Metastasis in central nervous system: Clinicopathological study with review of literature in a tertiary care center in South India

Rashmi Patnayak, Amitabh Jena[1], Bodagala Vijaylaxmi[2], Amancharla Y. Lakshmi[2], BCM Prasad[3], Amit Kumar Chowhan, N. Rukmangadha, Bobbit V. Phaneendra, Mandyam Kumaraswamy Reddy

Abstract

Background: Secondary central nervous system (CNS) tumors are common in Western countries, but in Indian literature, scant data are available. With the advent of newer imaging techniques, the confirmatory histopathological diagnosis has become comparatively easier. Hereby, we have analyzed our data from a single tertiary care center in south India. **Materials and Methods:** In this retrospective study from January 2000 to December 2010, histopathologically diagnosed secondary CNS tumors were reviewed along with clinical, imaging, and relevant immunohistochemical findings. Meningeal, lymphoproliferative, and myeloproliferative tumors and autopsy data were not included in the study group. **Results:** There were 40 secondary CNS tumors. Male to female ratio was 2.3:1. Age range was wide (28-75 years). Majority of cases were seen in the fourth and fifth decade. Imaging-wise, (computed tomography and magnetic resonance imaging) majority were single lesions ($n = 34, 85\%$). Most commonly, these single lesions were present in the cerebral hemisphere ($n = 20, 50\%$) followed by cerebellum ($n = 10, 25\%$). Adenocarcinoma accounted for maximum number of cases ($n = 25, 62.5\%$) with lungs being the most common primary. **Conclusion:** We have noted 25% metastatic adenocarcinomas in cerebellar location, which is higher when compared with available world literature. However, we also encountered a good number of cases (30%) due to unknown primary. Though histopathological examination with use of immunohistochemical markers can reliably distinguish primary from secondary CNS tumors in addition to available clinical and imaging data, particularly in developing countries, still a better work-up with an array of immunohistochemical markers and newer imaging modalities is desirable.

Key words: Immunohistochemistry, metastasis, pathology, secondary central nervous system tumors

Introduction

In Western literature, brain metastases vastly outnumber primary brain tumors.[1] Worldwide, lung cancer, breast cancer, and melanoma account for majority of brain metastases from primary tumors.[2] Brain metastases significantly contribute to the morbidity and mortality of patients with solid tumors, despite the brain's reputation as a site with a very low rate of metastases. Tumor interactions with the blood–brain barrier, microglia, and various matrix proteins, cytokines, and growth factors play a central role in brain metastasis.[3] Though various models have been proposed over the years to explain how the tumors metastasize to central nervous system (CNS), yet till now the exact molecular mechanism remains unknown.[4,5] Recent standard modes of treatment for brain metastases include surgical resection, whole brain radiation therapy (WBRT) or combined radio-surgical procedures.[6] For metastatic malignant melanoma cases, recently, it has been hypothesized that BRAF-mutation positive patients may benefit from ipilimumab.[7] We have analyzed the secondary CNS tumors with respect to clinical, imaging, and histopathological data including relevant immunohistochemistry (IHC) from a single institution in south India.

Materials and Methods

In this retrospective study from January 2000 to December 2010, all cases diagnosed histopathologically as secondary CNS tumors were retrieved from the computerized hospital information system (HIS). Lymphoproliferative, myeloproliferative, and meningeal tumors were not included in the study group. These tumors were reviewed with clinical and imaging findings from medical records. Routine hematoxylin and eosin (H and E) stained sections of formalin fixed paraffin embedded tissue were reviewed in all cases. Depending on the histopathological findings, the immunohistochemical markers used for different cases included glial fibrillary acidic protein (GFAP), cytokeratin (CK), epithelial membrane antigen (EMA), synaptophysin, chromogranin, neuron specific enolase (NSE), HMB-45, leukocyte common antigen (LCA), β-human chorionic gonadotropin (HCG), estrogen receptor (ER), progesterone receptor (PR), and prostate-specific antigen (PSA). GFAP and epithelial markers (EMA, CK) were used in those tumors where the differential diagnoses were between

Departments of Pathology, [1]Surgical Oncology, [2]Radiology, [3]Neurosurgery, Sri Venkateswar Institute Of Medical Sciences, Tirupati, Andhra Pradesh, India

Correspondence to: Dr. Rashmi Patnayak,
E-mail: rashmipatnayak2002@yahoo.co.in

primary tumor of glial origin and metastases. Markers like synaptophysin, chromogranin, and NSE were used to demonstrate neuro-endocrine differentiation. LCA was used to exclude tumors of lymphoid origin. HMB-45, PSA, HCG, ER, and PR were used to confirm diagnosis of specific tumors.

IHC was done on three micron paraffin sections on 3-amino propyl ethoxy silane (APES) coated slides, using prediluted antibodies, with known positive controls by polymer horse radish peroxidase (HRP) IHC detection system, using manufacturer's instructions. All the markers were from BioGenex. The slides were stained with 3, 3′-diaminobenzidine tetra hydrochloride (DAB) chromogen, counterstained with hematoxylin and mounted.

Data from autopsy have not been included in this study.

This study mainly involves the histopathology review of the paraffin blocks submitted to the department of pathology. The patients and their relatives have given consent to utilize the information for publication purpose as noted from the standard case sheet record obtained from the medical records department. As the study had no intervention other than standard care, we have not obtained permission from the institutional review board.

Results

In the study period, 40 secondary CNS tumors were encountered. Male to female ratio was 2.3:1. Age range was wide (28-75 years). Majority of cases were seen in the fourth and fifth decades. Most of the patients presented with symptoms of increased intracranial pressure. On imaging, (computed tomography and magnetic resonance imaging) most of the cases encountered were single lesions (*n* = 34, 85%). These single lesions were most commonly present in the cerebral hemisphere (*n* = 20, 50%) followed by cerebellum (*n* = 10, 25%) [Table 1]. All the cases with multiple lesions were adenocarcinomas (*n* = 6). Overall, adenocarcinoma accounted for the maximum number of cases (*n* = 26, 65%). After surgical removal of the metastatic lesion, few patients (*n* = 11) opted for further treatment with radio and chemotherapy and for these patients follow-up was available for a period ranging from 2 months to 4 years. Rest of the patients refused further treatment due to financial constraints.

Discussion

The most common mass lesions in the brain are metastatic tumors. Brain metastasis commonly takes its origin from systemic cancers of the lung, breast, skin, or colorectum. Primary lung tumors account for 50% of all metastatic brain tumors.[2,7,8] Melanoma is the most common malignant tumor with high propensity to metastasize to brain.[7] Metastases in CNS can be seen in cerebral hemispheres (80%), cerebellum (10-15%), brain stem (2-3%), spinal cord, bones, dura mater, leptomeninges, pituitary, and choroid plexus. Metastases in cerebellum are commonly from colorectal, uterine, and renal carcinomas.[8-10] The spinal epidural metastases most commonly are from the prostate, breast, lung, and kidney.[11] Metastases usually manifest as late presentation of a primary tumor. Nevertheless they may occur when systemic disease is still not apparent.[4] The route of metastasis to CNS may be both by hematogenous dissemination and by direct extension of primary solid tumors.[7,8,9,10,11] The majority of CNS metastases usually reach the brain either through arterial circulation or via Batson venous plexus. The great majority of metastatic deposits are present in the supratentorial or infratentorial brain compartments owing to their volume and blood supply. In the cerebrum, most of the lesions are found in the frontoparietal cerebral tissue, which is supplied by the middle cerebral artery.[3]

The neurological signs and symptoms described in patients with intracranial metastases are usually attributed to increased intracranial pressure or local effect of the tumor on the adjacent brain tissue. These signs and symptoms in variable degrees were noted in the medical case records of nearly all the cases included in our study.

Cells with similar embryologic origins generally express similar sets of adhesion molecules. Melanoma cells are closely related to CNS cells due to their embryonic origin and they share common antigens. Approximately 40-60% of patients with melanoma will have brain metastases. Certain metastatic suppressor genes like nm23 and CD44 play an important role in CNS metastasis of malignancies like melanoma, breast cancer, etc.[6] In addition, several clinical trials have shown that breast cancers that are – Her-2 positive have a greater tendency to metastasize to brain.[3,12,13]

Table 1: Distribution and types of single metastatic lesions (*n*=34)

Location	Types												
	Primary site												
Cerebral hemisphere *n*=20	Adenocarcinoma					Squamous cell carcinoma			NEC	MM	Germ cell		Undifferentiated
	Lungs	Thyroid	Prostate	GB	Unknown	Lungs	ES	Unknown	Lungs	Skin	Testis	Chorio carcinoma	
	3	1	1		3	1	1	3	1	2		1	3
Cerebellum *n*=10	4				5							1	
Spine *n*=4	2			1				1					

NEC=Neuro-endocrine carcinoma, MM=Malignant melanoma, GB=Gall bladder, ES=Esophagus

Metastatic disease from the breast, thyroid, renal, and colon carcinoma are more commonly found as a single metastatic lesion, whereas metastatic disease from lung cancer and melanoma are more commonly multiple lesions.[3] In the present study, most of the cases encountered were single lesions on imaging studies (85%) [Figure 1].

In our study, we found cerebral hemispheres to be the most common locations for single lesions (*n* = 20, 50%) followed by cerebellum (*n* = 10, 25%). Adenocarcinoma accounted for maximum number of cases (*n* = 26, 65%) followed by squamous carcinomatous metastasis (*n* = 6, 15%).

Compared with the world literature, our study showed comparatively higher cerebellar location of brain metastases. All the cases of cerebellar metastases were histopathologically diagnosed as adenocarcinoma. In one case, the primary was germ cell tumor of testes and in another case signet ring cell colorectal carcinoma was detected as the primary. In four cases of cerebellar metastasis, primary foci were present in lungs, as demonstrated by imaging modalities. In rest of the cases primary remained unknown.

Similarly in cerebral hemisphere adenocarcinomatous metastases due to unknown primary were nine in number followed by primary in lungs in five cases. In addition, there were cases where the primary was located in thyroid and prostate. Regarding spinal adenocarcinomatous metastases, 50% were from lungs, in one case the primary was in gall bladder and in another, it was of an unknown primary origin. All except one of the squamous carcinomatous metastases were located in the cerebral hemisphere. In four cases the site of the primary tumor was not known. Rest of the cases showed primary in lungs (one case) and esophagus (one case). Metastasis of esophageal squamous cell carcinoma to brain is quite uncommon.[14] In addition, we had cases where breast carcinoma, neuro-endocrine carcinoma and malignant melanoma metastasized to brain [Figure 2]. We also encountered one case of choriocarcinomatous metastasis to brain in a young female [Figures 3 and 4]. She had high β-HCG levels at the time of diagnosis. She later on received 6 cycles of chemotherapy, after which the levels of β-HCG became normal [Table 1].

In our study we had only one case of brain metastasis from breast carcinoma. This needs further study of breast malignancy cases as regarding their tendency to metastasize to different organs. One explanation may be that female patients, particularly with advanced disease, seldom visit hospitals, especially in developing countries.

According to literature, metastases of unknown primary origin accounts for around 3% of cases.[15] Even at autopsy the primary site may not be known always. Because of these reasons immunohistochemical diagnosis of such cases is essential. In most cases of unknown primary CNS metastasis, lung or pancreas are the primary sites.[16]

In our study, we encountered high number of unknown primary cases (*n* = 12, 30%). Out of these, eight were

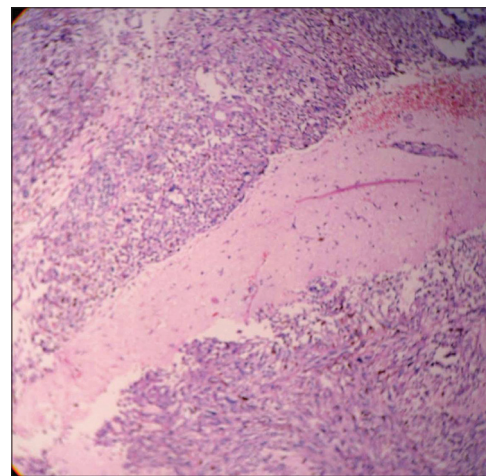**Figure 1:** CT image of single brain metastasis of breast carcinoma

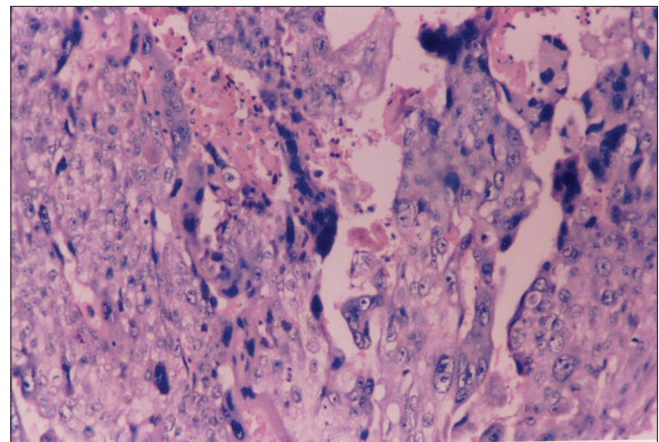**Figure 2:** Metastatic deposits of malignant melanoma (H and E ×20)

Figure 3: Metastatic deposits of choriocarcinoma (H and E ×40)

adenocarcinomas. But in all these cases the routine chest X-ray was normal.

Histopathologically, CNS metastases resemble the primary neoplasm. Usually there is a line of sharp demarcation between reactive neuroglial tissue and metastatic tumors. [Figure 5]. Many a times, it is difficult to determine the primary site of metastatic tumor even on histopathological
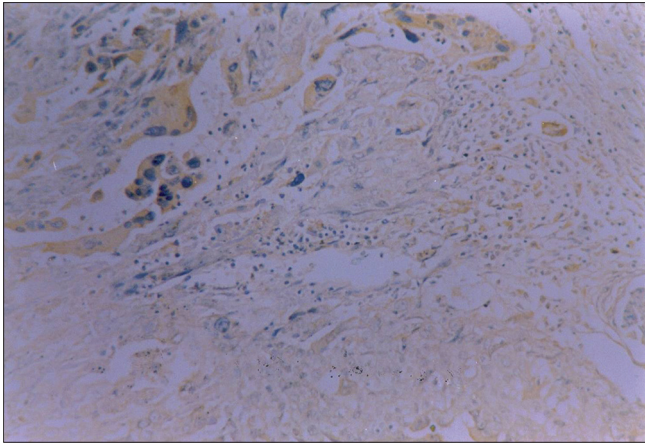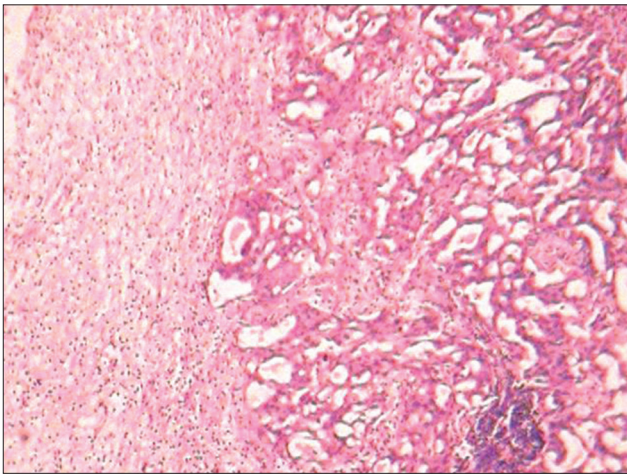
Figure 4: Immunoreactivity for β-HCG (IHC ×40)

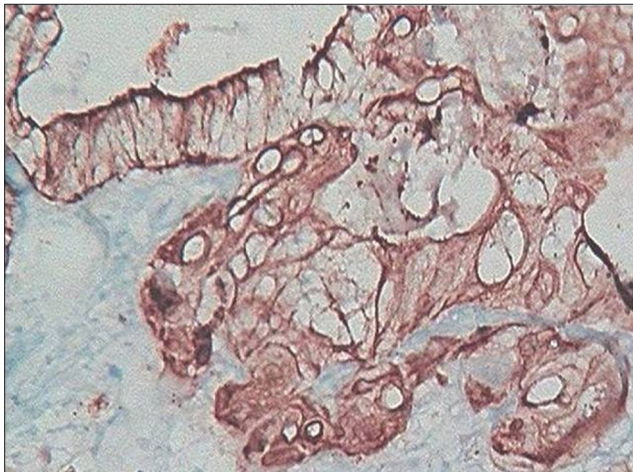**Figure 5: Metastatic adenocarcinomatous deposit with adjacent sharply demarcated brain parenchyma (H and E ×40)**

Figure 6: Metastatic tumor showing strong reactivity to epithelial marker (IHC ×40)

examination. IHC plays an important role in such problematic cases. The common antibodies used to distinguish different tumors are GFAP for glial neoplasms, LCA for lymphoma, CK for metastatic carcinomas, and HMB-45 for melanoma.

—Currently, a number of primary antibodies are available,

which may help in the immunophenotypic diagnosis and identification of different primary sites including the most common sources of brain metastasis like lung, breast, colorectal, renal carcinomas, and melanoma. But cost factors play a role in implementing all these markers, especially in the developing countries.

Many literature data are available regarding the diagnosis of metastatic tumors by immunohistochemical methods.[17,18] However, further evaluation was not possible in our study due to unwillingness of the patients and their attendants and also due to nonavailability of some of the organ specific IHC markers. We have used epithelial markers and GFAP, mainly to distinguish three cases of metastatic epithelial malignancies from poorly differentiated glial neoplasms. In these metastatic cases CK was strongly positive and GFAP was negative [Figure 6]. Synaptophysin, chromogranin, NSE were used for confirmation of neuro-endocrine carcinomas, HMB-45 for melanomas, ER, PR for breast carcinoma, PSA for prostatic carcinoma, and β-HCG for choriocarcinoma.

Cytology also helps in the diagnosis of primary in case of metastatic CNS lesions.[19] In this study, fine needle aspiration cytology of breast and thyroid helped to identify the primary. In one case of adenocarcinomatous metastasis in spine, the pleural effusion revealed metastatic deposits.

We conclude that histopathological examination in addition to available clinical and imaging data can help in the diagnosis of CNS metastatic tumors, especially in developing countries. When feasible, use of a wide array of IHC markers can help to establish the location of the primary tumor.

Acknowledgment

References

1. Patchell RA. The management of brain metastases. Cancer Treat Rev 2003;29:533-40.
2. Johnson JD, Young B. Demographics of brain metastasis. Neurosurg Clin N Am 1996;7:337-44.
3. Subramanian A, Harris A, Piggott K, Shieff C, Bradford R. Metastasis to and from the central nervous system: The 'relatively protected site'. Lancet Oncol 2002;3:498-507.
4. Zhang C, Yu D. Microenvironment determinants of brain metastasis. Cell Biosci 2011;1:8.
5. Fidler IJ. The role of the organ microenvironment in brain metastasis. Semin Cancer Biol 2011;21:107-12.
6. Kamar FG, Posner JB. Brain metastases. Semin Neurol 2010;30:217–35.
7. Ascierto PA, Simeone E, Giannarelli D, Grimaldi AM, Romano A, Mozzillo N. Sequencing of BRAF inhibitors and ipilimumab in patients with metastatic melanoma: A possible algorithm for clinical use. J Transl Med 2012;10:107.
8. Gavrilovic IT, Posner JB. Brain metastases: eEpidemiology and pathophysiology. J Neurooncol 2005;75:5-14.
9. Salvati M, Frati A, Russo N, Brogna C, Piccirilli M, D'Andrea G, *et al.* Brain metastasis from prostate cancer. Report of 13 cases and critical analysis of the literature. J Exp Clin Cancer Res 2005;24:203-7.
10. Nathoo N, Chahlavi A, Barnett GH, Toms SA. Pathobiology of brain metastases. J Clin Pathol 2005;58:237-42.

11. Mut M, Schiff D, Shaffrey ME. Metastasis to nervous system: Spinal epidural and intramedullary metastases. J Neurooncol 2005;75:43-56.
12. Altaha R, Crowell E, Hobbs G, Higa G, Abraham J. Increased risk of brain metastases in patients with HER-2/neu-positive breast carcinoma. Cancer 2005;103:442-3.
13. Mayer M. A patient perspective on brain metastases in breast cancer. Clin Cancer Res 2007;13:1623-4.
14. Almasi S, Bashashati M, Rezaei N, Markazi-Moghaddam N. Brain metastasis from esophageal carcinoma. Neurol India 2004;52:492-3.
15. Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. Arch Neurol 1988;45:741-4.
16. Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeutic management of cancer of unknown primary. Eur J Cancer 2003;39:1990-2005.
17. DeYoung BR, Wick MR. Immunohistologic evaluation of metastatic carcinomas of unknown origin: An algorithmic approach. Semin Diagn Pathol 2000;17:184-93.
18. Drlicek M, Bodenteich A, Urbanits S, Grisold W. Immunohistochemical panel of antibodies in the diagnosis of brain metastases of the unknown primary. Pathol Res Pract 2004;200:727-34.
19. Pomjanski N, Grote HJ, Doganay P, Schmiemann V, Buckstegge B, Böcking A. Immunocytochemical identification of carcinomas of unknown primary in serous effusions. Diagn Cytopathol 2005; 3:309-15.

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