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Original Article

Clinicopathological Profile and Immunohistochemical Evaluation of Metastatic Central Nervous System Lesions

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ABSTRACT

Background: Metastatic tumours are the most common intracranial neoplasms in adults. Histopathological examination, supplemented by immunohistochemistry (IHC), is essential for confirming the diagnosis and identifying the primary tumour, particularly in patients presenting with metastatic lesions of unknown origin.

Objectives: To evaluate the clinical, histopathological, and immunohistochemical characteristics of metastatic deposits in the central nervous system (CNS) and correlate them with the primary site of malignancy.

Materials and Methods: This prospective observational study included 30 histopathologically confirmed cases of metastatic CNS tumours diagnosed between October 2015 and September 2017 at a tertiary care centre. Clinical presentation, radiological findings, histopathological features, and immunohistochemical profiles were analysed. IHC was performed in selected cases to establish the primary tumour origin when routine histopathology was inconclusive.

Results: Most patients belonged to the 50–59-year age group (46.7%), with a male predominance (63.3%). Solitary lesions constituted 70% of cases, and the parietal lobe was the most frequently involved site. Headache was the commonest presenting symptom. Histopathological examination showed adenocarcinoma (73.3%) as the predominant subtype, followed by poorly differentiated carcinoma (16.7%) and squamous cell carcinoma (10.0%). The lung (50%) was the most common primary site, followed by the gastrointestinal tract (13.3%). Immunohistochemistry was useful in identifying the primary tumour in diagnostically challenging cases and in patients with no known primary malignancy.

Conclusion: Histopathological examination combined with immunohistochemistry is invaluable in the diagnosis and characterization of metastatic CNS tumours. Integration of clinical, radiological, histopathological, and immunohistochemical findings improves identification of the primary tumour and facilitates appropriate patient management.

Keywords: *Brain metastasis; Central nervous system; Histopathology; Immunohistochemistry; Adenocarcinoma; Metastatic tumour.*

INTRODUCTION

Brain metastases are the most common intracranial neoplasms in adults and represent a major cause of cancer-related morbidity and mortality.(1) They occur in approximately 20–40% of patients with systemic malignancies.(2) Advances in systemic cancer therapy, improved patient survival, and widespread use of modern neuroimaging have contributed to the increasing incidence of brain metastases worldwide.(3)

The lung is the most frequent primary site of brain metastases, followed by breast carcinoma, malignant melanoma, colorectal carcinoma, and renal cell carcinoma.(4) Although many patients have a known history of malignancy, brain metastasis may occasionally be the first manifestation of an occult primary tumour.(5) Accurate identification of the primary site is essential because treatment strategies, targeted therapies, and prognosis differ according to the tumour of origin.(6)

Patients with metastatic brain tumours commonly present with headache, vomiting, seizures, focal neurological deficits, altered sensorium, and visual disturbances resulting from raised intracranial pressure or involvement of eloquent brain regions.(1) Contrast-enhanced magnetic resonance imaging (MRI) is highly sensitive for detecting metastatic lesions.(7) However, radiological findings alone are often insufficient to differentiate metastatic tumours from high-grade gliomas, primary CNS lymphomas, or other intracranial lesions.(8)

Histopathological examination remains the gold standard for confirming metastatic deposits in the central nervous system.(9) Routine haematoxylin and eosin staining permits classification of metastatic lesions into adenocarcinoma, squamous cell carcinoma, melanoma, lymphoma, sarcoma, or poorly differentiated carcinoma.(10) Nevertheless, morphology alone may not accurately identify the primary site, particularly in poorly differentiated tumours or metastatic lesions of unknown primary origin.(11)

Immunohistochemistry (IHC) has become an indispensable adjunct in the evaluation of metastatic CNS tumours by improving diagnostic accuracy and facilitating identification of the primary site.(12) A systematic immunohistochemical approach using cytokeratin markers (CK7 and CK20), followed by organ-specific markers such as thyroid transcription factor-1 (TTF-1), CDX2, PAX8, GATA3, mammaglobin, GCDFP-15, HMB-45, Melan-A, S-100, CD45, and glial fibrillary acidic protein (GFAP), significantly improves diagnostic precision.(13) Such an approach is particularly valuable in patients presenting with metastatic brain lesions without an identifiable primary tumour.(14)

An integrated clinicopathological evaluation combining clinical history, radiological findings, histopathology, and immunohistochemistry is therefore essential for the accurate diagnosis of metastatic brain lesions.(15) This multidisciplinary approach not only differentiates metastatic lesions from primary CNS tumours but also facilitates early identification of the primary malignancy, guides site-specific therapy, and minimizes unnecessary diagnostic investigations.(16)

Although several studies have described the clinicopathological spectrum of metastatic brain tumours, regional variations in the pattern of primary tumours and immunohistochemical expression continue to exist.(17) Furthermore, Indian data correlating clinical presentation, histopathological findings, and immunohistochemical profiles remain limited.(18) Therefore, the present study was undertaken to evaluate the clinicopathological features of metastatic deposits in the central nervous system, differentiate metastatic lesions from primary CNS tumours using histopathology and immunohistochemistry, and analyse the spectrum of primary tumours responsible for CNS metastases.

MATERIALS AND METHODS:

Study design and setting

This prospective observational study was conducted in the Department of Pathology, Osmania General Hospital, Hyderabad, Telangana, over a period of two years from October 2015 to September 2017. The study included patients with metastatic deposits involving the central nervous system (CNS) who underwent neurosurgical excision or biopsy.

Study population

A total of 30 histopathologically confirmed cases of metastatic CNS lesions were included in the study. Clinical details, demographic characteristics, radiological findings, and histopathological features were obtained from patient records and correlated with immunohistochemical findings.

Inclusion criteria

- All surgically excised or biopsied CNS lesions diagnosed histopathologically as metastatic deposits.

Exclusion criteria

- Primary brain tumours.
- Infectious lesions of the central nervous system.

Clinical and radiological evaluation

Clinical information, including age, sex, presenting symptoms, previous history of malignancy, radiological findings, and anatomical location of the lesion, was recorded for all patients. Radiological evaluation included assessment of lesion number (single or multiple) and intracranial location based on available neuroimaging findings.

Histopathological examination
Resected specimens and biopsy samples were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin wax. Sections of 4–5 µm thickness were prepared and stained with haematoxylin and eosin (H&E). Histopathological examination was performed to establish the diagnosis and classify metastatic tumours according to their morphological characteristics.

Immunohistochemical analysis
Immunohistochemistry (IHC) was performed in selected cases where histomorphology alone was insufficient to identify the primary tumour or when confirmation of tumour origin was required. Four-micrometre-thick paraffin sections mounted on poly-L-lysine-coated slides were subjected to heat-induced antigen retrieval followed by immunostaining according to standard laboratory protocols. Appropriate primary antibodies were selected based on the histomorphological features and differential diagnosis. The immunohistochemical findings were interpreted in conjunction with clinical history, radiological findings, and routine histopathology to determine the probable primary site of metastatic lesions.

Statistical analysis
The collected data were entered into Microsoft Excel and analysed using descriptive statistics. Continuous variables were expressed as mean ± standard deviation where appropriate, whereas categorical variables were presented as frequencies and percentages. The results were summarized using tables and charts.

RESULTS:
A total of 30 patients with histopathologically confirmed metastatic deposits of the central nervous system were included in the study. Most patients belonged to the 50–59-year age group (46.7%), followed by the 60–69-year age group (30.0%). Patients younger than 40 years constituted only a small proportion of the study population. (Table 1)

Table 1. Age distribution of patients (n = 30)

Age group (years)	Number	Percentage (%)
10–19	1	3.3
20–29	1	3.3
30–39	2	6.7
40–49	3	10.0
50–59	14	46.7
60–69	9	30.0

Male patients predominated, accounting for **63.3%** of cases, with a male-to-female ratio of approximately **1.7:1**. (Table 2)

Table 2. Sex distribution

Sex	Number	Percentage (%)
Male	19	63.3
Female	11	36.7

Single intracranial metastatic lesions were more common than multiple lesions, comprising **70.0%** of the study population. (Table 3)

Table 3. Radiological distribution of lesions

Type of lesion	Number	Percentage (%)
Single	21	70.0
Multiple	9	30.0

The majority of patients (**76.7%**) had **no previous history of malignancy**, and the brain lesion represented the first clinical manifestation requiring further evaluation. (Table 4)

Table 4. Previous history of malignancy

Previous history	Number	Percentage (%)
Present	7	23.3
Absent	23	76.7

The **parietal lobe** was the most frequently involved site (30.0%), followed by the **frontal lobe** (26.7%). Cerebellar and occipital metastases were relatively uncommon. (Table 5)

Table 5. Anatomical distribution of metastatic lesions

Site	Number	Percentage (%)
Parietal	9	30.0
Frontal	8	26.7
Temporal	5	16.7
Temporoparietal	5	16.7

Frontotemporal	3	10.0
Cerebellum	3	10.0
Occipital	1	3.3

Headache was the most common presenting symptom (66.7%), followed by **vomiting** (53.3%). Neurological deficits and seizures were also frequently observed. (Table 6)

Table 6. Clinical presentation

Clinical feature	Number	Percentage (%)
Headache	20	66.7
Vomiting	16	53.3
Neurological deficit	10	33.3
Seizures	9	30.0
Visual symptoms	5	16.7

Adenocarcinoma was the predominant histopathological subtype, accounting for **73.3%** of metastatic CNS lesions. (Table 7)

Table 7. Histopathological diagnosis

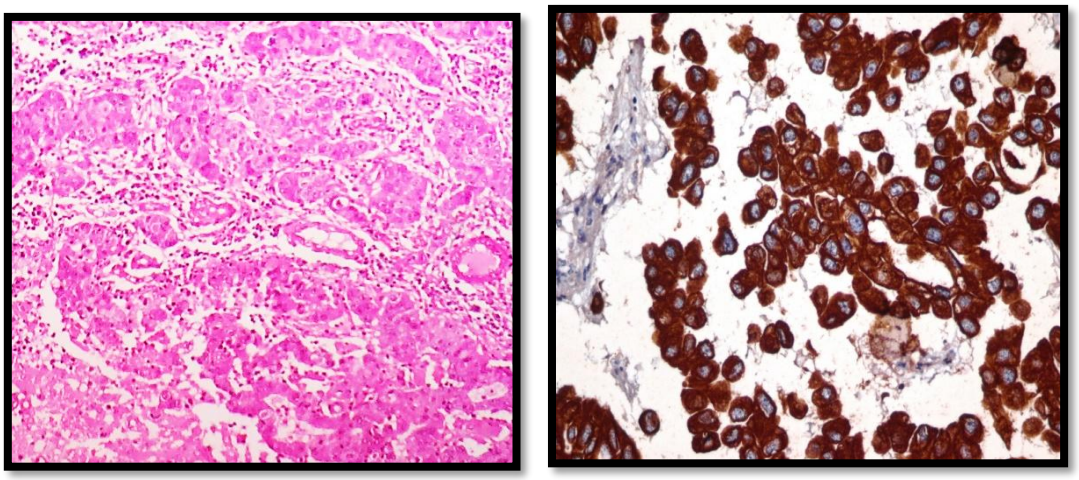
Histopathological diagnosis	Number	Percentage (%)
Adenocarcinoma	22	73.3
Poorly differentiated carcinoma	5	16.7
Squamous cell carcinoma	3	10.0

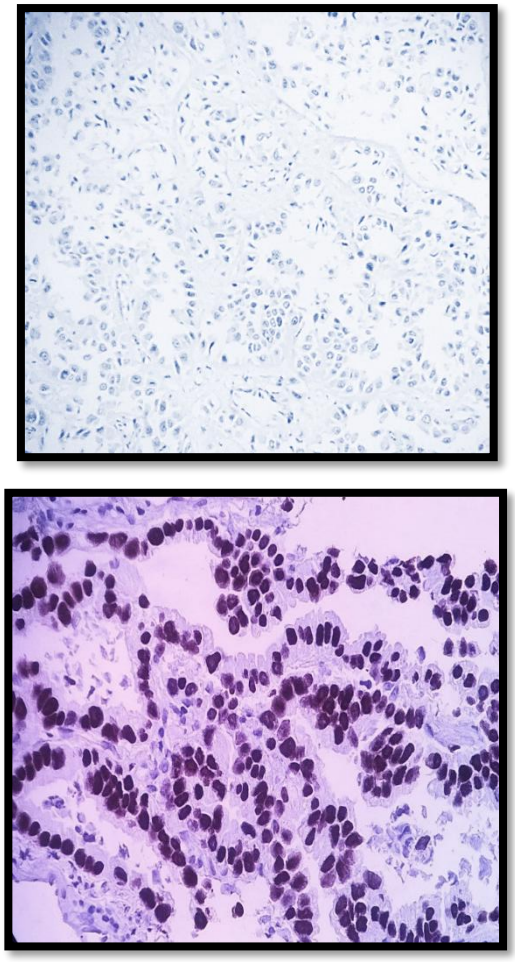
The **lung** was the most common primary site, accounting for **50.0%** of all metastatic CNS lesions. Gastrointestinal malignancies were the second most frequent primary site (13.3%). Despite histopathological examination and immunohistochemical evaluation, the primary tumour remained unidentified in **6.7%** of cases. (Table 8)

Table 8. Primary site of metastatic tumour

Primary site	Number	Percentage (%)
Lung	15	50.0
Gastrointestinal tract	4	13.3
Breast	2	6.7
Thyroid	2	6.7
Cervix	2	6.7
Kidney	1	3.3
Palate	1	3.3
Malignant melanoma	1	3.3
Unknown primary	2	6.7

Fig 1: METASTATIC DEPOSITS OF LUNG ADENOACARCINOMA





DISCUSSION:

Brain metastases are the most common intracranial tumours in adults and continue to pose significant diagnostic and therapeutic challenges. Accurate identification of the primary tumour is essential because treatment strategies and prognosis vary according to the site of origin. In the present study, clinicopathological findings were correlated with immunohistochemistry to characterize metastatic CNS lesions and identify their primary source.

The majority of patients were in the fifth and sixth decades of life, with the highest incidence observed in the 50–59-year age group (46.7%). Similar age distributions have been reported by Nayak et al., who observed that brain metastases occur predominantly in middle-aged and elderly individuals because of the higher incidence of systemic malignancies in these age groups.(19) Schouten et al. also reported a peak incidence between the fifth and seventh decades of life.(20)

A male predominance (63.3%) was observed in the present study, which is consistent with previous reports.(20,21) This finding is largely attributable to the higher prevalence of lung carcinoma among males, which was also the commonest primary tumour identified in our series.

Headache was the most frequent presenting symptom, followed by vomiting, focal neurological deficits, and seizures. These findings are comparable with those reported by Achrol et al., who described headache and focal neurological deficits as the predominant manifestations of metastatic brain tumours.(21) Most patients presented with symptoms related to raised intracranial pressure or tumour location rather than symptoms of the primary malignancy.

Radiologically, 70% of patients had solitary lesions, while multiple lesions were observed in 30%. Although multiple metastases are generally considered more common, several surgical series have reported a predominance of solitary lesions because patients with single accessible lesions are more likely to undergo surgical excision and histopathological evaluation.(22) In the present study, the parietal lobe was the most frequently involved intracranial site, followed by the frontal lobe, which is in agreement with the predilection of metastatic deposits for the cerebral hemispheres due to their abundant vascular supply.(23)

Histopathological examination revealed that adenocarcinoma (73.3%) was the predominant metastatic tumour, followed by poorly differentiated carcinoma and squamous cell carcinoma. This observation is consistent with previous studies

reporting adenocarcinoma as the commonest histological subtype because of the high frequency of pulmonary adenocarcinoma and gastrointestinal adenocarcinoma metastasizing to the brain.(24)

Immunohistochemistry played an important role in identifying the primary site, particularly in poorly differentiated tumours and in patients without a known history of malignancy. The use of organ-specific markers in conjunction with histomorphology enabled accurate classification of most metastatic lesions. Similar observations have been reported by Bishop et al., who emphasized that a panel-based immunohistochemical approach substantially improves the diagnostic accuracy of metastatic tumours of unknown primary origin.(25)

In the present study, the lung was the commonest primary site (50%), followed by gastrointestinal malignancies, while breast, thyroid, and cervical carcinomas contributed smaller proportions. These findings are comparable to those reported in large epidemiological studies, which consistently identify lung carcinoma as the leading source of brain metastases.(20,26) Despite detailed clinicopathological assessment and immunohistochemistry, the primary tumour remained unidentified in a small proportion of cases, reflecting the diagnostic challenges associated with metastatic tumours of unknown primary origin.(27)

CONCLUSION:

Metastatic CNS tumours predominantly affected middle-aged and elderly patients, with adenocarcinoma being the most common histological subtype and the lung the leading primary site. Histopathological examination, complemented by immunohistochemistry, proved valuable in identifying the primary tumour and differentiating metastatic lesions from primary CNS neoplasms. A multidisciplinary clinicopathological approach enhances diagnostic accuracy and supports appropriate patient management.

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