Case Report

A journey of neuroendocrine carcinoma of the brain from the primary to metastatic tumor

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ABSTRACT

The neuroendocrine tumors most commonly originate in the lung, liver, and gastrointestinal tract. They can be graded into a three-tiered system depending on their proliferation index. These tumors frequently metastasize to the regional lymph nodes. Neuroendocrine tumors of the brain are very rare. Most of them are metastatic and a handful of cases are primary. Hereby, we present a case of brain neuroendocrine carcinoma, which was solitary with no evidence of the primary tumor in the body at the time of neurosurgery. However, treating physicians vigilantly kept him on regular follow-up and investigated further. The patient was diagnosed to have a lesion in the lung 3 months after surgery. Thus, it was considered primary neuroendocrine carcinoma of the brain; however, regular follow-up and further positron emission tomography scan showed a small mass in the lung and adrenal gland. Based on this, a final diagnosis of metastatic neuroendocrine carcinoma of the brain was made.

Key words: Neuroendocrine carcinoma, Brain, Tumor

Neuroendocrine carcinoma belongs to the category of amine precursor uptake and decarboxylase. Most commonly, they arise in the lung, liver, and gastrointestinal tract [1]. They range from benign, indolent tumors to malignant tumors with metastases to the lymph nodes or distant metastases. Distant metastases occur in the liver, lungs, and bone. The brain is an uncommon site for metastatic neuroendocrine tumors [2]. The primary neuroendocrine tumors in the brain are still rarer.

Hereby, we present a rare case of neuroendocrine carcinoma of the brain which was initially thought of the primary tumor based on immunohistochemistry and radiological imaging features. However, on further follow-up investigations, it was found to be a metastatic carcinoma due to the presence of masses in the lung and adrenal gland.

CASE REPORT

A 56 years old male, a known case of hypertension since 10 years who was on regular medication, presented with headache and behavioral disturbances for 2 months. Headache was holocranial, dull aching, continuous in nature, and more intense in the morning. The patient was on routine analgesics, despite that, the intensity of the headache was the same.

On general examination, he was afebrile with a heart rate of 80/min and blood pressure of 130/80 mm of Hg. His respiratory rate was 18/min. There was no pallor, icterus, edema, cyanosis, clubbing, or lymphadenopathy. On central nervous system examination, he was conscious but confused. His attention and vigilance were impaired. However, comprehension and calculation were intact. On motor examination, the right-sided hemiparesis was present.

As a routine protocol in the pandemic situation, a reverse transcriptase-polymerase chain reaction test for coronaviral disease 2019 was done. It was negative and other blood investigations were within normal limits.

A computed tomography (CT) scan of the brain showed a heterogeneous hyperdense mass lesion in the left frontotemporal region with surrounding edema. The lesion was extending in the left basal ganglia region and causing compression of the foramen of Monroe and the left lateral ventricle. A midline shift of 5 mm was seen toward the right side. Magnetic resonance imaging of the brain showed the lesion to be heterogeneous hypointense on T1-weighted images and displaying heterogeneous peripheral and central contrast enhancement on post-contrast images. The lesion was heterogeneous iso-hypointense on T2 FLAIR sequences and

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caused a significant mass effect and midline shift (Fig. 1). A pre-operative provisional diagnosis of high-grade glioma was made and the patient was considered for the operation.

The gross-total resection of the tumor was done with left frontotemporal craniotomy and a combined subfrontal and transsylvian approaches. There was a well-defined plane between tumor and brain parenchyma. Peroperatively, the lesion was soft and highly vascular. Intraoperative consultation was done for squash preparation. Smears showed features of non-glial neoplasm, likely metastatic carcinoma.

In the immediate post-operative period, his Glasgow EMV scale (EMV: Best eye response, best motor response, best verbal response) was E4M6V4. He was dysphasic with the right-sided hemiparesis. He recovered in the next few days. During ward stay, he developed pleural effusion which showed inflammatory cells. No malignant cells were seen.

Meanwhile, histopathology showed a highly malignant tumor with large areas of tumor cell necrosis and peritheliomatous arrangement of the viable tumor cells. The cells displayed a high nucleocytoplasmic ratio and minimal anisonucleosis. Nuclei were oval, elongated, and hyperchromatic. Many apoptotic bodies and increased mitotic figures were also noted (2–3/high-power field). A primary report of undifferentiated malignancy was given and immunohistochemistry was performed. On the primary panel, tumor cells were negative for glial fibrillary acidic protein (GFAP), Vimentin, CD99, and CD45. Epithelial membrane antigen and cytokeratin were focally positive. Hence, in the second panel, prostate specific-antigen (PSA), thyroid transcription factor 1 (TTF1), synaptophysin, and chromogranin immunostains were done. PSA and chromogranin were negative. CD56 and Synptophysin showed strong and diffuse cytoplasmic granular positivity. TTF1 was also strongly and diffusely positive in the tumor cell nuclei. The proliferation index (PI) assessed by Ki67 immunostain was around 35%. Thus, this tumor was labeled as neuroendocrine carcinoma (Fig. 2).

Considering his age, metastatic poorly differentiated malignancy was one of the differentials, hence thorough imaging of the chest and abdomen was done in the immediate post-operative period; however, no mass lesion was found. In view of TTF1 positivity, in addition to high resolution CT, an ultrasound of the neck was done which did not show a mass lesion. Based on the immune profile and imaging, a rare diagnosis of the primary neuroendocrine carcinoma of the brain was considered.

For further management, the patient underwent a positron emission tomography (PET) scan. However, it was delayed until 3–4 months due to post-operative infection and economical constraints. On the PET scan, the right upper lobe of the lung showed a tiny nodule (SUV 3.8, Standardized Uptake Value). A similar large nodule of 4.5 × 2.3 cm in the right lower lung (SUV 3.5) was noted. FDG avid hyper-enhancing nodule was noted in the adrenal gland (SUV 18.9) and brain (SUV 19.9). Hence, the final diagnosis of lung neuroendocrine carcinoma with metastasis to the brain and adrenal gland was made. The patient succumbed to the death while on palliative chemoradiotherapy around 6 months post-operative period. Unfortunately, an autopsy cannot be performed.

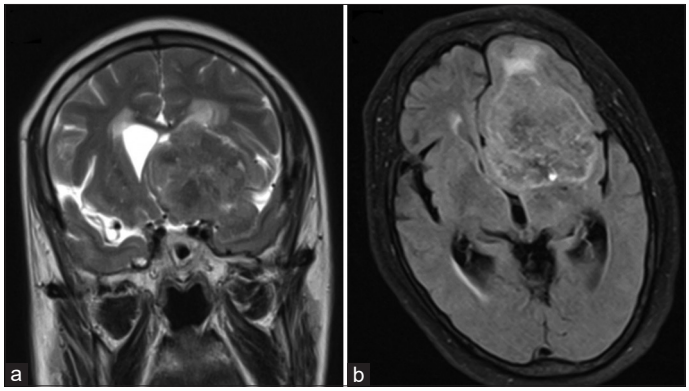

Figure 1: (a) Coronal T2 wt image showing mass lesion in the left frontotemporal region and basal ganglia causing compression of the left lateral ventricle and midline shift. (b) Axial FLAIR image showing lesion in the left frontotemporal and basal ganglia. Lesion is heterogeneous in intensity

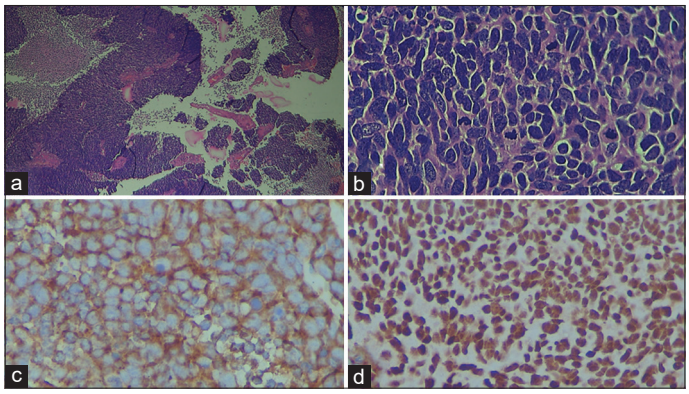

Figure 2: (a) Scanner view of hematoxylin and eosin-stained slide showing sheets of tumor cells with areas of necrosis and viable clusters around blood vessels. (b) High-power view of hematoxylin and eosin stained slide shows tumor cells with hyperchromatic, oval to elongated nuclei with scant cytoplasm. Many mitotic figures and apoptotic bodies are seen. (c) High-power view of tumor cells showing strong and diffuse reactivity for CD56 immunohistochemistry. (d) High-power view of TTF1 immunostain. TTF1 is strongly and diffusely positive in the tumor cells nuclei

DISCUSSION

Neuroendocrine carcinoma rarely metastasizes to the brain. Other rare sites include the pituitary gland, orbit, retroperitoneum, adrenal gland, pancreas, heart, ovaries, breast, and thyroid. These tumors commonly metastasize to the lymph nodes, liver, lung, and bones [2]. Conversely, tumors commonly metastasizing to the brain include lung cancer, breast cancer, and melanoma. They constitute around 67–80% of all cancers metastasizing to the brain [3]. Neuroendocrine tumors constitute 1.3–1.4% of all metastatic tumors of the brain [4]. Lung neuroendocrine tumors form the majority bulk (45%) of metastatic neuroendocrine tumors in the brain and most of them are neuroendocrine carcinoma [5]. This case presented as a solitary brain malignant tumor with no detectable primary at the time of operation and in the immediate post-operative period. Histopathology showed neuroendocrine carcinoma. Whenever the

brain shows neuroendocrine carcinoma, around 75% of patients have lymph node metastases and liver metastases in 50% of patients [6].

It is necessary to differentiate primary from the metastatic neuroendocrine tumor, because the primary neuroendocrine carcinoma of the brain has a much better prognosis as compared to metastatic neuroendocrine carcinoma [6,7]. Usually, the patients with metastatic neuroendocrine carcinoma of the brain die due to systemic disease progression as suggested by Mallory *et al*. [8].

Most commonly, metastatic neuroendocrine carcinoma of the brain arises from the lungs. In our case, the PET CT scan and immunohistochemistry profile suggested primary carcinoma in the lung with metastasis to the brain and adrenal gland. About 30–70% of incidentalomas in the adrenal gland having a history of cancer show metastases. In general, most common metastases occur from adenocarcinomas of the lung (39%) followed by the breast (35%). Metastatic spread to the adrenals can be hematogenous or by the lymphatic route. Possibly due to the rich sinusoidal blood supply, the adrenals are a common site of metastasis [9].

Some reports of the primary brain neuroendocrine carcinomas were TTF1 positive, so initially, primary carcinoma was entertained. However, TTF1 is also positive in lung carcinomas [10,11]. Other tumors such as lymphoma, glioblastoma, and metastatic prostatic adenocarcinoma were ruled out with Immunostains for CD45, GFAP, and PSA.

The neuroendocrine system is composed of nerve cells and epithelial cells. The nerve cells are located in the central nervous system and peripheral nerve ganglions. Epithelial cells are in the parenchyma of endocrine glands. They are also present in the mucosa of the respiratory and gastrointestinal systems. Nerve cells rarely give rise to proliferative lesions. The neoplastic proliferations are more common in epithelial neuroendocrine cells [10]. The world health organization classifies neuroendocrine tumors according to their PI as well-differentiated neuroendocrine tumor (PI <2%), moderate differentiated neuroendocrine carcinoma (PI: 2–15%), and poorly differentiated neuroendocrine carcinoma (PI >15%). These terminologies correspond to the carcinoid tumor, atypical carcinoid, and neuroendocrine carcinoma, respectively [10,12]. Our tumor had a PI of 35%, hence was considered to be poorly differentiated neuroendocrine carcinoma.

CONCLUSION

This case signifies that the neuroendocrine carcinoma of the brain should be thoroughly investigated and kept on a regular follow-up to determine the primary or metastatic nature as their prognosis is different. In resource-limited settings, neurosurgeon's vigilance will help in risk stratification and early intervention. Thus, we can say that in the absence of the primary malignancy also, neuroendocrine carcinoma of the brain should be thoroughly investigated to differentiate primary from secondary as their prognosis is different.

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