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Case Report
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Evidence of PSMA Uptake in Brain Metastases in a Patient with Breast Cancer Her2/Neu Positive

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Abstract

Breast cancer is one of the most common causes of brain metastases resulting in a poor survival. The blood-brain barrier is an obstacle to the delivery of chemotherapeutics to the brain; treatment includes whole brain irradiation, stereotactic radio surgery or neurosurgery with whole brain radiation.

The angiogenesis may be associated with metastasis independent of either invasion of normal tissue or intra vacation into normal blood or lymph node.

Prostate Specific Membrane Antigen (PSMA) expression is seen in the neovasculature of many types of tumors, such as prostate, renal, lung and recently breast cancer.

Positron Emission Tomography (PET) imaging with ^{68}Ga-PSMA is very useful in the diagnosis of recurrent prostate cancer, mainly retrospective studies describe the value of ^{68}Ga-PSMA ligand PET/CT in recurrent prostate cancer and most recently as the ragnostic agent, if required provide therapy with ^{177}Lu-PSMA.

These case report suggest that PSMA expression in tumor associated neovasculature may be related to the degree and nature of neoangiogenesis. In addition the present case is the first evidence in which tumor viability is demonstrated in brain metastasis in patients live corroborated by PET-CT with ^{68}Ga-PSMA.

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Keywords: Breast cancer; Neoangiogenesis; Neovasculature; Intra vassation

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Introduction

The breast cancer in Mexico is the first place in incidence with 20,444 and mortality of 5,680 per year [1].The HER2/neu (c-erbB2), located on chromosome 17q, which encodes a transmembrane protein of 185 kDa (p185), is part of the family of tyrosine kinase receptors including the epidermal growth factor receptor c-erbB11, this proto-oncogene present in 10%-30% of invasive breast carcinomas and serves as a biological target for trastuzumab therapy. Nevertheless, 15-30 % of patients with metastatic breast cancer HER2/neu positive will develop brain metastases. Treatment includes whole brain irradiation, stereotactic radio surgery or neurosurgery with whole brain radiation, resulting in a poor survival. The blood-brain barrier is an obstacle to the delivery of chemotherapeutics to the brain [2-4].

A potentially effective therapeutic strategy may derive from the finding that the transmembrane Prostate Specific Membrane Antigen (PSMA) expression is seen in the neovasculature of many types of tumors, such as prostate, renal, lung and recently breast cancer [5,6].

PSMA is heavily expressed by the tumor vascular endothelium in a variety of solid cancers, including prostate cancer, glioblastoma and primary adenocarcinoma of the breast, but is not evident in normal vascular endothelium and to only very low levels in normal prostate. Molecular imaging has become an indispensable tool in cancer research, clinical trials and medical practice. Imaging is attractive because most imaging techniques are either non- or minimally invasive, non-destructive, provide dynamic, real-time data and permit repeated measurements. Positron Emission Tomography (PET) imaging with ^{68}Ga-PSMA is very useful in the diagnosis of recurrent prostate cancer, mainly retrospective studies describe the value of ^{68}Ga-PSMA ligand PET/CT in different clinical scenarios in prostate cancer; however, there is insufficient evidence of the usefulness in

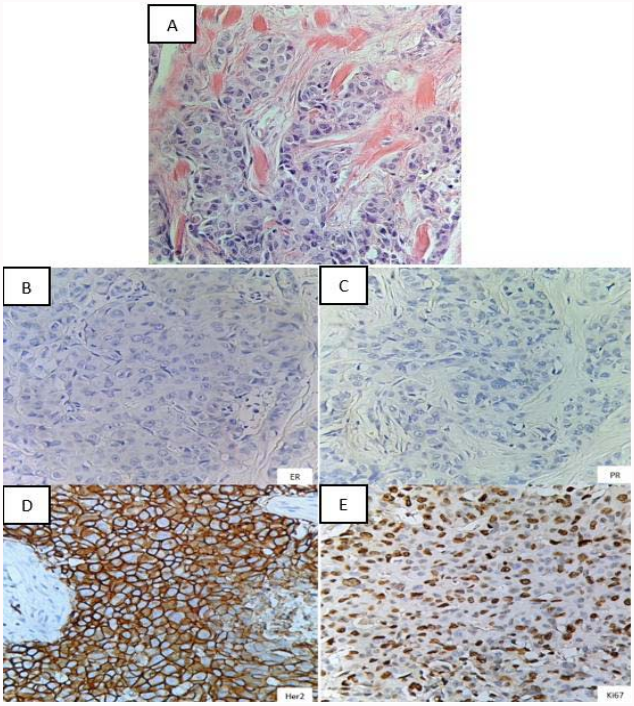

Figure 1: (a) Mastectomy specimen. Showed a high grade ductal carcinoma with necrosis of 10%, and infiltration papillary dermis and nipple, lymphovascular and perineural permeation (Hematoxylin and Eosin stain, original magnification x200. (b) Nuclear staining of ER was negative. (c) Nuclear staining of PR was negative. (d) Membrane staining of HER-2/neu was positive. Ki-67 positive in 90%.

breast cancer [7-8].

These case report suggest that PSMA expression in tumor associated neovasculature may be related to the degree and nature of neoangiogenesis. In addition the present case is the first evidence in which tumor viability is demonstrated in brain metastasis in patients live corroborated by PET-CT with 68Ga-PSMA.

Case Presentation

A forty-five-year-old woman, having nodule in the right breast with 2 years of evolution. Biopsy was performed fine needle aspiration whose histopathologic report was fibro adenoma; the injury progresses after a year with increased size. Ultrasound and mammography was performed, where a radiopaque mass of high density is evident in Upper Outer Quadrant (UOQ) right breast, with the presence of pleomorphic calcifications grouped. Right axillary adenopathy suspicious looking Birads 5. Trucut biopsy was performed reporting infiltrating ductal carcinoma SBR9 (Figure 1a and b). She was undergoing to neoadjuvant chemotherapy, receiving 12 cycles of paclitaxel / trastuzumab (with previous ventriculography normal, up 60%), and then four cycles of colony stimulating factor plus trastuzumab scheme; and continues with trastuzumab each three cycles per week. Once completed chemotherapy she was underwent modified radical mastectomy more right pectoralis major impeller. Pathology report infiltrating ductal carcinoma with 75% of necrosis. The patient fails to radiation oncology, and loses track for 6 months for unknown reasons. She was return after 4 months with history of progressive headache, dizziness and respiratory symptoms treated out our institute high at the time of valuation refers moderate headache and dizziness that limit progress. For this reason, brain MRI was performed, evidence lesion supratentorial and intra-axial (Figure 2),

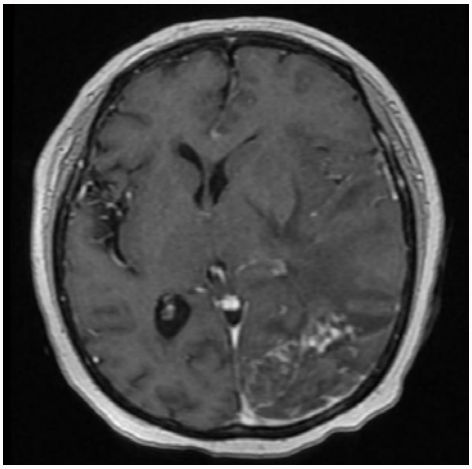

Figure 2: Brain MRI with contrast. Showed in the occipital region of the left side and ipsilateral wedge a ring enhancement after the intravenous contrast observing vasogenic edema which clears the parietal-occipital sulcus ipsilateral with maximum axis of 45 millimeters.

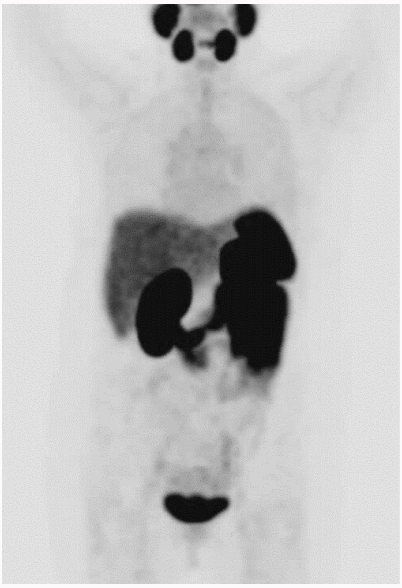

Figure 3: MIP of ^{68}Ga-PSMA PET. Note the normal biodistribution of ^{68}Ga-PSMA 1 h after injection. Accumulation is seen in salivary glands, nasal mucosa, liver, spleen, bowel, kidneys and bladder, and no focal abnormal uptake.

concluded as known primary reservoir and central nervous system progression is established.

Holocraneal patient initiates radiotherapy 30Gy in 10 fractions plustemozolomide, and restart trastuzumab plus capecitabine. It documented disease progression despite treatment.

It was decided to perform PET-CT ^{68}Ga-PSMA with reflected normal distribution without abnormal uptake in body, but increased uptake of radiotracer in brain, corresponding to brain metastases (Figure 3 and 4).

Discussion

The PSMA is a type II membrane glycoprotein consisting of 750 amino acids (100-120 kDa), with a 19 amino acid intracellular component, a 24 amino acid intramembrane segment, and a large 707 amino acid extracellular component. PSMA gene is located

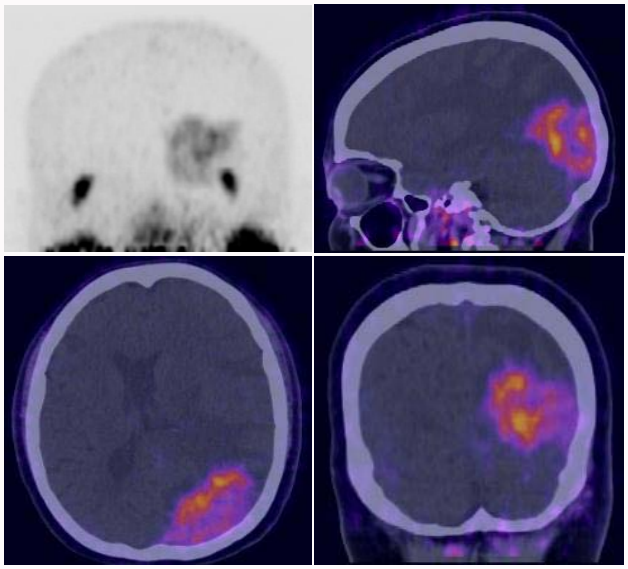

Figure 4: (upper left) MIP of skull showed abnormal uptake in brain. (rest of pictures) encephalomalacia area front temporo-occipito parietal left and area poorly defined irregular administration of contrast enhancement in parietal-occipital region ipsilateral surrounded by edema in the white matter of the ipsilateral hemisphere diversion line middle right associated with increased concentration of radiopharmaceutical.

on chromosome 11, and exhibits folate hydrolase/glutamate carboxypeptidase II enzymatic activity [9,10].

Instead, PSMA regulates tumor cell invasion and tumor angiogenesis by modulating integrin signal transduction in endothelial cells. The transcription of PSMA can be selectively activated through a transcriptional enhancer region in endothelial cells of the tumor neovasculature, but this region is absent in normal blood vessels [11-13].

PSMA PET/CT imaging seems to be a valuable imaging modality for evaluation of primary prostate cancer and it seems to have potential for the detection of lymph node and bone metastases, meanwhile this demonstrated that other tumors have overexpression of this glycoprotein *in vitro*, and the PET technique can be demonstrated *in vivo* [7-9].

Chang et al. [14] were perhaps the first to demonstrate by immunohistochemistry the presence of PSMA in 5 of 6 cases of breast cancer, characterized by the monoclonal antibody 7E11 and those of four recently developed anti-PSMA mAbs (J591, J415, and Hybritech PEQ226.5 and PM2J004.5), each of which binds a distinct epitope of PSMA; this study confirm PSMA expression in the neovasculature of a wide spectrum of malignant neoplasms.; rather than a PSMA-like molecule, is expressed in tumor-associated neovasculature.

More over Liuet al. [15] studied four external domain-binding anti-PSMA mAbs (J591, J415, J533, and E99) and showed that each bound the tumor-associated neovasculature in several variety of carcinomas (including lung, colon, breast, and others).

Wernicke et al. [16] they have the largest study in patients with breast cancer. Ninety-two patients had primary breast cancer (invasive breast carcinoma with or without co-existing ductal carcinoma *in situ* (DCIS) or DCIS alone). In addition, 14 patients with breast cancer metastases to the brain. Tumor-associated vasculature was PSMA-positive in 68/92 (74%) of primary breast cancers and in 14/14 (100%) of breast cancers metastatic to brain. PSMA was not detected in normal breast tissue or carcinoma cells.

Vascular Endothelial Growth Factor (VEGF) is one of several agents promoting angiogenesis. Some members of the VEGF family promote lymphogenesis as well. These newly formed blood and lymph vessels may be more susceptible to tumor cell invasion than normal vessels. A recent experimental model suggests that angiogenesis may be associated with metastasis independent of either invasion of normal tissue or intravasation into normal blood or lymph node.

These and other observations are remarkable given presence of PSMA expression in tumor-associated neovasculature of other cancer types [17].

Once tumor cells have infiltrated the brain, they require an adequate blood supply to grow and develop a metastatic lesion. The mechanisms that are involved in blood vessel recruitment by brain metastases cells appear to be strongly dependent on tumor origin as well as the metastatic microenvironment [18].

The importance of angiogenesis in breast cancer is well documented, and endothelial cell expression of PSMA appears highly restricted to tumor-associated neovasculature and may represent a novel target therapy with ^{177}Lu-PSMA.

Further analyses are required to confirm our findings and to further evaluate the characteristics of different types of metastases in different hormonal status, where it is demonstrated by PET-CT ^{68}Ga-PSMA tool, with the aim of administer therapeutic doses with ^{177}Lu-PSMA.

Conclusion

Understanding the molecular changes that breast tumor cells is crucial in obtaining novel targeting brain metastases therapeutics.^{68}Ga-PSMA PET/CT is a recent modality of molecular imaging especially for the diagnosis of recurrence in treated prostate cancer patients, meanwhile the heterogeneity of breast cancer requires a thorough analysis to identify those potential patients to receive therapy with the ^{177}Lu-PSMA may represent a promising approach. This case report further highlights to improve the value of PET-CT in this scenario.

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