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Original Research Article

Multifaceted central nervous system metastases: An analysis of the clinicopathologic spectrum

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Abstract

Background: Central nervous system (CNS) metastases are the most common causes of neurologic abnormalities in patients with systemic malignancies. They can often be the initial manifestations of an undetected primary elsewhere.

Materials and Methods: This is a retrospective study which included 55 patients diagnosed with either brain or spinal cord metastases. The study period was four years. The cases were classified based on histopathology and immunohistochemistry was performed in cases of metastases from unknown primary. Primary CNS tumors were excluded from the study.

Results: In the study period, a total of 169 CNS neoplasms were diagnosed, including 114 (67.5%) primary and 55 (32.5%) secondary tumors. Most of the patients were in the 5th-6th decade of life, with a male preponderance (M:F ratio of 2.6:1). The most common site for metastases in CNS was cerebrum (n=30, 54.5%) followed by spinal cord (n=19, 34.5%) and cerebellum (n=6, 11%) respectively. The most common histological type was adenocarcinoma (65.4%) followed by poorly differentiated carcinoma (20.1%) and squamous cell carcinoma (12.1%). Primary sites could be detected in 48 cases (71.8%). The most common site of primary malignancy was lung (n=16, 29%) followed by kidney (n=7, 12.7%) and prostate (n=6; 10.9%). Two unusual cases with metastatic urothelial carcinoma were identified.

Conclusion: Metastatic tumors of brain and spinal cord are a major cause of morbidity and mortality and may pose a diagnostic difficulty on clinical and radiological examination. Histopathologic examination with the aid of immunohistochemistry is of utmost importance to render the correct diagnosis.

Keywords: Brain, Central nervous system, Metastases, Spinal cord.

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1. Introduction

Metastases are the most common tumors of the central nervous system (CNS). The incidence of developing CNS metastases in patients with solid tumors any time during the course of their disease is approximately 20% to 40%.[1,2] Some patients with malignancy elsewhere in the body might sometimes present for the first time to the clinician with symptoms related to CNS metastases. The detection of CNS metastases has greatly increased over the past few decades. This might be due to improved screening and diagnostic methods, leading to early detection of systemic disease.[1,3,4]

Despite improvement in therapeutic strategies, advances in neurosurgery and radiotherapy, CNS metastases are still associated with shorter survival and impaired quality of life as compared to extracranial matastases.[2,5] A large majority of brain metastases arise from solid malignancies, in decreasing order of incidence from lung (50-60%), breast (15-20%), melanoma (5-20%), kidney (~10%) and gastrointestinal tract (GIT) (4-6%).[6,7] On radiologic examination, CNS metastases can mimic high grade gliomas and infectious pathology like tuberculosis. Therefore, establishment of a correct diagnosis

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requires a systematic approach correlating clinical, radiological, and histopathological findings along with use of relevant immunohistochemistry.[7,8]

2. Materials and Methods

This was a retrospective observational study which included 55 cases of CNS (brain and spinal cord) metastases diagnosed in a tertiary care hospital in India. The study period was four years. Hematolymphoid and meningeal tumors were excluded from the study. The cases were identified by an initial electronic search and through the departmental records. The variables noted were age, sex, clinical history, radiological findings and histopathologic details. Routine hematoxylin and eosin (H and E) stained sections of formalin fixed paraffin embedded tissue were reviewed in all cases. In all the cases, the histopathological pattern of tumor was first studied to classify the tumor as adenocarcinoma, squamous cell carcinoma, neuroendocrine carcinoma, poorly differentiated carcinoma and others such as melanoma and sarcoma. Depending upon the histopathological findings, immunohistochemical stains were applied to detect the possible primary malignancy in cases of metastases from unknown primary. Various immunohistochemistry (IHC) markers such as glial fibrillary acid protein (GFAP), cytokeratin (CK), Human Melanoma B (HMB)-45, vimentin, estrogen receptor (ER), progesterone receptor (PR), human epidermal receptor (HER) 2neu, CK7, CK20, thyroid transcription factor (TTF)-1, alpha methyl acyl co-enzyme racemase (AMACR), Wilms' tumor suppressor gene (WT)1 and GATA binding protein-3 (GATA-3), were applied in cases of metastases with unknown primary.

3. Results

In the study period, a total of 169 CNS neoplasms were diagnosed histopathologically, including 114 (67.5%) primary and 55 (32.5%) secondary tumors. Out of these 55 secondary cases, 36 were of metastatic brain tumors and 19 cases were of spinal cord metastases. The mean age of the patients was 55±11.0 years. Most of the patients were in the 5th-6th decade of life. Males (n=40) outnumbered females (n=15) with a male to female ratio of 2.6:1. Majority of patients with brain metastases presented with headache (n=17, 47.2%) followed by vomiting (n=12, 33.3%) and seizures (n=7, 19.4%). All the patients with spinal cord metastases presented with backache (100%).

On computed tomography (CT) scan and magnetic resonance imaging, most of the cases encountered were single lesions (92%). Ill-defined lesions (80%) with ring enhancement were more commonly encountered than well-defined (20%) and multiple lesions (8%). Imaging characteristics were enhancement, perilesional edema, nodule or mass and space occupying solid and cystic lesion in 36.3% (n = 20), 25.4% (n = 14), 23.7% (n = 13), and 14.6% (n = 8) of cases, respectively. The most common site for metastases in CNS was cerebrum (n=30, 54.5%) (frontal>temporal> frontoparietal>parietooccipital) followed by spinal cord (n=19, 34.5%) and cerebellum (n=6, 11%) respectively. Right cerebral hemisphere was more commonly involved than left side.

On histopathological examination, most common histological tumor type identified irrespective of site was adenocarcinoma (n= 36, 65.5%), followed by poorly differentiated carcinoma (n=11, 20%) and squamous cell carcinoma (n=7, 12.7%). Only one case of metastatic sarcoma (1.8%) was reported in spinal region. Amongst all the 55 CNS metastases, lung was found to be the most common site of primary malignancy (n=16, 29%) followed by kidney (n=7, 12.7%), prostate (n=6; 10.9%), 4 cases each (7.2%) from breast, colon and thyroid, 2 cases each (3.6%) from esophagus, ovary and urinary bladder and one case from pancreas (1.8%). In seven cases (12.7%), the primary site of malignancy could not be determined even on application of immunohistochemistry. Among 19 cases of spinal metastases, 4 cases (21%) each were from prostate, kidney and lung, 2 cases (10.5%) each of metastases from colon and thyroid and 3 (15.7%) cases of PD Ca with unknown primary.

The lung was the most common site of primary in both men and women. Adenocarcinoma (n=6, 40%) of the lung was the most common subtype followed by squamous cell carcinoma (n=5, 33.3%) and poorly differentiated carcinoma (n=4, 26.7%). Out of the six cases of adenocarcinoma, one was reported as mucinous adenocarcinoma. There was no case of neuroendocrine tumor of the lung as a source of CNS metastases. One case of metastatic sarcoma in spinal cord was diagnosed as undifferentiated pleomorphic sarcoma, not otherwise specified (UPS, NOS) on lung biopsy. **Figure 1**a shows metastatic squamous cell carcinoma from lung.

Seven cases of CNS metastases were from renal cell carcinoma (RCC), all of them had clear-cell RCC histomorphology. Out of these 7 cases, 5 tumors were WHO/ISUP grade 3 and two were WHO/ISUP grade 4. In cases of prostate cancer, Gleason score ranged from 7 to 9. Among the six cases of prostatic adenocarcinoma, 3 (50%) patients had Gleason score 9 (Gleason pattern 4+5 or 5+4), two (33.3%) patients had Gleason score 8 (Gleason pattern 4+4) and one (16.7%) patient had Gleason score 7 (Gleason pattern 3+4).

All four cases of breast metastases were invasive breast carcinoma, no- special type (NST) on histology, three being grade III tumors (75%) and one grade II (25%) according to the modified Bloom Richardson Scoring system. Half of the cases (n = 2) were triple negative, 25% (n = 1) were ER, PR positive and HER2 negative and 25% (n = 1) were ER, PR negative and HER2 positive.

Follicular carcinoma of thyroid was the histological subtype reported in all cases (n=4) of metastases from thyroid malignancy. All the four cases showed characteristic morphologic features, precluding the need of immunohistochemistry. Two (3.6%) cases of metastases of oesophageal squamous cell carcinoma to brain were encountered. In patients with CNS metastases from colon, adenocarcinoma was reported as the only subtype. Both the cases of metastatic ovarian carcinoma exhibited morphological features of high grade serous carcinoma. (**Figure 1**b)

We encountered two unique cases of intracranial metastases from urothelial carcinoma. The tumor cells were strongly immunoreactive for CK7 and CK20 and showed nuclear immunoreactivity for GATA3. The combined morphologic features and IHC findings were consistent with metastatic urothelial carcinoma. (**Figure 1**c-f)

Histopathologically, 11 cases were poorly differentiated carcinoma, out of which the primary site could be determined in 4 (36.4%) cases, all of them being metastases from lung. In seven cases of metastatic poorly differentiated carcinoma, primary site could not be identified. **Figure 2** shows a case of metastatic adenocarcinoma with unknown primary. On IHC, the tumor cells were positive for CK7 and TTF-1, and were negative for CK20, WT1, GATA-3. The case was reported as metastatic adenocarcinoma from lung.

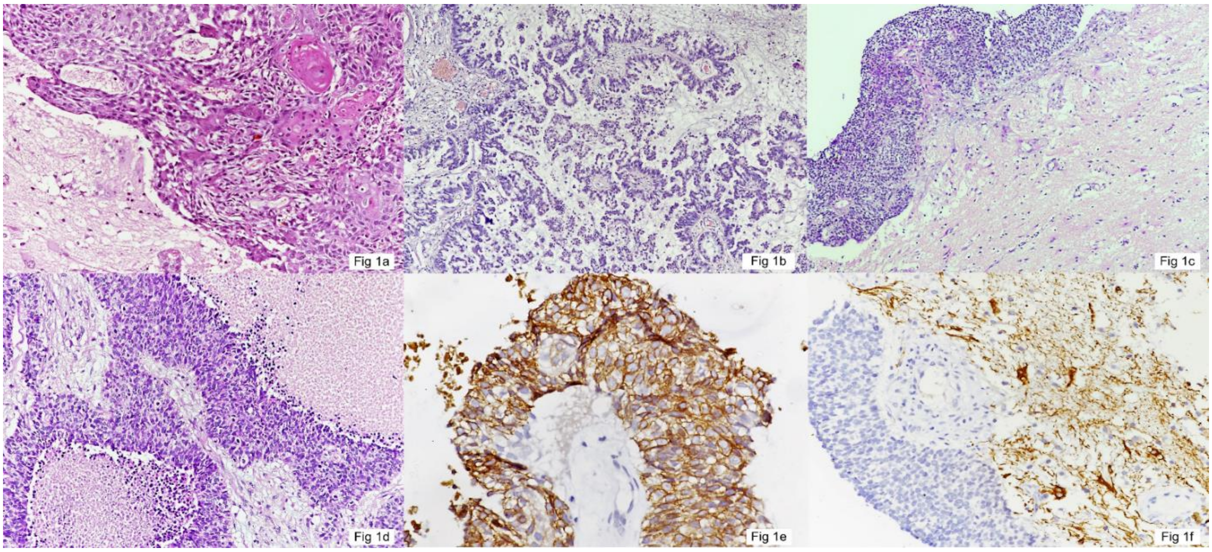

Figure 1: a): Brain metastasis from a case of squamous cell carcinoma of lung (H&E, x 200). **b):** Metastatic tumor arranged in papillary pattern from a case of high grade serous carcinoma of ovary (H&E, x 200). **c):** Metastatic tumor deposits in brain from a case of urothelial carcinoma (H&E, x 100). **d):** Higher magnification showing high grade cytological features and areas of necrosis in metastatic urothelial carcinoma (H&E, x 200). **e):** Tumor cells positive for CK 20 in metastatic urothelial carcinoma (x 200). **f):** GFAP positivity in underlying glial tissue, tumor cells are negative (x 200)

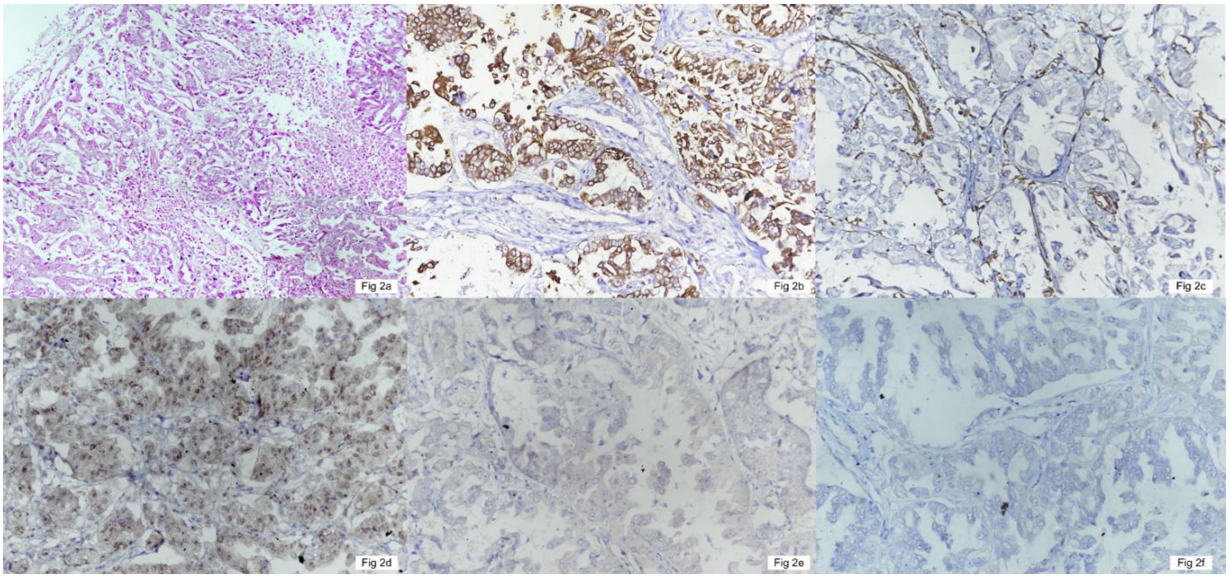

Figure 2: Metastatic adenocarcinoma with unknown primary. **a):** Tumor cells are arranged in a glandular pattern (H&E, x 200); **b)**: Tumor cells showing membranous positivity with CK7 (x 200); **c)**: Tumor cells negative for Vimentin (x 200); **d)**: Tumor cells showing nuclear positivity with TTF-1(x 200); **e):** Tumor cells negative for CK20 (x 200); **f):** Tumor cells negative for GATA 3 (x 200)

Table 1: Histopathological diagnoses and corresponding primary sites of CNS metastases

Primary	Metastatic adenocarcinoma (n=36)	Metastatic squamous cell carcinoma (n=07)	Poorly differentiated carcinoma (n=11)	Sarcoma (n=1)	Total (n=55)
Lung	06	05	04	01	16
Kidney	07				07
Prostate	06				06
Breast	04				04
GIT	04				04
Thyroid	04				04
Esophagus		02			02
Ovary	02				02
Bladder	02				02
Pancreas	01				01
Unknown			07		07

On follow- up of all the patients, we observed that most of the patients died within 5 years of diagnosis of CNS metastases. But patients with lung cancer CNS metastases died earlier, i.e., within 2 years.

4. Discussion

Metastases in CNS can be seen in cerebral hemispheres (80%), cerebellum (10-15%), brain stem (2-3%), spinal cord, dura mater, leptomeninges, pituitary gland, and choroid plexus.[9,10] The route of metastasis to CNS could be hematogenous dissemination or by direct extension of primary solid tumors.[9-11] Majority of hematogenous CNS metastases reach the brain either through arterial circulation or by Batson venous plexus. Ten to 50% of patients with systemic malignancy develop brain metastases during the course of their disease, being four times more common than primary brain tumors in adults.[6,12] Metastases to the spine can involve the vertebrae, epidural space, leptomeninges, and spinal cord. The spine is the third most common site for metastatic disease, following the lung and the liver.[13,14]

The present study analysed the clinical, radiological and pathological profile of metastatic CNS tumors presenting at a tertiary care hospital in North India. In 12 cases (21.8%) diagnosed histopathologically as metastases, the clinical diagnosis was discordant with histopathological diagnosis. Discrepancies were observed in 8 (22.2%) cases of brain metastases and 4 (21.0%) cases of spinal metastases, clinical diagnosis being either glioblastoma (n=4, 7.2%) or tuberculosis (n=8, 14.5%). On radiological findings, 2 cases (3.6%) with well-defined hypointense lesions and peripheral oedema reported as tuberculoma, turned out to be metastatic lesions on histopathological examination. These findings were in concordance with previously published study by Pekmezci M et al[15] which showed that metastases might be misinterpreted as glioblastoma, notably in cases with a solitary lesion and in absence of a known primary.

According to the literature, lung is the most common site of primary resulting in CNS metastases. Among the epithelial lung tumors, small-cell lung cancer (SCLC) is more likely to metastasize to the CNS than non-small cell lung cancer (NSCLC). Adenocarcinoma more commonly metastasizes to the brain than squamous carcinoma among the NSCLC.[1,7] A panel of immunohistochemical markers including cytokeratins (CK7 and CK20), Napsin A and TTF-1 is quintessential for the diagnosis of metastatic deposits from lung adenocarcinoma. Occurrence of CNS metastases from adenocarcinoma of lung may be explained by a plethora of factors, most important of which is aggressive biological behavior. The distribution of CNS metastases also differs according to the genetic composition of lung cancer. Patients with mutant EGFR had a higher frequency of brain metastasis than those with wild-type EGFR.[16,17] In our study, adenocarcinoma of the lung was the most commonly observed followed by squamous cell carcinoma. However, we did not observe any case of metastatic small cell carcinoma. This was consistent with previously reported data regarding the propensity of lung cancer to metastasize to the CNS.[17,18] Out of 15 cases, 11 cases could be followed up with a survival rate ranging from 5 months to 2.8 years.

Renal cell carcinoma is the most common renal malignancy. CNS metastases are observed in about 6.5% cases of RCC at the time of initial presentation and first diagnosis.[19] Vertebral metastases occur in an even higher percentage (~30%) of patients with RCC.[20] The likelihood of developing CNS metastases is believed to be associated with the nuclear grade of the tumor. Expression of certain chemokines and chemokine receptors such as CCL7, CCR2 and CXCR4 result in increased vascular permeability with subsequent disruption of blood brain barrier, contributing to brain metastases of RCC.[20,21] All the cases of metastatic RCC in this study had a high WHO/ISUP nuclear grade (either 3 or 4).

Patients with HER-2 positive and triple negative (ER, PR, HER-2 negative) breast cancers are more likely to develop brain metastases.[22] Triple negative breast cancers have an even higher rate of CNS metastases as compared to HER2 positive cancers. This might be explained by the disruption of blood–brain barrier due to expression of Glut1 and BCRP in cerebral vessels.[23] We had four cases of metastatic breast carcinoma. Among these patients, 50% were triple negative, 25% were HER2-positive, and 25% were hormonal receptor negative. These findings are in agreement with other studies. However, the incidence of breast metastases to CNS was 7.2% in our study, which was less as compared to other studies.[24] The explanation for the lower frequency of breast metastases in our study may be the fact that in developing countries, women with advanced disease seldom visit hospitals for treatment. Out of 4 cases, 3 patients came for follow up, out of which one patient died within three months and two patients tolerated treatment well and are alive.

CNS metastases from urothelial cancer are exceedingly rare, accounting for approximately 1% to 7%.[25,26] The most common sites for metastases are lymph nodes, liver, lung, bone, and adrenal gland. UCs are often associated with a poor prognosis. Up to19% of patients with UC have been reported to present initially with metastatic disease.[27] On follow up, one of patient did well for approximately 5 months while the other one died within 2 months after diagnosis of metastases. We did not encounter any case CNS metastasis from melanoma and the conspicuous absence of melanoma in our study could be due to low incidence of melanoma in our population.

5. Source of Funding

None.

6. Conflict of Interest

None.

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