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DIAGNOSTIC VALUE OF CSF CYTOLOGY IN HEMATOLYMPHOID AND SOLID TUMOURS: A TERTIARY CARE CENTRE EXPERIENCE.

Oncopathology

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ABSTRACT

Introduction: CNS involvement is serious complication of hematological and solid tumours.Among the malignancies, acute lymphoblastic leukemia remains the commonest to have CSF involvement. **Methods:** A retrospective study of cytomorphological analysis of CSF cytology was made from January 2022 to December 2022 .Cases were analysed for the involvement of CSF by hematolymphoid and non hematolymphoid solid malignancies **.Results:** Total of 90 samples were reported as positive for malignancy out of the total 1985 samples sent.19 were from solid malignancies. Lung adenocarcinoma, malignant round cell tumours including retinoblastoma, medulloblastoma, rhabdomyosarcoma being the primaries. Remaining 71 cases were involvement from hematolymphoid malignancies, Acute lymphoblastic leukemia being the commonest. **Conclusion:** Diagnosis of CSF involvement by malignant cells by cytological examination is important for timely targeted chemoradiation. CSF cytology remains the most simple and effective way for diagnosis.

KEYWORDS

CSF, Metastasis, Hematolymphoid, Solid.

INTRODUCTION

Central nervous system (CNS) involvement is a major complication of haematological and solid tumors with an incidence that ranges from 5-10% in solid malignancies ,10-15% and even up to 25% in specific leukaemia or lymphoma subtypes(1).It more frequently represents late complication of longstanding neoplastic disease, but in 10–15% of patients maybe the first-ever manifestation of otherwise occult cancer(1).Acute lymphoblastic leukemia is the commonest hematolymphoid neoplasm involving the CSF.Neoplastic meningitis can be caused by metastasis from solid tumors, which is termed as carcinomatous meningitis, or by infiltration by leukemia or lymphoma which is termed as leukemic or lymphomatous meningitis, respectively (2).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 spill over of primary brain tumors (1–2%) is seen.

Adenocarcinoma is the most common type of carcinomatous meningitis. The commonest primaries to metastasize to the leptomeninges and/or CSF are lung,breast and melanoma (3). CSF cytology is a simple tool that has a high specificity (up to 95%) which helps in early diagnosis and successful treatment.(4).

METHODS :

A retrospective study of cytomorphological analysis of 1985 samples of CSF cytology was made from January 2022 to December 2022 for involvement of hematolymphoid and non hematolymphoid solid malignancies reported as positive for malignancy. The total samples sent were 1985. Only cases reported as positive for malignant cells were included and those reported as negative, suspicious, atypical cells were excluded from the study.CSF smear is prepared immediately on receiving the samples as the cells undergo rapid degeneration. After centrifuging for 10 min in Remi revolutionary general purpose centrifuge (R-8C BL),the samples are loaded into Thermo Scientific Cytospin 4 Centrifuge, automated machine and centrifuged for 3 minutes at 800 RPM. The 6mm smears prepared on slides by cytospin technique are fixed by immersing in methanol for 20minutes. The slides are then stained by pap staining with Gemini AS Automated stainer.

RESULTS:

Out of total 1985 cases, 90(4.5%) cases were reported as positive for malignancy.25 were females and 65 cases were males.The table 1 shows distribution of solid tumours found in CSF .The commonest found was small blue round cell tumour with retinoblastoma being the highest with 13 (14.4%)cases. Cells are small round cells in clusters and occasional rosettes with scant cytoplasm, irregular, hyperchromatic and moulded nuclei (Fig 1a, b). Others like medulloblastoma,2 cases (2.2%) from CNS, and rhabdomyosarcoma 2 cases (2.2)% from nasal mass also were found. Rhabdomyosarcoma showed discrete cells having scanty cytoplasm, some with dense eosinophilic cytoplasm, and with hyperchromatic nuclei. Cells in metastases from medulloblastoma were small scattered singly, in small clusters and some in rosettes. Cells having scanty cytoplasm, occasional readily visible cytoplasm and was sometimes elongated. The nuclei were hyperchromatic. Prominent nucleoli were clearly visible in some cases.

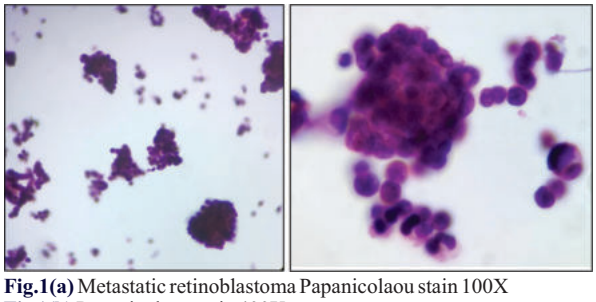

Fig.1(a) Metastatic retinoblastoma Papanicolaou stain 100X
Fig 1(b) Papanicolaou stain 400X

Epithelial malignancy of lung primary was found in 2 (2.2%) cases. Scattered and small clusters of malignant large cells having abundant cytoplasm, pleomorphic vesicular nuclei and some cells with intracytoplasmic mucin were noted (Fig 2).

Table 2 shows distribution of hematolymphoid malignancies found in our study. Commonest among the acute leukemia , acute lymphoblastic leukemia, B cell type with 40 cases(44.4%). Monotonous lymphoblasts were medium sized cells having scanty cytoplasm, round nuclei, some with clefting ,fine chromatin and some with prominent nucleoli (Fig 3). Acute myeloid leukemia involvement is seen in 4 cases(4.4%) showing blasts which were large cells with moderate cytoplasm,high N/C ratio, round or oval nucleus, dispersed chromatin and 1-2 prominent nucleolus. Apart from acute leukemias, Non Hodgkins Lymphoma was also found in our study. Burkitt's lymphoma 6 cases (6.6%) ,diffuse large B cell lymphoma 2cases (2.2%).Burkitt's lymphoma showed discrete malignant lymphoid cells.The nuclei were spherical ,with a fine to coarse chromatin and with two to five distinct nucleoli and scanty cytoplasm.Starry sky pattern was identified in some cases as a result of tingible body macrophages.Necrotic debris and mitotic figures were noted. Cells from diffuse large B cell lymphoma were predominantly dispersed large lymphoid cells having with non cleaved cells. The non cleaved cells had round to ovoid nuclei with smooth nuclear membrane,fine chromatin and one or more distinct nucleoli ,having moderate cytoplasm. Mantle cell lymphoma in 1 case (1.1%) and anaplastic large cell lymphoma 1case(1.1%).Cells from mantle cell lymphoma

were small to intermediate sized lymphoid cells with nuclear membrane irregularities and indendations,fine nuclear chromatin, inconspicuous nucleoli having scant pale basophilic cytoplasm. Anaplastic large cell lymphoma showed large cells with pleomorphic ,hyperchromatic nucleus , with one or more prominent nucleoli, and occasionally multinucleation. Cells had abundant deeply basophilic abundant cytoplasm. CLL involvement was seen as monomorphous population of small round lymphocytes with nuclei having a checkerboard pattern of clumped chromatin, with scanty cytoplasm.

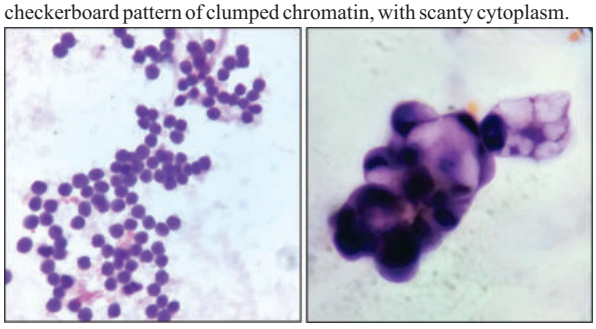

Fig. 2 Acute lymphoblastic leukemia blasts in CSF Papanicolaou stain 400X

Fig. 3 Metastatic adenocarcinoma from Adenocarcinoma lung. Papanicolaou stain 1000X

In our institution, CSF cytology in Acute lymphoblastic leukemia is done routinely at the time of diagnosis. If suspecting relapse,in a known case which is in remission, CSF cytology is sent for again. When CSF cytology is positive intrathecal medications are added and during treatment CSF cytology is done twice weekly till three consecutive cytology comes negative. After that weekly Triple Intrathecal Therapy is given for 6 doses, biweekly for 4-6 months and then monthly, CSF is sent each time.

For AML, CSF cytology is done if symptomatic.

Table 1:Distribution of cases involved by solid non hematolymphoid malignancies

Site of primary	Tumour type	CSF interpretation	Number of cases
Epithelial malignancies Lung	Adenocarcinoma	Positive	2(2.2%)
Small blue round cell tumour Eyeball	Retinoblastoma	Positive	13(14.4%)
CNS	Medulloblastoma	Positive	2(2.2%)
Nasal mass	Rhabdomyosarcoma	Positive	2(2.2%)

Table 2: Distribution of hematolymphoid malignancies

Type of malignancy	CSF interpretation	Number of cases
Acute myeloid leukemia	positive	4 (4.4%)
Acute lymphoid leukemia- B cell	positive	40(44.4%)
Acute lymphoid leukemia- T cell	positive	8 (8.8%)
Burkitt lymphoma	positive	6 (6.6%)
Diffuse large B cell lymphoma - GCB type	positive	2(2.2%)
Mantle cell lymphoma	positive	1(1.1%)
Anaplastic large cell lymphoma	positive	1 (1.1%)
Chronic myeloid leukemia,with blast crisis	positive	8(8.8%)
Chronic lymphoid leukemia	positive	1 (1.1%)

DISCUSSION:

The meaning of a positive CSF cytology has been studied by Glass *et al*.(5)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.Neoplastic Meningitis has been associated with a dismal prognosis of 2–4 months, with patients presenting with a wide range of clinical features from simultaneous involvement of multiple locations throughout the neuraxis (6).In the event of clinical suspicion of NM, the 2 main diagnostic tools are MRI and CSF analysis.Gadolinium-enhanced MRI of the brain and spinal cord is the neuro imaging technique of choice in patients with suspected NM; this technique presents 70%-80% specificity.The best testfor diagnosing however is NM in patients with hematological malignancies and solid tumours is CSF cytology, which demonstrates the presence of tumour cells with sensitivity of 60%-90% and specificity of 95%.(7).Accurate diagnosis also requires appropriately processed and well-stained smears. Due to rapid cellular degeneration within the hypo-osmotic CSF, slide preparation should occur ideally within 2 h following aspiration(8).

In the study by Vandana Rana et all (9) of 375 samples of CSF, 131 were positive for blasts in follow up cases of ALL.As with literature ,our study showed ALL involvement is found to be the highest among all the cases.In acute lymphoblastic leukemia (ALL), CNS involvement is more common and about 5% of adults are presenting with CNS leukemia at initial diagnosis, having a shorter OS in comparison with patients, who did not develop CNS leukemia.The CSF infiltration by hemato lymphoid malignancies can be difficult to diagnose 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.Flow cytometry improves the diagnostic rates in cases with scant blast cellularity or reactive lymphocytosis, because cytology is often difficult and problematic to evaluate using cellular morphology alone(10).Flow cytometry have been able to reliably detect phenotypically abnormal cells representing 0,01% of events (1 cell in 104) and is a useful tool for monitoring minimal residual disease in acute leukemia (11).

In the study done by A Silvani et al, in 12 months, 26 patients with neoplastic meningitis from solid extra-CNS tumors were diagnosed. Pierre Giglio, M.D. et all studied the involvement of CSF by adenocarcinoma of gastrointestinal tract.11 patients showed positive for malignant cells in CSF.Our study showed two cases with CSF positivity from lung adenocarcinoma.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%)(3). CNS involvement of 2 cases of high grade non hodgkins lymphoma namely Diffuse large B cell lymphoma, GCB type (NHL-DLBCL,GCB).1 case of mantle cell lymphoma were found in our study. The primary was identified earlier in lymph nodes and immunohistochemistry was done in the lymph nodes and proved in all the cases.

A single CSF sample has a sensitivity of about 50% and this percentage increases to 85–90% after multiple punctures. Henceforth whenever there is strong clinical suspicion or when etiology of chronic meningitis uncertain repeated CSF puncture might be indicated.(12)

Involvement of CSF by malignant cells is an indication for intrathecal chemotherapy(13).Intrathecal administration of methotrexate, cytarabine,cytarabine liposome, thiotepa, topotecan are being included in therapeutic protocols according to the malignancy(5).

The limitations of this study was the retrospective nature and relatively small number of subjects.

CONCLUSION

CSF involvement is a severe effect, that is the leading cause of acute leukemia-related deaths and that is encountered often during the progression of this disease. Misdiagnosis of neoplastic meningitis occurs frequently because of its diverse clinical symptoms and its association with high mortality and major neurological disability.CSF cytology remains a simple tool for identifying neoplastic cells. (5)It is of great importance to recognize its presentation and to improve the diagnosis(14).In solid tumours also studies indicate CSF involvement has poor prognosis and affects survival adversely. CSF involvement in an already known patient is relatively easier than in unknown primary where other tests like immunohistochemistry might be needed. Early and accurate diagnosis through CSF cytology, improved MRI techniques and flow cytometry are the steps to an early detection of the disease.The best types of treatment are: targeted chemo-or radiation therapy to the CNS and high doses of systemic chemotherapy.

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