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Case Report

CAM5.2 Expression in Metastatic Tumours of CNS: A Diagnostic Tool

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Abstract

Introduction: Secondary tumours or metastases account for more than half of all brain tumours in adults. Central nervous system is most commonly a target of metastatic dissemination. The judicious use of selected immunostains is unquestionably helpful in diagnostically challenging cases. CAM 5.2 being highly specific, is emerging as a specific marker to diagnose metastatic carcinoma.

Presentation of case: Total six metastatic tumours were studied using CAM5.2. Histopathological sections of brain tissue were stained by routine hematoxylin and eosin (H&E) as per standard technique. Representative sections were subjected to immunohistochemical staining with CAM 5.2. Skin biopsy act as a positive control for cytokeratin.

All of the 6 cases showed positivity for CAM 5.2. CAM5.2 expression in metastatic tumours was statistically significant (sensitivity 100% & 100% specificity).

Conclusion: We conclude in our study that CAM5.2 was significantly associated with metastatic tumours, as they were positive using this specific marker.

Keywords: CAM5.2; Metastatic CNS tumours; Cytokeratin

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Consent: We confirm that the patient has given their informed consent for the case report to be published.

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Introduction

Central nervous system (CNS) tumours are the neoplasms constituting 1-2% of all the neoplasms [1]. Secondary tumours or metastasis account for more than half of all brain tumours in adults. Ten to 50% of patients with systemic malignancy develop brain metastasis during their disease [2]. Most common route of spread is through blood stream. Central nervous system is most commonly a target of metastatic dissemination from lung carcinoma (18-60%), breast carcinoma (5-21%), melanoma (4-16%), genitourinary (3-10%) and gastrointestinal malignancies (5-12%). Most of the metastasis is located in the brain hemispheres (80%), especially in the parietal lobe, followed by frontal and occipital lobes [3].Immunohistochemistry (IHC) has become an important tool in the diagnosis of brain tumours**.** Although conventional hematoxylin-eosin staining is the mainstay for pathologic diagnosis, IHC has played a major role in differential diagnosis.

GFAP is the most frequently used marker in diagnostic neuro-oncology [4]. Cytokeratins monoclonal antibodies are useful in identification of the epithelial nature of neoplasm. CAM 5.2 is the mouse monoclonal antibody raised against colon carcinoma cell line HT29. It stains normal epithelial cell with the exception of stratified squamous epithelium [5].

Various studies have been conducted on metastatic brain tumours using non specific cytokeratins. Role of CAM 5.2 being highly specific is emerging as a specific marker to diagnose metastatic carcinoma. IHC using monoclonal or polyclonal antibodies has greatly influenced the diagnosis of various neurological disorders. Using this technique the presence of characteristic antigen can be precisely defined in a sensitive and reproducible manner, thereby providing a better tool for making an accurate diagnosis of brain tumours [6].

Materials and Methods

After gross examination of the specimen and proper sampling, the tissues were processed by routine histological technique for paraffin embedding and sectioning at 4 micron thickness. Histopathological sections were stained by routine hematoxylin and eosin (H&E) as per standard technique. Special stain was employed wherever needed. Representative sections were subjected to immunohistochemical staining with CAM 5.2. Skin biopsy act as a positive control for cytokeratin. Negative control staining was obtained by substituting the primary antibody with an antibody of unrelated specificity. GFAP staining was also used to detect primary tumours of CNS.

Observations

Six cases were diagnosed as metastasis to CNS. Out of these, 4 cases were of metastasis from adenocarcinoma **(Fig. 1),** one case was from Follicular carcinoma thyroid **(Fig. 2**) and renal cell carcinoma each**(Fig. 3**). Three cases were observed in age group 51-60 years. Average age for metastatic tumour was 55 years. Male to female ratio for metastatic tumours was 2:1. The most favoured site for metastasis (3 cases) was temporal lobe. Only one case was seen in cerebellum. Out of six cases of metastasis, five cases were enhancing and one case was hypodense **radiologically**. It seems that enhancement is a feature of metastatic tumours. All of the 6 cases showed positivity for CAM 5.2**(Fig. 4 & 5).** CAM5.2 expression in metastatic tumours was statistically significant (sensitivity 100% & 100% specificity) as shown in table below.

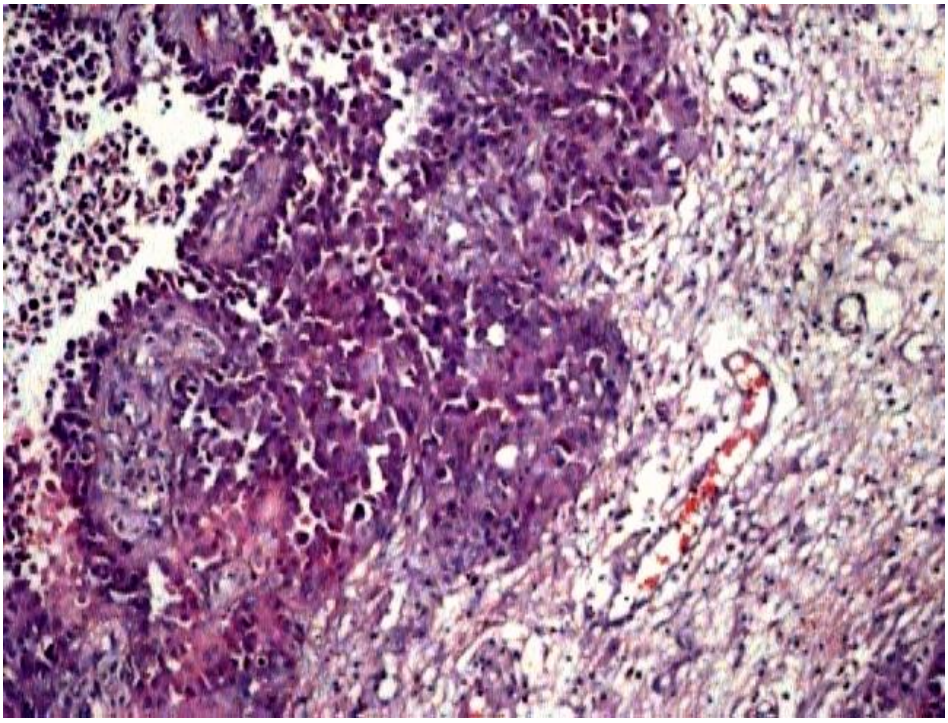

Figure 1 photomicrograph showing papillary adenocarcinoma invading glial tissue H&E(x200)

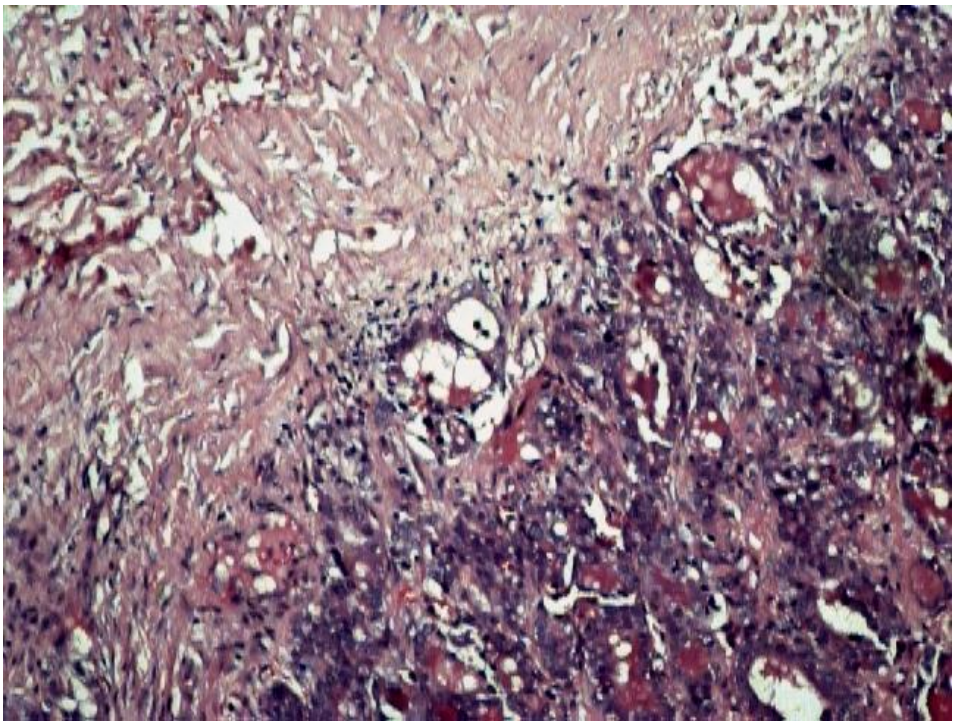

Figure 2 photomicrograph showing metastatic follicular carcinoma thyroid in CNS. H&E(x100)

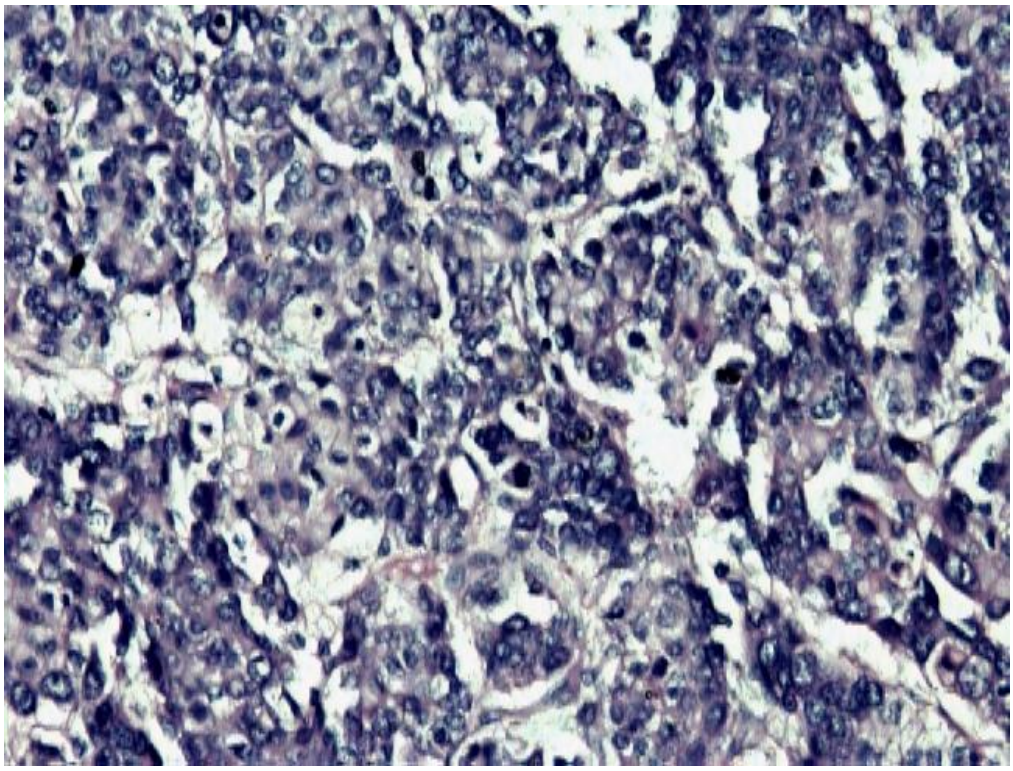

Figure 3 photomicrograph showing metastatic renal carcinoma – clear cell variant H&E(x200)

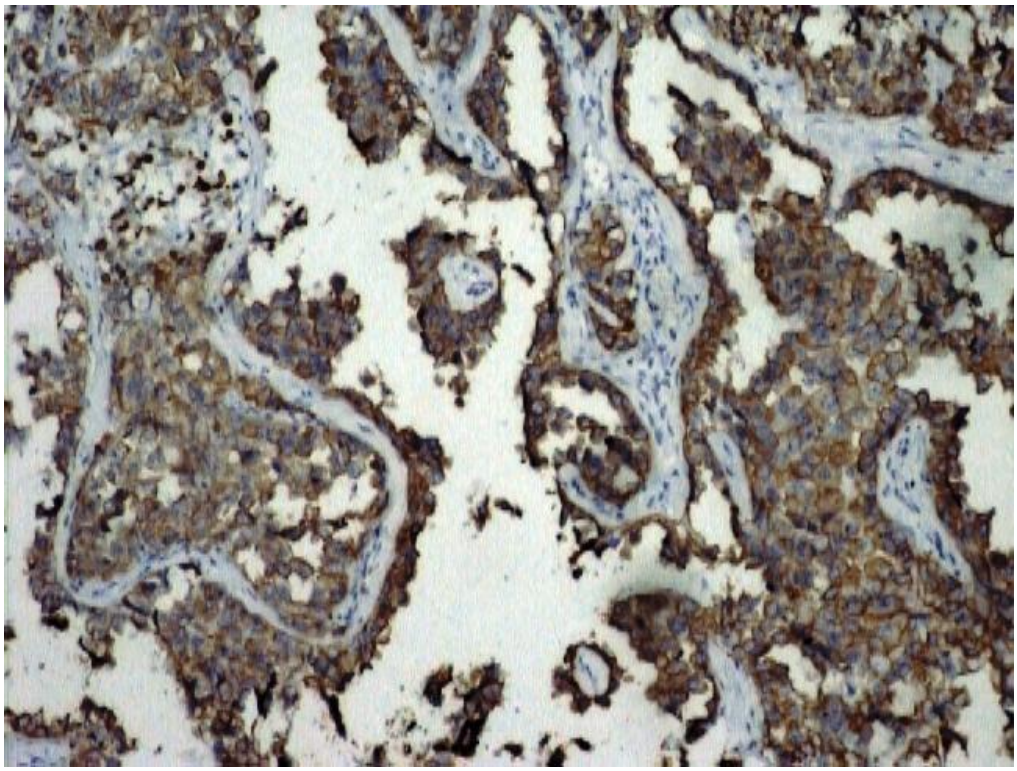

Figure 4 photomicrograph showing CAM5.2 positivity in metastatic papillary adenocarcinoma IHC (CAM5.2; x100)

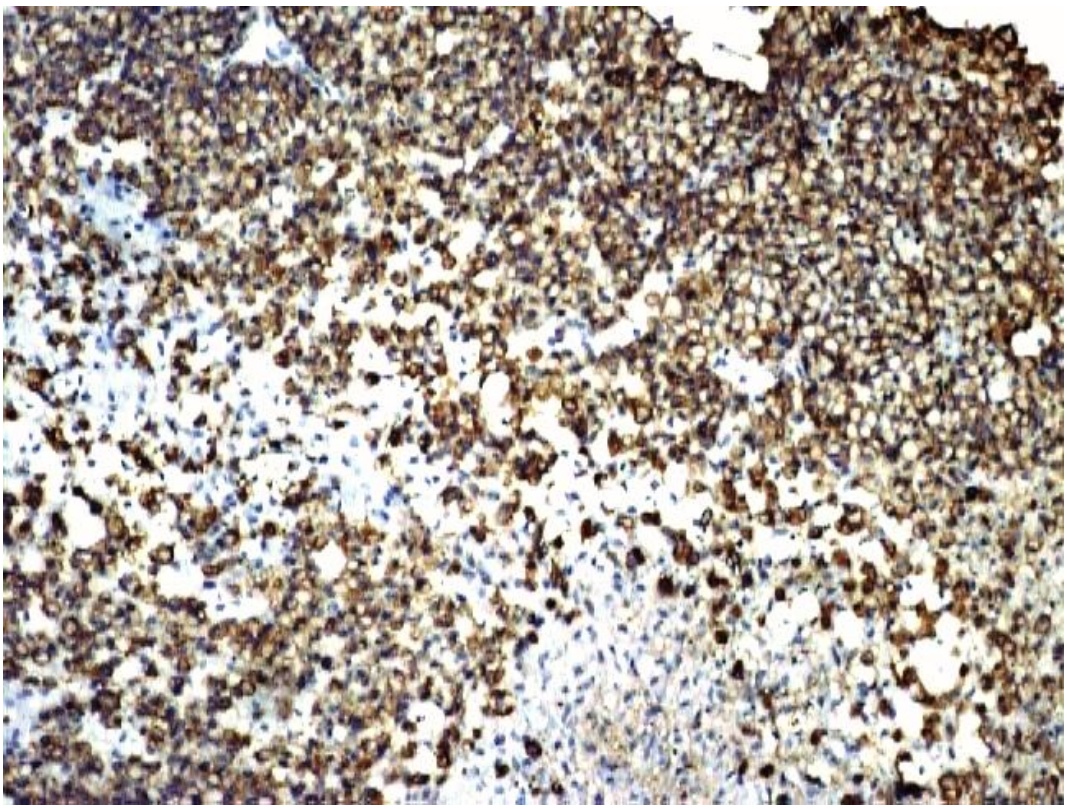

Figure 5 photomicrograph showing CAM5.2 positivity in metastatic renal carcinoma – clear cell variant IHC (CAM5.2; x100)

Table 1 Comparison of Staining of GFAP & CAM5.2 in Metastatic tumours

Metastatic tumours	Total number of cases	CAM 5.2 (+)	GFAP staining(+)
Renal cell carcinoma	1	1	0
Follicular carcinoma thyroid	1	1	0
Adenocarcinoma	4	4	0
Total no. of cases	6	6	0

Discussion

Although conventional H & E staining is mainstay for pathological diagnosis, IHC has played a major role in differential diagnosis and in improving the diagnostic accuracy in neurooncologic pathology. The judicious use of a panel of IHC is unquestionably helpful in diagnostically challenging cases. In fact, IHC is also of great help to grade and to predict the prognosis in certain brain tumours also. An understanding of the pathology of CNS tumours plays a vital role in the management of patients and in clinical and biological research. There are now a number of techniques that are used to detect the location and physiological properties

of intracranial tumours. They include CT, MRI, PET (Positron emission tomography) and the use of cerebral angiography for localization of tumours. Apart from the angiographic demonstration of lesions of vascular tissue, none of the other technique allows a specific diagnosis to be made with absolute certainity and biopsy is still the gold standard in establishing the diagnosis in the majority of intracranial and intraspinal tumours [7]. Although CT and MRI allow accurate localization of intracranial and spinal lesions, and often serve as a very good guide to the nature of the lesion, the final diagnosis of a tumour relies almost exclusively on histological evaluation of tissue taken at biopsy or autopsy. Pathology, radiology and clinical evaluation all play key role in the diagnosis of metastatic tumours of the nervous system. An accurate diagnosis of metastatic tumours is usually possible after careful assessment of routine microscopic features with sufficient clinical and radiological information

A combination of immunostains as studied by Prayson *et al*., included GFAP and cytokeratin CAM5.2 in 23 patients of glioblastoma multiforme and 22 patients with metastatic carcinomas to the brain. Primary tumour**s** were lung, breast and endometrium. Glioblastoma multiforme is characterized by the features often encountered in poorly differentiated metastatic carcinomas. The information regarding pattern of cytokeratin expression in GBM is little in literature. Only one GBM stained for CAM5.2. Three cases of metastatic carcinomas stained for GFAP. The staining in these cases was focal and limited to less than 10% of malignant cells. They concluded that CAM5.2**[deleted 2 words] is** most useful stain in studying carcinomas**.[delete one sentence]** .The combination of GFAP with CAM5.2 is most useful in sorting out difference among glial **[deleted 1 word]** and metastatic tumours**.[delete one sentence]** [8]. In the study of Biernat *et al*. Ck profile was indispensible in determining the site of primary tumour. He also found that metastasis to the brain from lung carcinoma also expressed CAM 5.2 [3]. Pavlidis *et al.* studied that metastatic carcinomas of central nervous system from an unknown primary, is diagnosed with either a solitary lesion or with multiple metastasis. Upto 15% of all patients with CNS metastasis had no clearly identified primary site despite an intensive investigation. Histopathologically, intracranial lesions are most frequently metastatic adenocarcinomas or metastatic squamous cell carcinomas. Patients with solitary lesion are candidate for surgery and have better prognosis. The development of monoclonal antibodies against various cytokeratins have opened up new avenues in investigating the normal and cancerous epithelial cells [9]. Perry *et al.* studied the diagnosis of metastatic adenocarcinomas to the brain of unknown primary. Sixty eight cases of metastatic adenocarcinomas to the brain with known primaries were immunostained with antibodies to cytokeratin 7 (CK 7), cytokeratin (CK 20) and CAM 5.2. None of the keratin antibody stained reactive astrocytes or other normal CNS parenchymal elements in any of the cases. Breast carcinoma and renal cell carcinoma also expressed CAM5.2. It is a useful confirmatory stain in suspected metastatic adenocarcinoma to the brain. Unlike non specific AE1/3, CAM5.2 does not stain astrocytes. AE1/3 antibody should be avoided in the brain because of the common staining of both normal and neoplastic astrocytes, but CAM 5.2 does not suffer this drawback and it is expressed in metastatic tumours to the brain [10]. Murakata *et al.* did a study on immunohistochemical expression of metastatic renal tumours (clear cell variant) and found them to be positive for cytokeratin (7, 18 and 19) [11]. Expression of CAM5.2 was observed by Listrom *et al*. in poorly differentiated tumours and it was concluded that areas of necrosis and hemorrhage to be avoided because these areas tend to trap antibody which increased the background staining and made interpretation difficult [5].

Table 2 Correlation of GFAP and CAM5.2 staining in Metastatic tumours in various studies

Study	Year	Total cases of metastasis	GFAP		% of GFAP positivity	CAM 5.2		% of CAM 5.2 positivity
			+	_		+	_	
Listrom *et al*.[5]	1987	65	-	-	-	40	25	61.5%
Prayson *et al*.[8]	1999	22	3	19	13.6%	22	-	100%
Goswami *et al*. [12]	2004	10	-	10	0%	10	-	100%
Present study	2012	6	-	6	0%	6	-	100%

Conclusion

To conclude in our study, CAM5.2 was significantly associated with metastatic tumours. However, the expression may vary with IHC due to various parameters including case selection, sample size & hence need to be standardized by more studies using the same IHC technique and a bigger sample size for better results. High grade gliomas like GBM are fairly encountered in routine surgical neuropathology & it's crucial to differentiate them from metastatic tumours. Categorization is more problematic in such cases due to various parameters including presence of necrosis & small sample size due to stereotactic biopsies. From the present study it is concluded that IHC is a valuable technique & the best effective combination in diagnosing metastatic tumours of central nervous system are GFAP & CAM5.2.

Acknowledgements

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