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Neoplastic meningitis: clinico-radiological features, outcome and prognostic factors

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Abstract

Objective: This retrospective hospital based study aimed to describe clinico-radiological features and outcome of neoplastic meningitis (NM) and to evaluate the significance of the presence of malignant cells in CSF and identifiable primary in NM. *Methods:* The diagnosis of NM was based on the presence of malignant cells in CSF cytology, meningeal biopsy, post mortem examination or compatible clinico-radiological features in patients with known primary malignancy. For subgroup comparisons, Mann Whitney test and Fisher's exact test were used for continuous and categorical variables respectively. Relative risk of survival in positive CSF cytology for malignant cells and known primary versus negative were calculated. *Results:* There were 25 patients (mean age 44.5 $\pm$ 17.6 years) of NM during the study period (2000-2008). They presented with raised ICP headache (72%), cauda equina syndrome (28%), or hemiparesis (12%). Meningeal enhancement and hydrocephalus were seen in 60% and 21% respectively. CSF analysis revealed hypoglychorrachia (64%), raised protein (68%) and pleocytosis (48%). CSF cytology for malignant cells was positive in 76% and cumulative positivity increased by 31% from 1st to 3rd lumbar punctures. A primary could be identified in 56% cases. At last follow up, 16 out of 18 had died. Hypoglychorrachia was the only variable analyzed, which predicted the cytology positivity (p=0.01). The mean duration of survival from the onset was significantly less in cytology positive group (p=0.001). The relative risk of survival at 90 days, 120 and 150 days were significantly higher in cytology and primary negative group compared to positive group.
Conclusion: NM with positive cytology or with an identifiable primary tumor has a more aggressive course when compared to the negative groups and former have shorter lifespan. The possibility of positive cytology is high with hypoglychorrachia.

INTRODUCTION

Neoplastic meningitis (NM) occurs in 3-23% of all cancers.[1,2] The most common primary for NM is carcinoma of the breast and lung, melanoma and high-grade hematological malignancies.[1,2] Often it is difficult to make definitive diagnosis of NM because of the practical difficulty in demonstrating malignant cells in CSF. A single CSF examination may yield malignant cells only in less than half the cases.[3,4] Though magnetic resonance imaging (MRI) can give valuable information, cytological evidence is crucial for diagnosis. The alternative diagnostic criteria involving clinico-radiological features and excluding the need to demonstrate malignant cells in CSF have been suggested.[4] The role of aggressive treatment of malignancy after extensive involvement of the meninges is controversial as the life expectancy is only marginally increased and risk to benefit ratio is questionable.[5] The median survival rate after diagnosis is 4 to 8 weeks in untreated cases[1] and 6 months in treated cases.[1,5] Primary site of malignancy cannot be identified in up to 7% of cases even with extensive investigations.[1,6] In this background, it is unclear how far and persistent should clinicians pursue the precise source of the malignancy. Case series with sizeable number of patients with NM has not been reported from India. Very few studies have looked into the clinico-radiological and outcome difference between the cytology/primary positive versus negative patients group. In this background, we aimed to analyze the clinico-radiological and CSF features of NM diagnosed in our centre and to determine the factors that can predict the positive cytology for malignant cells as well as identifiable primary with standard investigations.

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METHODS

Cases were identified from the elaborate medical records in the hospital database from November 2000 to August 2008 by systematically screening the in-patient records. We abstracted their data on a structured proforma with special reference to their demographic features, clinical characteristics, past history of primary malignancy, imaging and CSF findings, treatment received, and outcome. The current status of the patient and outcome were updated by contacting the patients or their relatives by telephone or mail. Then the interval between the onset of symptoms and presentation, and onset of symptoms and death was calculated. We included only those cases where the diagnosis of NM was established either by CSF cytology, meningo-cortical biopsy, postmortem or by compatible clinico-radiological picture in a patient with known primary malignancy after ruling out other etiologies. CSF cytology was done with the help of cytospin method and interpreted after the hematoxylin and eosin stain by experienced senior neuropathologist. If the primary was unknown, patients underwent detailed evaluation which included clinical examination including gynecological and breast examination, chest x-ray, ultrasound scanning of the abdomen, skeletal screening by x-ray, peripheral blood smear study, stool for occult blood, and urine for Bence Jones protein. The CT scan of the chest and abdomen, endoscopy of the gastrointestinal tract, bone marrow biopsy, mammography and radioisotope scan were carried out selectively depending upon the merit of the case and physical fitness of the patients.

Statistical analysis

The quantitative data were summarized as percentages, median, range and mean ± standard deviation. Mann Whitney test was used for continuous variables and Fisher's exact test for categorical variables for subgroup comparisons. A p value ≤0.05 was considered as significant.

RESULTS

During the study period, there were 25 cases that satisfied the selection criteria for NM. Their clinico-radiological features and outcome are summarized in Table 1. The median age at diagnosis was 48 years (range 10-75years). Only 2 patients were below the age of 18 years. Female to male ratio was 3 : 2. The mean duration between the onset of symptoms and to the presentation was 75 ± 70 days. Raised intracranial pressure type of headache was noted in 18 (72%), altered sensorium was seen in 10 (40%) and behavioral problems in 4 (16%) patients at presentation. Five (20%) had 6th nerve palsy as a false localizing sign due to raised intracranial pressure and another 6 (24%) had other cranial nerve palsies. The imaging included CT scan of the head (n=12) and magnetic resonance imaging (MRI) of the brain (n=16) and MRI of the both brain and spine (n=5). All patients underwent contrast enhanced imaging. Cranial meningeal enhancement was noted in 9 (38%), (Figure 1 and 2) spinal leptomeningeal enhancement (Figure 3) and clumping of the lumbosacral root was seen in 6 cases (24%), and vertebral lytic lesions in 2 cases. The CSF analysis showed mean cell count of 486/mm^3 (range=2-10,800 cells mm^3), mean protein of 192 ± 218mg/dl and mean sugar of 47±19mg %. There were 13 (52%) patients with normal cell count and 16 (64%) with hypoglychorrachia. Neuroinfections were ruled out in all cases by gram stain, Zeihl-Nelson stain for acid-fast bacilli, and culture for bacteria, mycobacterium tuberculosis and fungus. CSF cytology was positive for malignant cells in 19 (76%) patients. Eleven had cytology positivity in the first lumbar puncture (LP), 5 in 2nd LP, one in 3rd LP and another 2 in the 4th study. Hence, cumulative positivity increased from 57.9 % in first analysis to 84.2% by 2nd, and 89.5% by 3rd analysis. In others, NM was proved by histopathology of meningo-cortical biopsy (2), vertebral biopsy (1) and by post mortem examination (1). There were 3 patients with known primary, clinico-radiological findings compatible with NM in whom other causes of meningitis had been excluded.

There were 14 (56%) patients with identified primary malignancy and another 11 with unknown primary even after detailed evaluation. The primary was known prior to the presentation with meningitis in 9 (64.2%) of the 14 with identified primary. The mean duration between primary and the onset of carcinomatous meningitis was 1.9 ± 3.7 years. The primary malignancy was in the lung (5), breast (1), or submandibular gland (1). Five patients had non-Hodgkin's lymphoma, and 2 had acute myeloid leukemia. There was one patient who had melanoma of the meninges detected during postmortem. However, in view of selective postmortem of the brain and meninges, primary versus secondary melanoma could not be differentiated.

Only 5 out of 18 patients received treatment, 3 received palliative radiotherapy and 2 received

Table 1: Clinico-radiological features and CSF findings and outcome of the study cohort

Variables	Number (%)
Demography	
Mean age at presentation (years)	45 ±187
Male: Females	2:3
Clinical features	
Mean duration of illness before presentation (days)	75 ±70
Seizures	7 (28)
Papilloedema	13 (52)
Meningeal signs	11 (48)
Total cranial nerve palsy	11 (48)
Cranial Nerve palsy other than 6th nerve	6 (24)
Hemiparesis	3 (12)
Paraparesis	8 (32)
Cauda equina syndrome	7 (28)
Radiological findings:	
Cranial meningeal enhancement	9 (38)
Spinal meningeal enhancement	6 (24)
Hydrocephalus	6 (21)
Multiple parenchymal lesions	4 (16)
CSF findings	
CSF pleocytosis (cmm)	12 (48)
CSF raised protein (gm)	17(68)
Hypoglychorrachia	16 (64)
Mean CSF Cell count (cmm)	486 ± 2153
Mean CSF protein (gm %)	192 ±219
Mean CSF blood sugar (mg %)	47 ±19
CSF cytology positivity for malignant cells	19 (76)
Fist CSF cytology positivity for malignant cells	11 (46)
Primary malignancy	
Solid primary	7 (40)
Hematological primary	7 (16)
Unknown primary	11 (44)
Treatment given	5 (28)
Last follow up available	18 (72)
Symptoms onset to death (days)	153 ± 96

chemotherapy. Six had death in the hospital. Out of 18 patients for whom follow up data were available, only 2 (11%) were surviving. Both were alive at three months of follow up with marked cognitive and physical disability, one had intrathecal chemotherapy and the other patient did not have any specific therapy. The mean time-interval between onset to death 152.9 days (range 26-392 days) and interval between discharge from hospital and death was 51days (range 0-182 days).

Cytology/primary positive versus negative

For subgroup analysis, we subcategorized the study cohort into 2 groups: Those with positive (n=19) versus negative (n=6) CSF cytology for malignant cells and those with identified primary malignancy (n=14) and unknown primary (n=11).Those who had positive CSF cytology for malignant cells had trend towards shorter duration of illness at presentation (60 ± 56 days vs 120 ± 94 days, p=0.069). Also the interval between onset and death was significantly (p=0.001) shorter for

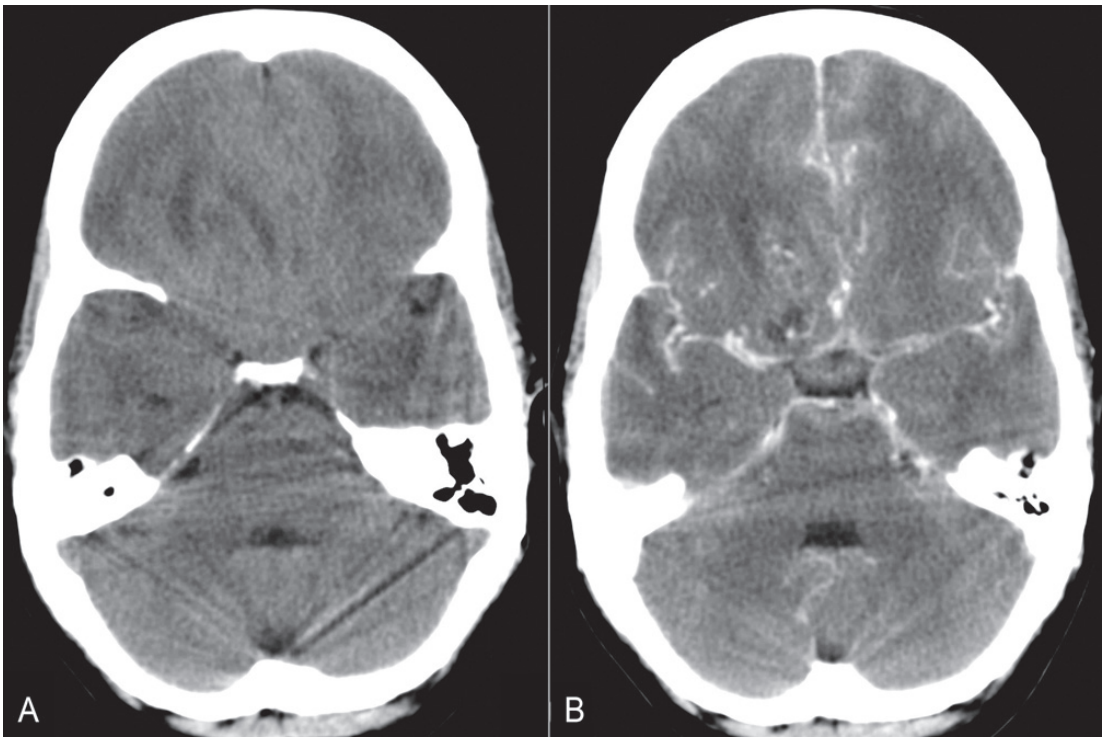

Figure 1: Pre contrast (A) and post contrast (B) axial computed tomography of brain of a 35 years old lady with CSF cytology confirmed neoplastic meningitis secondary to round cell carcinoma of the submandibular gland show diffuse brain edema and diffuse meningeal enhancement.

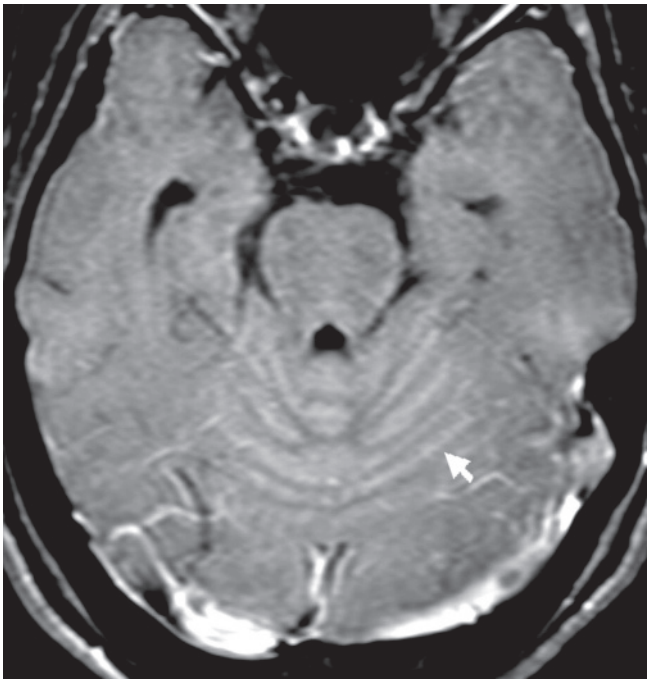

Figure 2: Post contrast T1W axial sequence of MRI of brain of a 45 years old lady with cytology positive neoplastic meningitis secondary to unknown primary shows leptomeningeal enhancement in the region of cerebellar folia.

the CSF cytology positive cases (104 ±39 days) compared to the CSF cytology negative group (259 ±99 days). There was positive association between presence of malignant cells in the CSF and the likelihood of hypoglychorrachia (p=0.012). The mean CSF sugar was also significantly lower in cytology positive group (41.7 ± 18.1 vs 63.3 ±11.7 mg%, p=0.021). Nevertheless, the various other clinical, radiological and CSF parameters did not have any significant association with positive CSF cytology. Those with identified primary had shorter symptomatic period at presentation (58±76 days vs 97±58 days, p=0.033). There was a trend towards shorter life expectancy in patients with identified primary (131±101 vs 189±88 days, p=0.073). When we calculated the relative risk of survival at 90, 120 and 150 days, it was significantly higher in cytology negative and unknown primary group compared to that of positive group (Table 2).

DISCUSSION

In this study we had examined the clinic-radiological features and the outcome of consecutive 25 cases of NM that were diagnosed in a tertiary care center for neurosciences. This constituted 5.5% of total 453 cases screened for chronic meningitis during the study period. This is the largest series of NM from India. 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 were similar to chronic meningitis due to other causes. There was little in the clinical characteristics to suspect NM except a history of malignancy in a third of patients. The clinical features for this cohort are in agreement with the published series.[1,2,7,8] In general, MRI and CSF cytology are better for the diagnosis of NM secondary to solid tumors and hematological malignancies respectively.[9] Imaging showed positive findings in all of our patients. CT scan head was normal in 8 out of 12 (66.7%) patients who underwent this test. In other reports positive CT findings were observed in 56% of NM[10] and contrast enhanced CT was inferior to contrast enhanced MRI in demonstrating abnormality.[11] We found hydrocephalus, cranial/spinal meningeal enhancement and multifocal brain pathology in 21%, 60% and 16% respectively. Meningeal enhancement on contrast administration is a useful finding but probably is not a reliable indicator of NM, as it may be absent in the substantial proportion of patients with NM (40%) and present in other chronic meningitis.

CSF examination showed elevated protein, pleocytosis and hypoglychorrachia in 68%, 48% and 64% respectively. This is in agreement with the published results.[1-3,6] We found positive cytology for malignant cells with first lumbar puncture in 46%, and total positive cytology for malignant cells in 76%. The cumulative positive rate increased by 32% from the first to 3rd sample. This varies between 20% and 34% in the literature[2,3,5,12] It is important to recognize that malignant cells may be detected in the CSF only on repeated examination, sometimes as late as fourth CSF sampling.[3] Repeated CSF sampling needs to be done whenever the etiological diagnosis of the chronic meningitis is uncertain. The possibility of positive cytology was higher in solid primary than hematological primary in NM.[2]

Table 2: Relative risk for shorter survival for neoplastic meningitis at different periods of follow up in relation to cytology and primary malignancy

Variables	Survival in days		
	90 days	120 days	150 days
Known primary (n=11)	9	4	4
Unknown primary (n=7)	7	7	4
Relative risk	0.82	2.75	1.57
95%CI	0.62-1.08	1.26-6.01	0.58- 4.32
Positive cytology (n=12)	10	5	2
Negative cytology (n=6)	6	6	6
Relative risk	1.2	1.2	3
95%CI	0.93-1.55	0.49-2.88	0.75-11.99

CI: confidence interval.

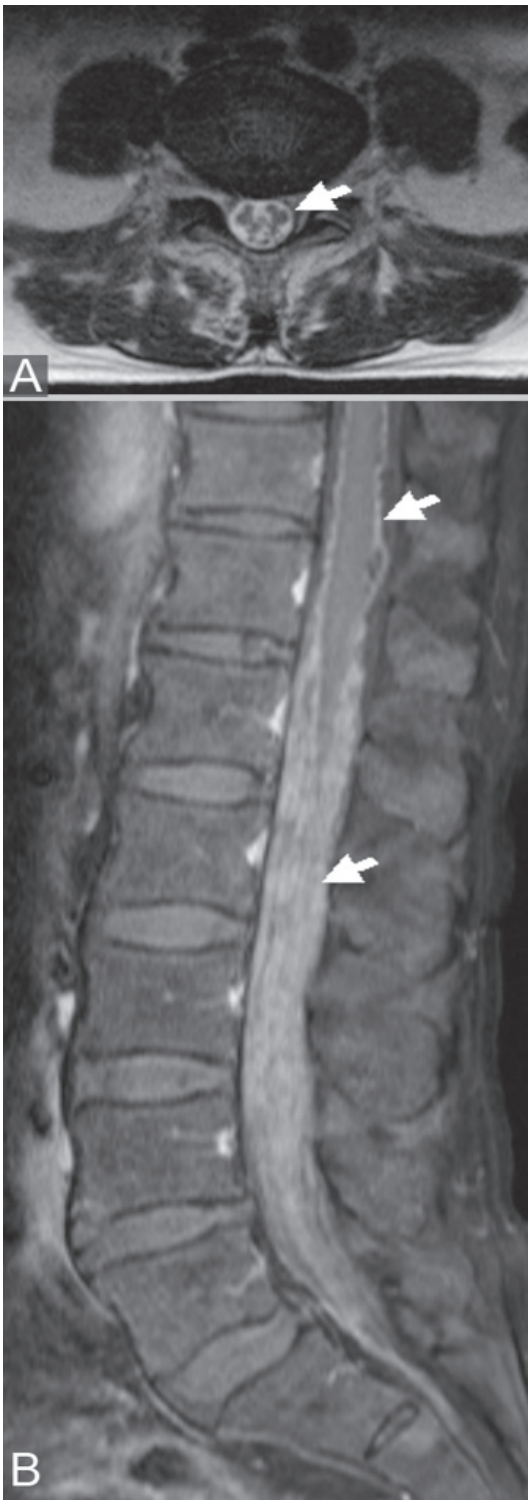

Figure 3: Axial (A) T2W and post contrast sagittal T1W MR imaging of spine of a 75 years old man with cytology positive neoplastic meningitis secondary to non Hodgkin's lymphoma, shows clumping of lumbo-sacral roots and diffuse meningeal enhancement (arrow).

In another study, higher positivity was noticed with cisternal puncture than lumber puncture.[13] Inability to find malignant cells in CSF may be due to adherence of tumor cells to meninges.[13,14] In negative cytology cases, CSF markers like carcino-embyonic antigen, lactate dehydrogenase and beta-2 microglobulin are useful.[15,16]

We compared the sub group having positive CSF cytology with negative cytology. This comparison is important because more than a quarter of patients with NM may be negative for CSF cytology even after repeated sampling. Our findings indicate that those who had positive CSF cytology had a more aggressive course of illness with shorter duration of illness at presentation and early death. Compared to those who were negative for CSF cytology, the survival was shorter by 5 months for this subgroup. This is an important prognostic factor and in contrast to the conclusion by Chamberlain MC *et al*.[17] However, the majority of our patients did not receive treatment and this reflects the natural course rather than response to treatment as in Chamberlain's study. A study by Kaplan showed that cytology is likely to be frequently positive when CSF cell count and chemistries are normal.[7] In another study, where they correlated neuroimaging with cytology, cytology positivity was higher in patients with dural enhancement and hydrocephalus.[3] In our series, there was no association between presence of malignant cells in the CSF and the CSF cell count, the nature of malignancy or imaging findings. Nevertheless, we observed significant association between hypoglychorrachia and positive cytology. This can be helpful in predicting the positive cytology.[18] In this series, the primary malignancy could not be identified in 44% with the limited work up. The mean duration of illness at presentation and duration of survival from the onset was significantly less when the primary was identified, which is against the conclusion by ME Loghin.[19]

The commonly used chemotherapeutic agents include methotrexate, thiotepa and cytocine arabinoside, which are administered either intrathecally, intraventricularly or intravenously.[1,5,6] Radiotherapy is mainly useful to reduce the symptoms due to bulky deposits.[20-22] The various studies have shown median patient survival of 2-6 months with treatment.[5,21,22] However, in a study of 137 patients with NM who received combined modality therapy, the median survival was 23 months in 31 (23%) patients who showed sustained off therapy response.[23] Only 5 of our patient received treatment. The majority refused to

undergo any specific or palliative treatment after understanding the pros and cons of radiotherapy and chemotherapy. Hence, we could not ascertain the implications of treatment on long-term survival compared one who did not receive the treatment.

Limitations of this study were the retrospective nature and relatively small number of subjects. Exhaustive work up including several invasive procedures was not carried out to search for the primary. 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 malignant cells. Cytology for malignant cells is likely to be positive if hypoglychorrachia is present. The primary may remain elusive to detailed search in a substantial proportion of cases. NM with positive cytology or with a primary tumor has a more aggressive course when compared to the negative groups and they have shorter lifespan.

REFERENCES

1. Balm M, Hammack J. Leptomeningeal carcinomatosis: presenting features and prognostic factors. *Arch Neurol* 1996; 53:626-32.
2. van Oostenbrugge RJ, Twijnstra A. Presenting features and value of diagnostic procedures in leptomeningeal metastases. *Neurology* 1999; 53:382-85.
3. Freilich RJ, Krol G, DeAngelis LM. Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. *Ann Neurol* 1995; 38:51-7.
4. DeAngelis LM. Current diagnosis and treatment of leptomeningeal metastasis. *J Neurooncol* 1998; 38(2-3):245-52.
5. Grant R, Naylor B, Greenberg HS, Junck L. Clinical outcome in aggressively treated meningeal carcinomatosis. *Arch Neurol* 1994; 51:457-61.
6. Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastasis from solid tumors: experience with 90 patients. *Cancer* 1982; 49(4):759-72.
7. Kaplan JG. DeSouza TG, Farkash A, *et al*. Leptomeningeal metastases: comparison of clinical features and laboratory data of solid tumors, lymphomas and leukemia. *J Neurooncol* 1990; 9(3):225-9.
8. Theodore WH, Gendelman S. Meningeal carcinomatosis. *Arch Neurol* 1981: 38:696-9.
9. Zeiser R, Burger JA, Bley TA, *et al*. Clinical follow up indicates differential accuracy of magnetic resonance imaging and immunocytology of the cerebrospinal fluid for the diagnosis of neoplastic meningitis-a single centre experience. *Br J Haematology* 2004; 124:762-8.
10. Ascherl GF, Hilal SK, Brisman R. Computed Tomography of disseminated meningeal and ependymal malignant neoplasms. *Neurology* 1981; 31:567-74.
11. Chamberlain MC, Sandy AD, Press GA. Leptomeningeal metastasis: A comparison of gadolinium –enhanced MR and contrast-enhanced CT of the brain. *Neurology* 1990; 40:435-8.
12. Balhuizen JC, Bots GTAM, Schaberg A, Bosman FT. Value of cerebrospinal fluid cytology for the diagnosis of malignancies in the central nervous system. *J Neurosurg* 1978; 48:747-53.
13. Rogers LR, Duchesneau PM, Nunez C, *et al*. Comparison of cisternal and lumbar CSF examination in leptomeningeal metastasis. *Neurology* 1992: 42:1239-41.
14. Glass JP, Melamed M, Chernik NL, Posner JB. Malignant cells in cerebrospinal fluid (CSF): The meaning of a positive CSF cytology. *Neurology* 1979; 29:1369-75.
15. Chamberlain MC. Cytologically negative carcinomatous meningitis: Usefulness of CSF biochemical markers. *Neurology* 1998; 50:1173-5.
16. Corsini E, Bernadi G, Gaviani P, *et al*. Intrathecal synthesis of tumor markers is a highly sensitive test in the diagnosis of leptomeningeal metastasis in solid cancers. *Clin Chem Lab Med* 2009; 47(7):874-9.
17. Chamberlain MC, Johnston SK. Survival as a function of cerebrospinal fluid cytology. *Cancer* 2009; 115(9):1941-6.
18. Clatot F, Philippin-Lauridant G, Ouvrier MJ, *et al*. Clinical improvement and survival in breast cancers leptomeningeal metastasis correlate with the cytological response in Intrathecal chemotherapy. *J Neurooncol* 2009:June 26
19. Loghin ME, Groves MD. Neoplastic meningitis in unknown primary neoplasms. J Clinical Oncology 2006; 24(18S):11517 [abstract]
20. Pentheroudakis G, Pavlidis N. Management of leptomeningeal malignancy. *Expert Opin Pharmacotherapy* 2005; 6(7):1115-25.
21. Gleisner B, Chamberlain MC. Neoplastic meningitis. *Lancet neurol* 2006; 5(5):443-52.
22. Grossman SA, Finkelstein DM, Ruckdeschel JC, *et al*. Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. *J Clin Oncology* 1993; 11:561-69.
23. Tali Siegal T, Alexander Lossos A, M Raphael Pfeffer MR. Leptomeningeal metastasis: Analysis of 31 patients with sustained off-therapy response following combined-modality therapy. *Neurology* 1994; 44:1463-9.