68Ga-Prostate-Specific Membrane Antigen Uptake as a Surrogate Biomarker of Neovascularity in Hepatocellular Carcinoma

Abstract

68Ga-prostate-specific membrane antigen (68Ga-PSMA) is expressed in the endothelium of tumor-associated neovascularature of various solid malignancies possibly due to tumor-associated angiogenic factors and endothelial cell sprouting. We report a case of a 45-year-old man with known colorectal cancer, cirrhosis, and hepatitis C. Contrast-enhanced computed tomography (CT) showed a hypervascular lesion in the liver, and 18F-fluorodeoxyglucose positron emission tomography (PET) did not show any suspicious hepatic uptake. 68Ga-PSMA PET-CT showed predominantly heterogeneous perilesional uptake in a configuration similar to the arterial enhancement pattern on the diagnostic CT. 68Ga-PSMA uptake in hepatocellular carcinoma appears to be primarily neoangiogenesis driven, and its morphological and functional characterization can subsequently influence the selection of anti-neoangiogenic chemotherapy agents as well as guiding radionuclide ligand therapy.

Keywords: 68Ga-prostate-specific membrane antigen positron emission tomography/computed tomography, angiogenesis, hepatocellular carcinoma, positron emission tomography/computed tomography

A 45-year-old male, with an established history of hepatitis C and colorectal cancer treated with surgery 2 years back, showed a hepatic mass on ultrasonography suspicious for metastases. Carcinoembryonic antigen was normal with high alpha fetoprotein values. Contrast enhanced computed tomography (CECT), demonstrated a large predominantly hypodense lesion in segment VII [Figure 1i-k] with enhancement of the lesion in the arterial phase and rapid washout during the delayed phase, i.e., appearances highly suspicious of hepatocellular carcinoma (HCC). A subsequent fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) was negative, however, a 68Ga prostate specific membrane antigen (PSMA) PET CT [Figure 1a-h] showed heterogeneous uptake related to the mass. This was predominantly in a peripheral distribution, i.e., in a configuration quite similar to the enhancement pattern seen on arterial phase of CECT. Subsequent biopsy of the lesion confirmed HCC.

18F-FDG PET-CT has a limited role in HCC as only half of the cases are 18F-FDG avid.[1] However, 68Ga-PSMA uptake has been reported in solid malignant tumors including breast cancer, HCC, and renal cell carcinoma[2-4] and is thought to be in tumoral microvessels.[5] Preliminary data indicate that the detection rate of

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Access this article online
Website: www.ijnm.in
DOI: 10.4103/ijnm.IJNM_38_20

How to cite this article: Muzaffar S, Ahmed N, Rahman U, Al Kandari F, Usmani S. 68Ga-prostate-specific membrane antigen uptake as a surrogate biomarker of neovascularity in hepatocellular carcinoma. Indian J Nucl Med 2021;36:90-1.
$^{68}$Ga-PSMA PET-CT is superior to $^{18}$F-FDG in HCC. A recent study by Tolkach et al.\cite{7} reported that HCC has high levels of PSMA expression on tumor vessels and canalicular membrane of tumor cells. PSMA plays a major role in regulating angiogenesis and is expressed in the endothelium of tumor-associated neovasculature in these solid malignancies possibly due to tumor-derived angiogenic factors and endothelial cell sprouting.\cite{8,9}

Our case highlights the advantage of $^{68}$Ga-PSMA PET-CT in comparison to $^{18}$F-FDG PET-CT in characterizing focal hepatic lesions suspicious of HCC. These morphological features on CECT are usually secondary to abnormal handling of contrast material by newly formed vessels in a malignant lesion.\cite{10} Unsurprisingly, the typical pattern of enhancement on CECT imaging in HCC has been shown to correlate with microvessel density.\cite{11} The most interesting aspect of the current images is that the arterially enhancing peripheral component of the index liver lesion displaying higher $^{68}$Ga-PSMA uptake indirectly reflects the positive correlation between increased $^{68}$Ga-PSMA and lesion neovascularity.

This observation also highlights the potential of $^{68}$Ga-PSMA PET-CT in guiding therapeutic options in HCC. This includes suitability and response assessment with antiangiogenic chemotherapy and as a potential guide to radionuclide legend therapy with $\alpha/\beta$-emitters. Some recent studies have shown promising response rates of $^{177}$Lu-617 PSMA-targeted radioligand therapy\cite{12,13} and in the future, PSMA-targeted radioligand therapies can also be considered for other cancers including HCC.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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