did not come across case(s) of primary central nervous system (CNS) neoplasms metastatic to CSF [Table 1].

The mean age at presentation of leukemic meningitis was much lower than carcinomatous meningitis. The male:female ratio was 1:1.2. The mean CSF protein levels in carcinomatous meningitis is much higher than that of leukemic/lymphomatous meningitis [Table 2]. Most of the cases presented with symptoms of raised intracranial pressure such as headache (71%), vomiting (24%) and meningismus (10%). The clinical presentations of the cases of NM are depicted in Table 3.

The CSF analysis showed a median cell count of 80 cells/mm³ (IQR: 8–3000 cells/mm³), median protein of 103 mg/dl (IQR: 11–946 mg/dl) and median glucose of 42 mg/dl (IQR: 6–109 mg/dl). CSF pleocytosis was noted in 21 cases (80%). Elevated CSF protein was noted in 18 cases (68%) and hypoglychrorrachia in 19 cases (73%) [Table 4]. Infective meningitis was ruled out in most of the cases by Gram and Ziehl–Neelsen stains as well as by culture for bacteria, mycobacterium and fungus.

DISCUSSION
NM occurs in 3–23% of all cancers. [1–9] It occurs in patients with solid tumors having distant metastasis. The development of NM portends a significant worsening of prognosis with shortening of survival ranging from 4 to 16 weeks after its diagnosis. Despite attempts to improve survival with
intrathecal and systemic chemotherapy as well as radiation therapy, the outlook for patients remains grim.\(^5\)

Almost two decades ago, Glass \textit{et al.}\(^6\) investigated the meaning of a positive CSF cytology, and concluded that “malignant cells in the CSF mean that there is malignant tumor in the CNS (central nervous system).” It results from the spread of malignant cells to the leptomeninges and subarachnoid space and their dissemination within the CSF compartment.
Although NM has been described in nearly all types of solid tumors, the most common solid tumors causing NM are breast cancer (43%), lung cancer (31%) and melanoma (6%), a finding which concurred with our results. Both the incidence of NM and recognition of its clinical importance has increased. Though, scientific advances, including magnetic resonance imaging (MRI), assays for tumor markers, DNA amplification procedures, flow cytometry (FCM) and immunohistochemical techniques are now available to facilitate definite diagnosis the cytologic identification of malignant cells in the CSF remains the gold standard. The cytological features of metastatic adenocarcinoma to CSF are presence of acinar and singly scattered tumor cells, which have a high nuclear cytoplasmic ratio, moderate to scant cytoplasm with large nucleus, irregularly clumped nuclear chromatin and have a distinct nucleoli.

The diagnosis of lymphoma/leukemia in CSF can be difficult because of the presence of normal or reactive lymphocytes and scant cellularity. However, the cases of lymphomatous/leukemic meningitis will show an increased cell count. These blasts will be 2–3 times larger than the normal lymphocytes, and have moderate to scant cytoplasm with coarsely clumped chromatin and 2–3 prominent nucleoli. In some diseases like meningitis there may be a marked elevation of the white blood count, with a shift to immature forms, sometimes even including blasts. These findings do not necessarily indicate a diagnosis of lymphoma or leukemia. FCM is now used for the detection of lymphoid and myeloid neoplasms in CSF and is the most sensitive test in the present times. It allows detection of an abnormal population in samples with little cellularity that otherwise might go undetected on morphologic examination alone. It is a useful adjunct to cytologic examination because of the quantitative phenotypic information it provides. The problem in interpretation occurs in case of a traumatic tap. The admixture of the peripheral blood blasts with CSF will lead to dilemma, and hence a repeat CSF examination will be required for a definitive diagnosis.

Repeated CSF sampling needs to be done whenever the etiological diagnosis of the chronic meningitis is uncertain. The possibility of positive cytology is higher in solid primary than hematological primary in NM. A single CSF sample has a sensitivity of about 50% and this percentage increases to 85–90% after multiple punctures. It is important to recognize that malignant cells may be detected in the CSF only on repeated examination. In this study, we examined the cytological features and correlated with the clinical and biochemical findings of 36 cases of NM that were diagnosed in a tertiary care center. This constituted 9% of 400 cases screened for chronic meningitis during the study period. NM is a relatively infrequent cause of chronic meningitis. As a result, the clinicians are not sufficiently familiar with its diagnosis and management. The clinical features at the time of presentation are similar to chronic meningitis due to other causes. Most of our patients (80%) presented with the history of headache, vomiting and meningismus, which is in agreement with the earlier published results. Hence a high degree of suspicion is required for the clinical diagnosis of NM. In addition to clinical suspicion, MRI and CSF study are mandatory for diagnosis of NM. The CSF examination showed elevated protein, hypoglycorrhachia and pleocytosis in 69%, 73% and 80%, respectively. This is in agreement with the earlier published results [3,8] [Table 5].

We also found some rare cases of NM. A case of trilateral retinoblastoma was reported with metastasis to leptomeninges in a 5-year-old female child [Figure 1p–r]. The CT scan showed soft tissue density lesion in the pineal gland region causing obstructive hydrocephalus which was suggestive of a germinoma. Excision and histopathological examination of the tumor revealed a pineoblastoma. The CSF analysis showed the presence of rosettes in the smear. The CSF protein was 946 mg/dl and glucose was 82 mg/dl, with a cell count of 35 cell/cumm. TR is characterised by an intracranial neuroblastic tumor arising in the pineal region, associated with hereditary retinoblastomas which are usually bilateral but may also be unilateral as in our case. They are rare, occurring in 3% of cases and is usually fatal.

Another rare case was of PCLBCL-leg type with metastasis to CSF. It was seen in a 57-year-old male patient who complained of severe lymphedema in his lower limbs. On biopsy it was reported as PCLBCL-leg type, which was confirmed by immunohistochemistry. This patient then presented with symptoms of chronic meningitis with the CSF protein 472.5 mg/dl, glucose 11 mg/dl and cell count 250 cells/cumm. The CSF cytology showed atypical lymphoid cells. PCLBCL-leg type is a rare and aggressive neoplasm as defined by the recently updated World Health Organization–European Organization for Research and Treatment of Cancer classification of cutaneous lymphomas.

### Table 4: Cerebrospinal fluid findings

| CSF cell count and biochemical findings |
|----------------------------------------|
| CSF pleocytosis (>20 cells)            | 21/26 (80%) |
| CSF-raised protein (>50)               | 18/26 (69%) |
| Hypoglycorrhachia (<60)                | 19/26 (73%) |
| Median CSF cell count                  | 105 (IQR: 8-3000) |
| Median CSF protein                     | 103 (IQR: 11-946) |
| Median CSF sugar                       | 44 (IQR: 6-109) |

Note: Biochemical findings of 26 cases were available

### Table 5: Comparison of the neoplastic meningitis studies

| Variables            | Ramesha et al.[3] | Liu et al.[8] | Our study |
|----------------------|-------------------|---------------|-----------|
| Total cases          | 453               | -             | 400       |
| Positive cases       | 25                | 34            | 36        |
| CSF pleocytosis      | 48%               | 68%           | 80%       |
| CSF-raised protein   | 68%               | 74%           | 69%       |
| Hypoglycorrhachia    | 64%               | 50%           | 73%       |
Carcinomatous meningitis from gastric carcinoma and gallbladder malignancy are very rare, and only a few cases have been reported in the literature.16–18 We encountered one case each in our study.

In our study we did not find any case of primary brain tumor with metastasis to CSF. However, other studies19,20 have seen a predominance (86%) of pediatric brain tumors with metastasis to CSF.

The limitations of this study was the retrospective nature and relatively small number of subjects. Exhaustive work up including several invasive procedures and imaging was not carried out to search for the primary.

**Conclusion**

To conclude, NM is a relatively rare disorder in regular neurology practice. A wide variety of malignancies can present with NM. The diagnosis requires high index of suspicion and may require repeated lumbar punctures for definite detection of malignant cells. On finding elevated protein and hypoglychachria in biochemical analysis along with pleocytosis, the pathologist should initiate a diligent search for neoplastic cells in the CSF. While a prior history of malignancy makes the diagnosis of NM on cytology easier, in the absence of this history the primary may elude detection in some cases. This is a commonly encountered problem by the cytologist/pathologist the world over. In higher centers, flow cytometric analysis of the CSF has been a recent advance, used to rapidly pick up the source of metastasis to CSF. However, in a low cost setting, CSF cytology should initiate a diligent search for neoplastic cells in the CSF. While a prior history of malignancy makes the diagnosis of NM on cytology easier, in the absence of this history the primary may elude detection in some cases. This is a commonly encountered problem by the cytologist/pathologist the world over. In higher centers, flow cytometric analysis of the CSF has been a recent advance, used to rapidly pick up the source of metastasis to CSF. However, in a low cost setting, CSF cytology may be the only tool available for diagnosis and thus, plays an important role in further management of these cases.

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**Conflicts of interest**

There are no conflicts of interest.

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