

Brain Metastases: quest on primary site

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Abstract

Background: Secondaries of brain (Brain metastases, BM) are most common central nervous system (CNS) tumors and it may be initial manifestation of systemic malignancies. Histomorphology of brain metastatic tumors along with immunohistochemistry (IHC) will be helpful in the detection of unknown primary site (UPS) of brain metastases. **Aim:** To evaluate unknown primary site of brain metastases with help of immunohistochemistry. **Material and Method:** This study was conducted at the department of onco-pathology of our institute. Five years data from 2014 to 2018 were obtained from online Laboratory Information System (LIS), department of onco-pathology of our institute. IHC was performed on basis of histomorphology. **Results:** Total 128 brain metastatic tumors were retrieved. Of which the present study have applied IHC on 107 cases and in remaining 21 cases, systemic malignancies were already diagnosed. Out of 107 cases, primary site was detected in 92.53% cases (n=99) and in 7.47% cases (n = 8), not able to detect primary site even after IHC. Lung was the most common primary site detected (n = 73) followed Gastrointestinal tract (GIT, n = 9). **Conclusion:** Lung followed by breast are the most common primary malignancies for secondaries of brain (BM). Systemic approach using immunohistochemistry is really helpful in detection of unknown primary site of secondaries of brain (BM).

Keywords: Brain metastases, Central nervous system, Unknown Primary Site

Introduction

Secondaries of brain (BM) are most common and devastating condition of Central Nervous System (CNS). Metastatic tumours are the most common CNS neoplasms [1]. In western literature, brain metastases vastly outnumber primary brain tumors [2]. Due to underdiagnosis and inaccurate reporting, the incidence rate for brain metastases reported in the literature probably underestimate the true incidence [3,4]. Exact incidence is unknown, however, the incidence of BM according to population-based studies range 8.3 to 14.3 per 100,000 people [5].

The interval between diagnosis of the primary tumors and the CNS metastases is generally < 1 year for lung carcinoma but can be multiple years for breast cancer and melanoma [6]. In adults, metastases to the brain most commonly arises from primary tumors of lung (50-60%), breast (15-20%), skin (melanoma) (5-10%) and gastrointestinal tract (GIT) (4-6%) [2,7]. With the emergence of newer and better imaging technique, confirmatory diagnosis of brain neoplasm by histopathology has become easier [8].

However, up to 15% of all patients with secondaries of brain (BM) have no clearly detectable primary site despite an extensive evaluation [2,9,10]. A five-year data study was carried out to evaluate unknown primary site (UPS) of secondaries of brain (BM) with help of histomorphology, clinico-radiological findings wherever possible and developing algorithm of IHC markers on basis of histomorphology.

Material and Method

Setting: This study was conducted at the department of onco-pathology of our institute. **Duration:** Five years data from 2014 to 2018 were obtained from Online Laboratory Information System (LIS), department of onco-pathology of our institute.

Type of study: Retrospective study

Sampling method: The data of secondaries of brain were retrieved from Online Laboratory System (LIS). **Inclusion criteria:** Cases of brain metastases diagnosed on histomorphology were included with known and unknown primary site.

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Exclusion criteria: Other cases of primary brain tumors were excluded from this study. Haematoxylin and eosin (H&E) stained slides were reviewed.

The immunohistochemistry (IHC) was performed on formalin fixed paraffin sections (FFPS) by automated immune stainer (Benchmark XT Ventana, Ventana Medical Systems, Tucson AZ) using indirect method. The following antibodies were used from available resources at our institute: Cytokeratin 7 (CK7), Cytokeratin 20 (CK20), AE1, Cytokeratin 5/6 (CK5/6), Thyroid transcription factor 1 (TTF 1), CDX2, PAX 8, Leucocyte common antigen

(LCA), Hepatocyte Paraffin 1 (HepPar 1), Glypican 3, Melan A, OCT3/4, Epithelial membrane antigen (EMA) (Cell Marque), Carcinoembryonic antigen (CEA, Dako North America Inc.), Glial fibrillary acidic protein (GFAP), HMB-45, Placental alkaline phosphatase (PLAP), CA-125, Vimentin (Biogenex), p63, Estrogen receptor (ER), Progesterone receptor (PR), Human epidermal growth factor 2 (HER 2), CD 10 (Ventana).

Ethics: An ethical approval has been taken.

Statistical analysis: Data was analysed using Statistical Package for the Social Science (SPSS).

Results

During this 5 year period from 2014 to 2018, only 128 CNS tumors diagnosed histo-pathologically as secondary tumors from LIS were retrieved.

In this group of 128 patients, 92 were males and 36 were females. Male to female ratio is 2.5:1. The age range was from 22 year to 73 year as shown in Table 1.

Table-1: Demographic details

Age (year)	Male (n=92)	Female (n=36)	Total (n=128)
Mean age	54.50	54.88	54.88
Median age	56.50	57	57
Maximum age	73	70	73
Minimum age	22	28	06

Table-2: Histopathological diagnosis of metastatic CNS tumours with its primary site distribution

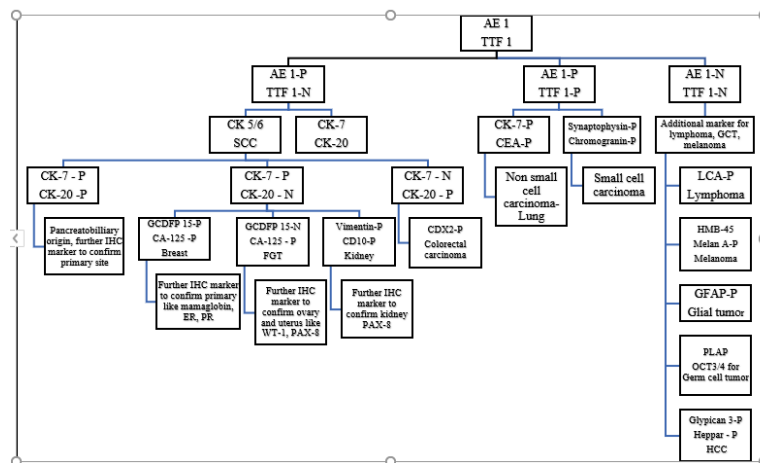
Primary site	Histopathological diagnosis											
	Adeno carcinoma	Poorly differentiated	Undifferentiated Carcinoma	Mixed carcinoma	SCC	MM	Metastatic carcinoma	NE tumors	OS	HCC	Oncocytic carcinoma	Total
Lung	56	4	1	2	6		1	4				74
Breast	15											15
GIT	10				1			1				12
Kidney	3						2					5
Head & neck		1			1				1		1	4
Skin						4						4
Liver										2		2
Prostate	2											2
Pancreato biliary	2											2
Unknown	3				4			1				8
Total	91	5	1	2	12	4	3	6	1	2	1	128

SCC-Squamous cell carcinoma, MM-Malignant melanoma, OS-Osteosarcoma, NE tumor-Neuroendocrine tumor HCC-Hepatocellular carcinoma

Table-3: Distribution of primary sites (n = 128)

Primary site	Number of cases (n = 107) (Unknown primary) (%)	Number of cases (n = 21) (known case of secondary malignancy)	Total cases (n = 128)
Lung	73 (68.22)	01	74
GIT	09 (8.42)	03	12
Breast	03 (2.80)	12	15
Kidney	03 (2.80)	02	05
Head & Neck	03 (2.80)	01	04
Skin	04 (3.74)		04
Liver	-	02	02
Prostate	02 (1.87)		02
Pancreatobilliary	02 (1.87)		02
Unknown site	08 (7.48)		08
Total	107 (100)	21	128

Table-4: Algorithm for evaluation of brain metastases with unknown primary



P-Positive, N- Negative, FGT- Female genital tract, GCT- Germ cell tumor

The distribution of the number of metastatic lesions was as follows: Single- 67%, Multiple- 33% (Figure 1).

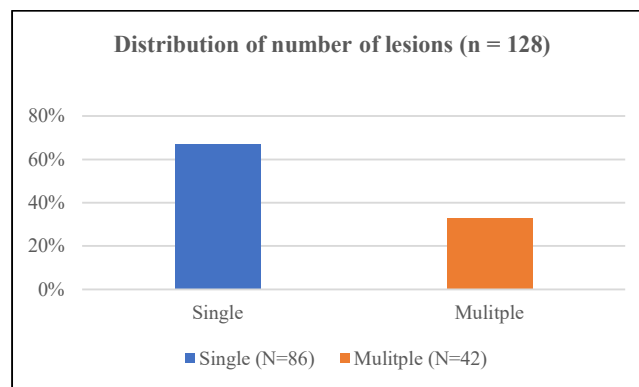


Fig-1: Distribution of number of lesions (n = 128).

The anatomical sites of metastatic lesions in brain were cerebrum (78.91%), cerebellum (14.06%), both cerebrum and cerebellum in (6.25%) and skull vault (0.78%). In the cerebrum, most common site was frontal (21.13%) followed by parietal (19.14%), occipital (20.79%) and temporal (17.85%).

The H & E stained slides were evaluated and various histomorphological diagnosis were made as shown in Table 2. In present study, immunohistochemical stains were applied in 107 cases of metastases of unknown origin and from that detection of primary sites in 99 cases (92.53%) and 8 cases (7.47%) primary was unknown. In remaining 21 cases of brain metastases, systemic malignancies were already diagnosed. (Table 3)

Discussion

Brain metastases is defined as tumour that originates outside the CNS and spread via the haematogenous route to the CNS or (less frequently) directly invades the CNS from adjacent anatomical structures. [11,12,13,14,15]. Autopsy studies have reported that CNS metastasis occur in about 25% of patients who die of cancer [12]. Secondaries of brain (BM) usually occurs late during the course of malignancy. The large majority of metastases arise from carcinomas and only 3% of patients with sarcoma develop metastases as reported by a study [7,10].

The incidence of brain metastasis has been reported to be highest among patients diagnosed with primary lung cancer at an age of 40-49 years with primary melanoma, renal cancer or colorectal cancer at an age of 50-59 years and with breast cancer at an age of 20-39 years [3]. Metastatic brain tumors are more common in adults with their incidence peaking in the age group of 50-80 years [16,17,18]. In present study median age was 57 year and mean age was 54.88 year which was comparable to the literature. Age range from 22 to 73 years which was comparable to other studies [8,19].

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. The spinal epidural metastases most commonly are from the prostate, breast, lung, kidney [12,13,14,15]. In present study cerebral metastases were most commonly observed in 101 cases (78.91%) followed by cerebellum in 18 cases (14.06%). In cerebral hemisphere, frontoparietal area is most commonly involved in 40 cases (39.60%) which was comparable to Subramanian A et al [20].

Multiple brain lesions are more suspicious for brain metastases [21]. Lung cancer and melanoma are more likely to be associated with multiple lesions whereas breast, thyroid, renal and colorectal carcinoma present with a solitary metastatic lesion [9,22]. In present study, it was observed that distribution of number of lesions single in 86 cases (67%) and multiple 42 cases (33%). This finding was comparable with Gupta et al [19], noted single lesions in 81.2% and multiple in 18.7%.

In general, the primary tumors which serve as sources of BM are those arising in the lung, breast, skin, kidney and gastrointestinal tract (GIT) [2,7,23,24,25]. In present study, out of 107 cases of unknown primary site of brain metastases, 73 (68.22%) cases had a primary site in the lung followed by gastrointestinal tract 9 cases (8.42%), skin 4 cases (3.74%) and breast 3 cases (2.80%). These findings were comparable with other studies like Sharma P et al [26], Le Chevalier et al [27] and Stoier et al [28] noted primary in lung in 68.9%, 45.2% and 29% respectively.

In present study, metastatic adenocarcinoma was observed in 91 cases (71.09%) followed by metastatic squamous cell carcinoma 12 cases (9.37%) which was comparable to Patnayak et al [8] noted 26 cases (65%) of metastatic adenocarcinoma and Gupta et al [19] noted 22 cases (68.7%) of metastatic adenocarcinoma. Lung was most common source of metastatic adenocarcinoma with 56 cases followed by gastrointestinal tract 10 cases.

Only a few small series examine CNS metastasis from sarcomas, emphasizing their relative rarity. The most common histologic subtypes include Osteosarcoma, pleomorphic undifferentiated sarcoma, Ewing's sarcoma and leiomyosarcoma [13,29,30,31]. In present study, one case of osteosarcoma already diagnosed primary site of head neck origin having brain metastases were noted.

Microscopically first step is to differentiate between the primary CNS tumor and metastases, followed by evaluate the tumor for morphology and architectural pattern like nested, glandular, trabecular, hepatoid, papillary, solid pattern. Presence of keratin material with squamous cells in dirty necrotic background suggest squamous cell carcinoma.

Presence of glandular pattern with cells having vesicular nuclei and prominent nucleoli suggest adenocarcinoma (Figure 2 and 3). Presence of monomorphic cells suggest lymphoid neoplasm and neuroendocrine origin tumor. Presence of mucinous material, brown pigmentation and colloid material are also helpful.

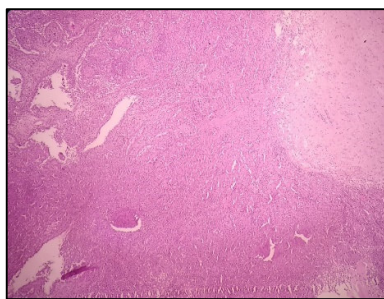


Fig-2: Metastatic adenocarcinoma deposit with adjacent brain parenchyma (H&E 40x).

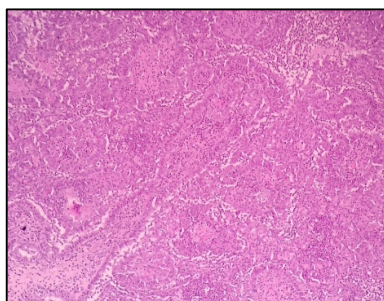


Fig-3: Metastatic deposit of adenocarcinoma (H&E 100x).

In recent era, IHC is most important tool to diagnose and to evaluate UPS of brain metastases. A basic IHC panel is widely accepted initial step in difficult and UPS cases such as GFAP (glioma), CK and EMA (carcinoma), S-100 (melanoma, glioma), synaptophysin, chromogranin and NSE (neuroendocrine tumors), LCA (lymphoma), HMB-45 (melanoma), ER and PR (breast carcinoma) and PSA (prostate carcinoma) [8,32].

The present study have used combination of several antibodies on a basis of histomorphology which is useful in evaluation of UPS. Thyroid transcription factor-1 (TTF-1) is a useful marker to identify lung as the primary site of tumor origin with its positivity rate of 78% noted by Srodon and Westra et al [33], 67% noted by Bohinski et al [34] and 78% noted by Sharma P et al [26]. Normal brain tissue and astrocytic tumors do not stain with TTF-1. Thus TTF-1 is an important marker in primary panel with fact keep in mind that lung is the most common primary in cases with unknown primary. TTF-1 negativity can rule out lung as a primary site and simultaneously other primary sites also needs to be thought about. Diagnosis of breast carcinoma is made with help of GCDFP 15, ER, PR and HER 2. Positivity for CA-125 and Vimentin and CEA negativity favors ovarian carcinoma. In present study, primary panel of immunohistochemical markers were applied on a basis of histomorphology in 107 cases of UPS of brain metastases and from that detection of primary sites in 99 cases (92.53%) and in 8 cases (7.47%) primary was unknown even after IHC. From above findings it can be proposed that an algorithm for evaluation of UPS of brain metastases. (Table 4) Limitation of present study was that even after IHC markers primary site was remained unknown in 8 cases (7.47%) and cost effectiveness of IHC markers. Patnayak et al [8] has observed that primary site remained unknown in 47% of cases with metastatic adenocarcinoma in brain. Sharma P et al [26] observed that primary site could not be diagnosed in 14% of cases even with IHC.

Conclusion

Secondaries of brain (BM) contribute significantly to morbidity and mortality of patients. In recent studies the reported improvements in overall survival of patients with brain metastases may be attributable to its earlier detection of metastases.

What the study adds to the existing knowledge?

Advantage: Findings of present study was comparable with other studies. From present study, it was observed that a systemic approach, consist of histomorphological

diagnosis, clinco-radiological findings whenever possible and immunohistochemistry to evaluate brain metastases is helpful in detection of unknown primary in majority of cases. With these, one can also be able to use limited number of IHC markers and thereby improves the survival patients with early detection of UPS.

Author's contributions

Dr. Jagdish Arvindbhai Prajapati: Concept, study design, manuscript preparation

Dr. Ashini Hemal Shah: Statistical analysis

Dr. Priti Pinakin Trivedi: Study design
Dr. Amisha Jigar Gami: Review and preparation of Manuscript
Dr. Vibha Rasesh Vyas: Data analysis, Manuscript preparation
Dr. Jahnavi Sanjay Gandhi: Manuscript preparation

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Conflict of interest: None declared

Ethical Approval: This study was approved by the Institutional Ethics Committee

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