

# Malignant metastatic carcinoid presenting as brain tumor

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## ABSTRACT

Carcinoid tumors are rarely known to metastasise to the brain. It is even more rare for such patients to present with symptoms related to metastases as the initial and only symptom. We present a case of a 60-year-old man who presented with hemiparesis and imaging features suggestive of brain tumor. He underwent surgery and the histopathology revealed metastatic malignant lesion of neuroendocrine origin. A subsequent work up for the primary was negative. Patient was treated with adjuvant radiotherapy. We present this case to highlight the pathophysiological features, workup and treatment options of this rare disease and discuss the methods of differentiating it from more common brain tumors.

**Key words:** Brain secondaries, hemiparesismetastatic, neuroendocrine tumor, presentation

## Introduction

Carcinoid tumors are a fascinating group of neuroendocrine tumor (NET) that develop either sporadically or as part of an inheritable syndrome. Many tumors arise in the bronchopulmonary or gastrointestinal tract. The malignant potential and clinical presentation of the tumors is varied depending on the site of their origin. There are only five reported cases of NET's that initially presented with symptoms related to brain metastases.

## Case Report

A 60-year-old male presented with complaints of headache, vomiting and recent onset weakness of left upper and lower limbs. On clinical examination, the patient was conscious oriented and had grade 2/5 power in left upper and lower limbs. A contrast enhanced computed tomography CT revealed ill-defined large solid cystic intra axial space occupying lesion SOL in right parietooccipital region [Figure 1]. A contrast enhanced MRI was done which showed a large heterogeneous

intra axial mixed solid cystic mass of 70 × 60 × 44 mm spread over right parietooccipital lobes with perifocal edema causing mass effect over and midline shift suggestive of mitotic nature [Figure 2]. Anti-edema measures were initiated and the patient was prepared for emergency surgery where right parieto occipital craniotomy was done and near total excision of tumor was done. Post operatively the patient recovered well and his weakness improved slightly. The tissue was submitted for histopathology where H and E, staining showed tumor cells having abundant cytoplasm and granular chromatin arranged in trabecular pattern [Figure 3]. Immunohistochemical studies revealed strong positivity for chromogranin, Neuron-specific enolase (NSE) and synaptophysin with few cells showing positivity for S-100 [Figure 4]. CD56 and vimentin were positive. Ki67/MIB index was variable from 10-30%. CK PAN (A/E 1, A/E 2), TTF-1, CEA, PSA, CK7, CK8, CK20, HMW (Keratin Beta E12), AFP and GFAP were negative in the tumor cells. A final diagnosis of metastatic malignant lesion possibly of neuroendocrine origin was made. A subsequent CECT chest and abdomen were performed and came out normal. Due to cost factors patient could not undergo somatostatin receptor scintigraphy or PET-CT which could have identified the source of the primary. Based on the results of immunohistochemical examination thyroid, lung, prostate, kidney, adrenal, brain and liver were unlikely sites of primary. Patient then underwent adjuvant radiotherapy. At last follow-up of 2 months patient was conscious with a residual weakness of grade 4/5 on the left side.

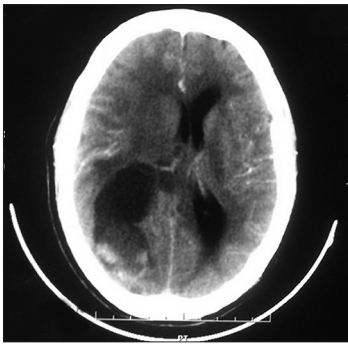
## Discussion

NET represent a heterogeneous group of slow growing neoplasms with malignant potential that arise from widely dispersed enterochromaffin cells. Carcinoid tumors often

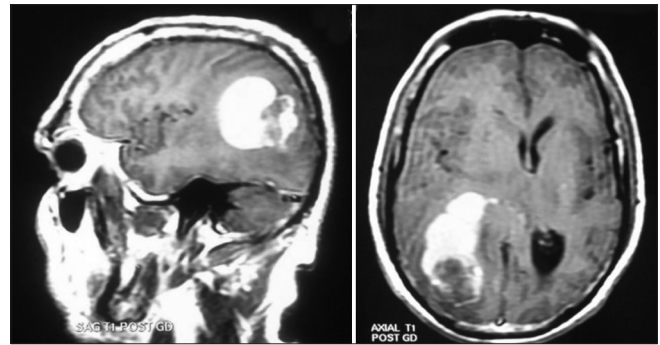
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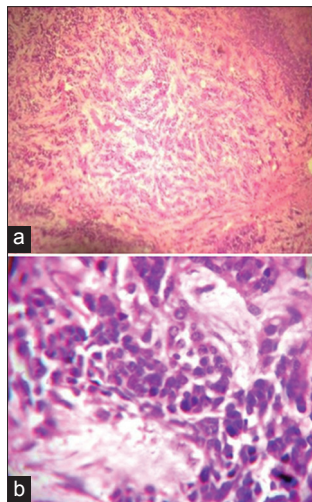
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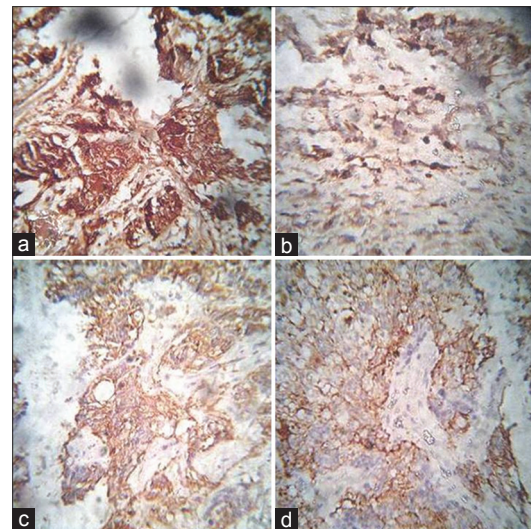
**Figure 1:** Computed tomography brain showing ill defined space occupying lesion in right parietooccipital reigon



**Figure 2:** Magnetic resonance imaging brain showing cystic/solid mass with surrounding edema and midline shift



**Figure 3:** H and E staining at low power (a) And high power; (b) Showing tumor cells having abundant cytoplasm and granular chromatin arranged in trabecular pattern



**Figure 4:** (a) Immunohistochemistry showing positivity for neuro-specific enolase; (b) S-100; (c) Synaptophysin and (d) Chromogranin

follow an indolent course with a propensity to metastasize. Metastases to the central nervous system are very rare with a reported incidence of 1.5-5%<sup>[1,2]</sup> whereas NETs are considered to be the cause of brain metastases in 1.3-1.4% of all patients with brain metastases.<sup>[3]</sup> However, since many patients do not undergo routine brain imaging as a component of metastatic assessment this figure is probably an underestimate. Approximately, 20% of patients with carcinoid tumors have metastatic disease at presentation, and in half of those patients the primary tumor is not located at initial imaging.<sup>[4]</sup>

There are only five reported cases of NET's that initially presented with symptoms related to brain metastases [Table 1].<sup>[3,5-8]</sup> Most of the patients who have brain metastases have single intraparenchymal brain metastases<sup>[2]</sup> and the median interval between diagnosis of the primary and development of a brain metastasis is 16 months.<sup>[1]</sup> Bronchopulmonary NETs appear to be the dominant source of cerebral metastases<sup>[9]</sup> although it has been reported with all primary locations of NET. In general, most patients with brain metastasis have either primary lung tumors or metastases to the lung at the time of brain metastasis.

Brain metastases are associated with headaches in more than 95% of the patients. Personality changes and unstable gaits are reported in up to 25%, cranial nerve deficits in more than 10% and seizures or nausea and emesis in less than 10% of the patients.<sup>[2]</sup>

Because of their neuroendocrine nature, carcinoid tumors produce and store a variety of biogenic amines, neuropeptides, and prostaglandins. The carcinoid syndrome, seen in around 10% of patients with NET's,<sup>[5]</sup> consists of flushing, intermittent diarrhea, and paroxysmal dyspnea and is caused by the oversecretion of serotonin, bradykinin, prostaglandins, and histamine. It usually occurs in the setting of widely metastatic disease with liver involvement. The most frequent sites of metastatic carcinoids were lymph nodes (89.8%), the liver (44.1%), the lungs (13.6%), the peritoneum (13.6%), and the pancreas (6.8%).

The usual mechanism of metastasis to the brain involves hematogenous dissemination from the lung. However, another mechanism is possible, especially in patients with pelvic or abdominal tumors. Batson's venous plexus connects pelvic

**Table 1: List of cases of metastatic carcinoid presenting as brain tumors**

Author	Year	Age	Presentation	Location of primary	Location/number of brain secondaries
Hussein <i>et al.</i> <sup>[5]</sup>	1990	NA	CNS syptoms	Lung	NA
Greene <i>et al.</i> <sup>[6]</sup>	1993	NA	Headache, seizures	Lung	Multiple cystic
Porter <i>et al.</i> <sup>[7]</sup>	2000	62/M	Headache/ataxia	None identified	Right cerebellopontine angle, single
Nakamura <i>et al.</i> <sup>[8]</sup>	2001	52/F	Headache/ataxia	Lung	Four in cerebrum, one in cerebellum
Maiuri <i>et al.</i> <sup>[3]</sup>	2004	54/M	Ataxia, speech disturbance	Lung	Cerebellar vermis, single
Present case	2012	60/M	Headache/hemiparesis	None identified	Right parieto-occipital, single

CNS: Central nervous system; NA: Not available

structures with the brain through a valveless set of veins that run in the spinal epidural space.

Brain metastases are usually identified on MRI or CT scanning although octreoscan and 68 Ga-DOTATOC-PET/CT may be helpful in the early detection of brain metastases, provided that the histological tumor type is well differentiated. Contrast enhanced brain MRI is the recommended imaging modality.

Because most NET's express somatostatin receptors, somatostatin receptor scintigraphy with <sup>111</sup>In-octreotide is widely used as the primary imaging method for diagnosis, staging, and monitoring. It has a sensitivity of 80-100% in localizing radiologically occult tumors.

Histologically, NETs are an example of "small blue cell tumors," showing uniform cells which have a round to oval stippled nucleus and scant, pink granular cytoplasm. The cells may align variously in islands, glands or sheets. Electron microscopy can identify secretory granules. There is usually minimal pleomorphism but less commonly there can be anaplasia, mitotic activity, and necrosis. NETs show tissue immunoreactivity for markers of neuroendocrine differentiation such as various chromogranins, synaptophysin and PGP9. NSE is less specific.

Neuroendocrine carcinoma (NEC) is a subtype of NET which shows evidence of metastases. In cases of NEC various immunohistochemical markers applied to the tissue help identify/rule out the tissue of origin. In our case chromogranin, NSE and synaptophysin were strongly positive in the tumor cells which helped identify neuroendocrine origin. Markers to identify the source of primary such as TTF-1 (thyroid, lung), CD 10 (kidney), AFP (embryonal origin), CKPAN (epithelial origin), CEA (prostate, kidney, adrenal), CK7/CK20 (Lung, prostate, RCC, Liver), PSA (Prostate), HMW (Well differentiated squamous cell origin) and GFAP (Glial origin) were all negative.

There are no established treatment guidelines for patients with brain metastases from carcinoid tumors. Treatments implemented in reported cases cover a spectrum of possibilities from chemotherapy as the only treatment, to whole body radiotherapy WBRT, surgery, or to surgical intervention followed by WBRT.

Steroids are the primary symptomatic therapy for brain metastases and help reduce brain edema. Functional NET's require somatostatin analogs as standard treatment prior to other interventions for metastatic sites. Interferon alpha can be used alternatively or in combination with somatostatin analogs. Chemotherapy is used according to tumor origin, differentiation status and biology. It is indicated in poorly differentiated NECs where cisplatin based regimens are recommended. Temozolomide can be used as basic therapy in brain metastases originating from foregut tumors, but midgut tumors appear to be much less responsive.

In general in patients with rare metastases such as brain, surgery has a palliative role but surgery is the method of choice for single brain metastases especially if causing a focal neurological deficit as in our case. Surgery followed by adjuvant radiotherapy appears to improve outcome.<sup>[2]</sup>

In patients with multiple brain metastases, external beam irradiation is the appropriate treatment.<sup>[2,3,10]</sup> It can be combined with surgery in individual cases, with the exception of poorly differentiated tumors. Systemic treatment is usually a better option as opposed to an aggressive local approach, especially when a neurosurgical intervention is not mandatory for neurological deficits.

Patient of NET's with brain metastases showed improved survival when they underwent surgery and received WBRT and hence this combination of therapeutic interventions seems to be indicated for all patients with brain metastases from NET's.<sup>[2]</sup> In our case the patient was unable to afford whole-body octreotide scan to identify the occult primary, but we proceeded with surgery and radiotherapy as it would have been the acceptable treatment for focal neurological deficit even if any primary had been detected.

The overall 5-year survival rate for patients having any carcinoid tumor regardless of primary site is 50.4% ± 6.4%.<sup>[3]</sup> There are limited data available on the survival in patients with carcinoid metastases to the brain with overall survival rates around 20% at 2 years and less than 5% at 5 years.<sup>[9]</sup>

## Conclusion

Neuroendocrine tumors presenting as metastases to the brain are rare and merit thorough investigation of the source of the

primary. Such tumors often mimic more common brain tumors radiologically, but histopathology and immunohistochemistry are differentiating. Metastatic brain disease in NET's merits surgery, if they are single and cause focal neurological deficits. Chemotherapy and radiotherapy are advised as per the tumor grade and stage.

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