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Case Series

Cerebrospinal fluid cytology: A theragnostic and prognostic tool- Experience from a tertiary cancer care centre in central India

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ABSTRACT

Background: CSF examination is the gold standard for diagnosing leptomeningeal metastases. Malignant cells may access the subarachnoid space by hematogenous dissemination, spreading directly from parenchymal brain lesions, or spreading along the spinal cord or cranial nerves. Cytological detection of malignant cells in CSF is still a crucial decision point for systemic and intrathecal chemotherapy, and it has prognostic significance even with improvements in biochemical analysis and CNS imaging.

Materials and Methods: Over the course of two years, a total of 397 patients—regardless of gender and age—were investigated. There were sixty-four cases with involvement of the central nervous system documented, comprising 42 hematologic malignancies and 22 solid tumors. Cell centrifugation (Cytospin) method were used to prepare smears and cell blocks where prepared, as feasible and indicated.

Results: A cytological analysis of the cerebrospinal fluid showed that metastatic tumors were much more prevalent than primary central nervous system tumours. Lung tumors were the most frequent primary site in our analysis, with breast, gastrointestinal, and female genital tract malignancies following closely behind. CNS involvement has been reported in patients with Lymphoma (DLBCL) and Leukemia (most commonly ALL, but also AML and JMML) among hematological malignancies. Two cases of Retinoblastoma and one each of Medulloblastoma and an Atypical teratoid/rhabdoid tumor were observed in the pediatric age group.

Conclusion: Cerebrospinal fluid cytology is a simple and useful method, used as a primary diagnostic method in the evaluation of leptomeningeal metastases. This helps in the early detection of secondary CNS lesions and allows for timely intervention, prognosis, and prediction of overall survival.

1. Introduction

Neoplastic meningitis also referred to as Carcinomatous meningiosis/ Leptomeningeal metastasis is a condition characterised by widespread multifocal involvement of the brain, spine, and/or roots by a metastatic or primary brain tumour. Depending on the underlying malignancy, this condition may be termed Leptomeningeal carcinomatosis, Lymphomatous meningitis, or Leukemic meningitis.

Cerebrospinal fluid examination is the gold standard in the diagnosis of leptomeningeal metastases. Malignant cells gain access to the subarachnoid space by hematogenous dissemination (crossing the Blood-Brain, Blood-CSF barrier), direct extension from a parenchymal brain lesion or[1] by tracking along the spinal or cranial nerves. Detection of malignant cells in the cerebrospinal fluid due to leptomeningeal metastasis is frequently associated with diverse neurological presentations. In several patients with

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a positive CSF, cytological examination strikingly provides the first documentation of a neoplasm. Spread of malignant cells into the CSF implies a limited prognosis with a median survival time of 2–6 months. The prognostic relevance of the cytological detection of malignant cells in cerebrospinal fluid remains, despite advancements in biochemical analysis and central nervous system imaging, a crucial component in the advocacy of systemic and intrathecal treatment.[2]

2. Aims and Objectives

1. To evaluate the role of CSF cytology in the assessment of Leptomeningeal metastases.
2. To study the cytomorphological features in various tumours i.e. both solid and haematological malignancies.
3. To subject the CSF samples to ancillary techniques like Cell Block preparation, Flow cytometry, Immunocytochemistry and Molecular tests (Mutation analysis).

3. Materials and Methods

3.1. Sample size (n)

397 cases.

3.2. Inclusion criteria

Patients of both the genders and ages ranging between 1-80 years. These included both haematological and solid malignancies.

3.3. Sample collection technique

Spinal tap (Lumbar puncture), VP shunt.

Leptomeningeal involvement was documented by the presence of malignant cells in the CSF.

The Cytocentrifuge (Cytospin) technique was employed to prepare smears for analysis. Smears were stained with May- Grunwald Giemsa and Haematoxylin & Eosin stains.

Cell blocks were prepared and studied wherever possible.

Cytocentrifuged smears were prepared and reviewed by four cytopathologists independently and were subsequently classified based on the consensus as positive or negative for malignant cells.

64 cases i.e. 22 patients with solid tumours and 42 cases of haematological malignancies with CNS involvement were studied.

Tumour types represented by these patients included:

3.4. Solid tumours

1. Lung carcinoma (NSCLC,
2. Breast carcinoma,
3. Epithelial ovarian carcinoma,
4. Gastrointestinal tumours
5. Primary CNS malignancies: Atypical Teratoid Rhabdoid Tumour (AT/RT, Medulloblastoma,
6. Other paediatric tumours: Retinoblastoma

3.5. Haematological malignancies

ALL, AML, JMML, NHL(DLBCL): Categorized as CNS 1/2/3.

Table 1: Categorizing CNS involvement in Leukemias on the basis of cell counts and cytocentrifuged smear findings

Categorization	Criteria
CNS 1	No detectable blasts in CSF
CNS 2	<5 leukocytes per microliter with detectable blasts in a cytocentrifuged preparation
CNS 3	5 or more leukocytes per microliter with Identifiable blasts, or presence of cranial nerve palsies

4. Observations & Results

Table 2: Primary CNS versus Metastatic tumours showing CNS involvement

S. No.	Primary/ Metastatic	Number of cases (% of positives)
1	Primary CNS neoplasms	2 (3.12%)
2	Metastatic malignancies	62 (96.8%)
Total no. of positives		64

Table 3: Different types of tumours demonstrated on CSF cytology

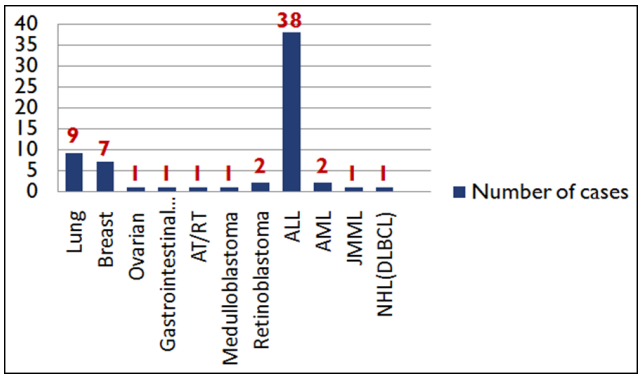
S.No.	Type of neoplasm	Number of cases (% of positives)
1	Primary CNS neoplasms	2 (3.12%)
2	Metastatic carcinomas	20(31.25%)
3	Haematological malignancies with CNS involvement	41 (64.06%)
4	Lymphomatous involvement	1 (1.56%)
No. of positives		64 cases
Total no. of cases		397 cases

5. Discussion

Significance of CSF cytology and its Clinical implications

Table 4: Various ancillary techniques employed on the CSF samples received

S. No.	Sample processed	Ancillary technique used	Diagnosis	Number of cases	Findings
1.	Cerebrospinal fluid	Cell block preparation and Hormone receptor analysis (ER/PR/ Her2 neu)	Carcinoma Breast	3	Groups of malignant ductal epithelial cells — Metastatic adenocarcinoma 2 cases of TNBC and I case Her2 neu enriched.
2.	Cerebrospinal fluid	Flow cytometry	DLBCL	1	B-NHL CD45, CD19, CD20, CD79a
3.	Cerebrospinal fluid	Mutation analysis on CSF cell block	Carcinoma Breast		PX3CA mutation detected



Graph 1:

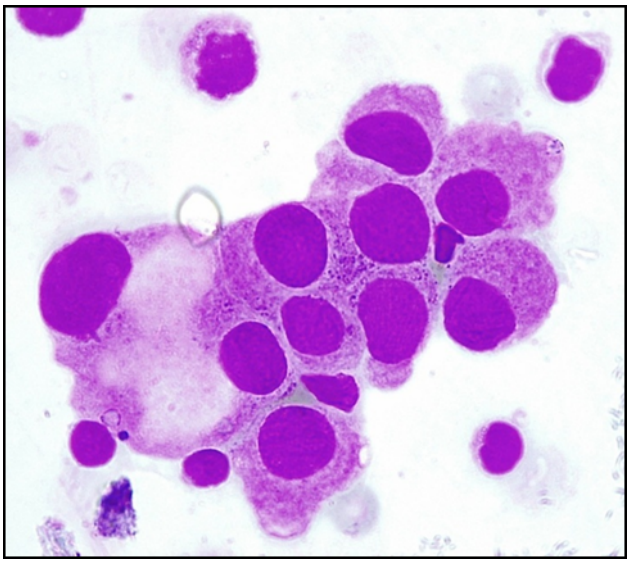


Figure 1: CSF Specimen from a patient with a histological and IHC confirmed Adenocarcinoma of the lung: tumour cells with compact, centrally or peripherally located nuclei and relatively abundant cytoplasm with hyperchromasia. (H&E 400x)

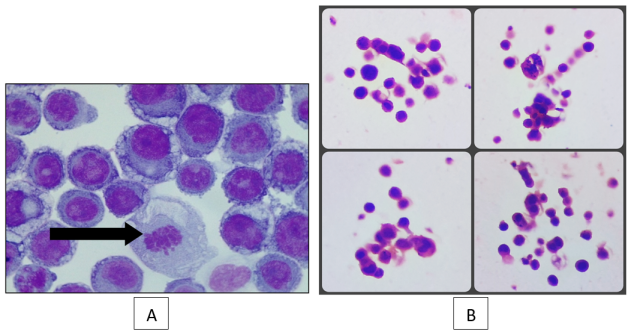


Figure 2: A): Discretely scattered mononucleate and binucleate cells, some of which are connected by cytoplasmic bridges, in a patient with highly aggressive Metastatic carcinoma of the Breast (TNBC). An atypical mitosis (arrowhead) is seen. MGG 400x; **B)**: Cell Block prepared from the CSF sample in a case of Triple Negative Breast Carcinoma showing loosely cohesive clusters of atypical cells with high nucleo-cytoplasmic ratio. (H&E 400x)

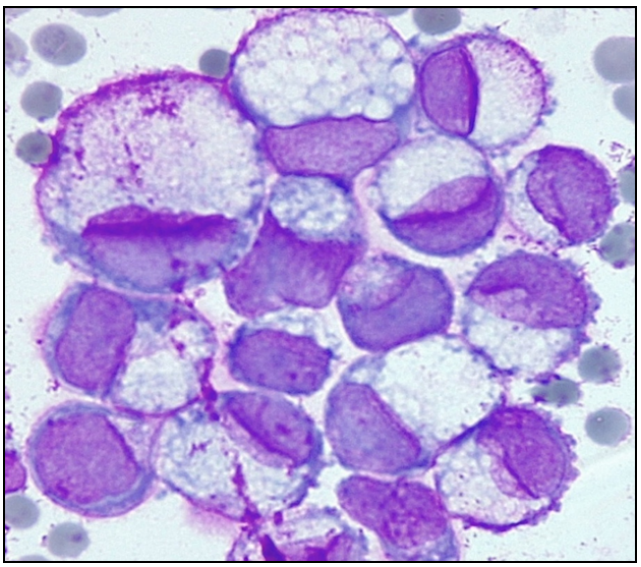


Figure 3: A cluster of pleomorphic tumour cells in a patient with a Metastatic adenocarcinoma anorectum. Intracytoplasmic mucin vacuoles are noted. (MGG 400x)

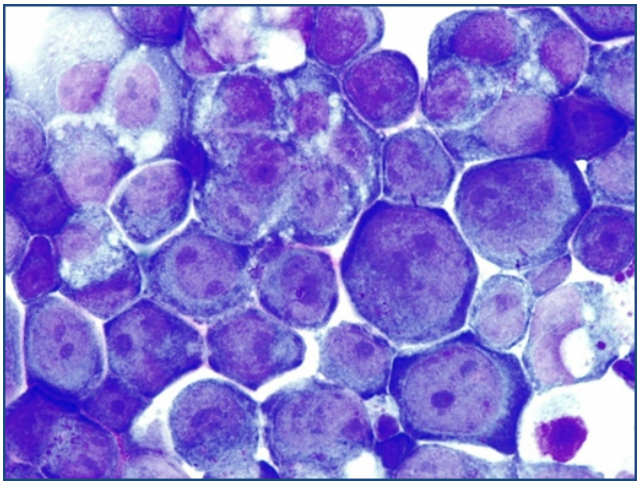


Figure 4: Discretely scattered tumour cells in a patient with an Epithelial Ovarian Carcinoma. Tumour cells show pleomorphic nuclei with prominent nucleoli, irregular nuclear membranes and high nucleo-cytoplasmic ratio. (MGG 400x)

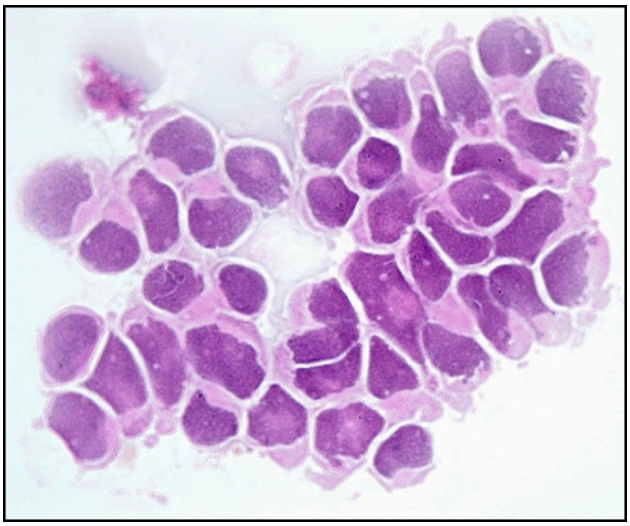


Figure 5: Tumour cells in a patient with Medulloblastoma displaying hyperchromasia, variable nuclear size and high nucleo-cytoplasmic ratio. (MGG 400x)

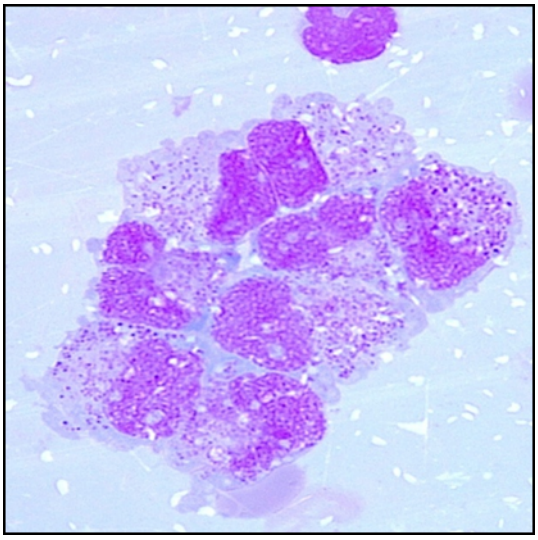


Figure 6: Cytospin preparation in a diagnosed case of Atypical Teratoid/ Rhabdoid Tumour (AT/RT) showing loosely scattered large cells with eccentrically placed nuclei, prominent nucleoli and abundant cytoplasm. (H&E 400x)

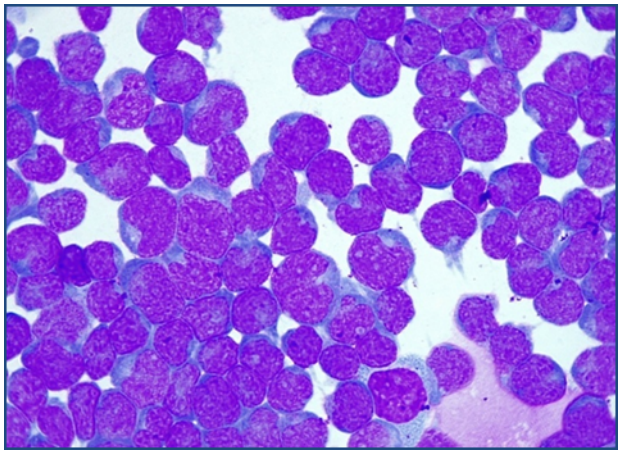


Figure 7: Cytospin preparation in a diagnosed case of T-acute lymphoblastic lymphoma/ leukemia showing discretely scattered large cells with pleomorphic convoluted nuclei, nuclear grooving/cleaving, fine chromatin and scant cytoplasm. (MGG 400x)

1. The clinical value of an early and accurate diagnosis of metastatic tumours in CSF is high even in neurologically asymptomatic patients who are in remission from neoplasms that were formerly rapidly fatal, because the effect of treatment contributes to quality of life, control of neurological symptoms and improved overall survival.
2. CSF examination is a routine procedure in the work-up of Pediatric Acute leukemias (Day 0). Also, CSF cytology serves to monitor the effect of Intrathecal chemotherapy in sequential CSF samples. Intrathecal therapy with drugs like Methotrexate, liposomal Cytarabine and corticosteroids is carried out until 2 consecutive CSF cytology samples are 'Negative for malignant cells'.

5.1. Prognosis

Associated with a grave prognosis because Leptomeningeal metastasis usually signifies extensive metastases.

Untreated median survival: 4-6 weeks;

Treated median survival: 2-3 months.

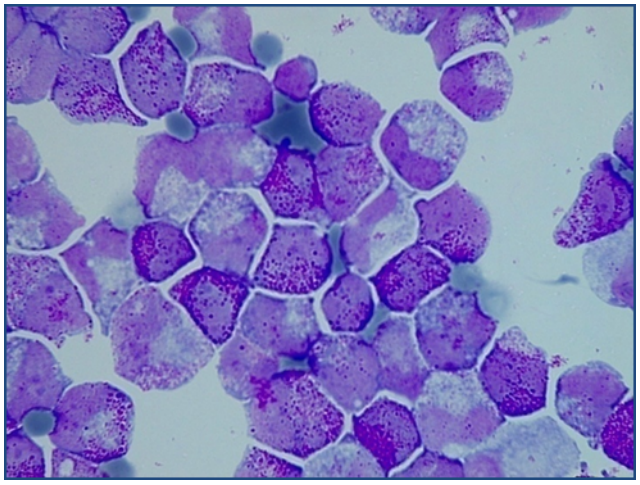


Figure 8: Cytospin preparation in a case of Acute Promyelocytic Leukemia (AML – M3) showing many promyelocytes with round to ovoid slightly irregular nuclei and reddish-purple cytoplasmic granulation. (MGG 400x)

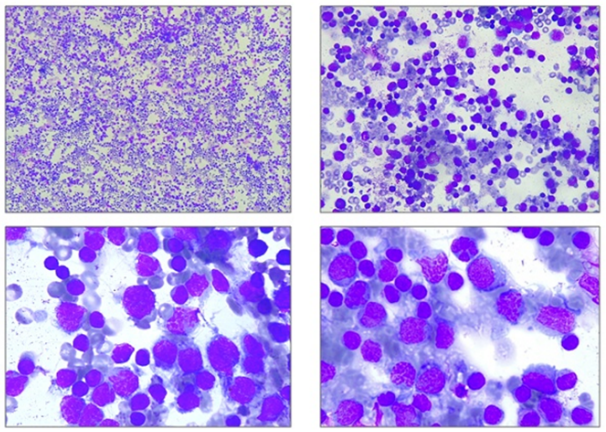


Figure 9: CSF Cytospin preparation in a case of High grade B-cell NHL (DLBCL) showing discretely scattered atypical lymphoid cells with round to lobulated nuclei, occasional prominent nucleoli and variably basophilic cytoplasm having smooth or irregular borders. (MGG 400x)

Table 5:

Similar studies	Time frame of study	Number of positive cases
Present study(2021)	02 years	64/ 397
Patel et al(2017)[3]	05 years	273/5394
Singh et al(2013)[4]	20 years	66/15430

6. Conclusion

This case series highlights the role of cerebrospinal fluid cytology as a simple and useful method that serves as a reliable diagnostic tool in the evaluation of leptomeningeal carcinomatosis. Early diagnosis is essential to maintain the quality of life and to improve survival time with treatments including intrathecal chemotherapy, systemic chemotherapy, and radiotherapy.[5] The Central Nervous System is increasingly becoming a common site for metastatic involvement as the longevity and quality of life of cancer patients is improving with the advent of newer systemic therapies.[6] In addition to this, many chemotherapeutic agents fail to cross the Blood-Brain and Blood- CSF barrier, leaving the CNS/ meninges as a potential tumour hideout.[7]

Consequently, the early identification of secondary CNS diseases made possible by cerebrospinal fluid cytology aids in prognosis, overall survival prediction, and prompt intervention.[8]

7. Source of Funding

None.

8. Conflict of Interest

The authors declare they have no competing interests.

9. Ethics Statement by all Authors

All authors take the responsibility of maintaining relevant documentation of records, slides and other relevant data pertaining to the cases included in the study.

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