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Unusual Increased Blood Pool Activity on ^{68}Ga-DOTATATE PET/CT in a Patient With Metastatic Neuroendocrine Disease

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Abstract: ^{68}Ga-DOTATATE is a well-established, positron-emitting, somatostatin receptor–binding radiopharmaceutical. We present an unusual case of transiently increased blood pool uptake of ^{68}Ga-DOTATATE in a patient with well-differentiated stage IV neuroendocrine tumor, with Ki-67 <2% (WHO grade 1) maintained on lanreotide. During serial ^{68}Ga-DOTATATE PET/CT examinations, increased blood pool accumulation of presumably unbound ^{68}Ga was demonstrated, which could impact the Kenning score and lead to a false treatment response assessment.

Key Words: ^{68}Ga-DOTATATE PET/CT, somatostatin receptor, neuroendocrine tumor, blood pool

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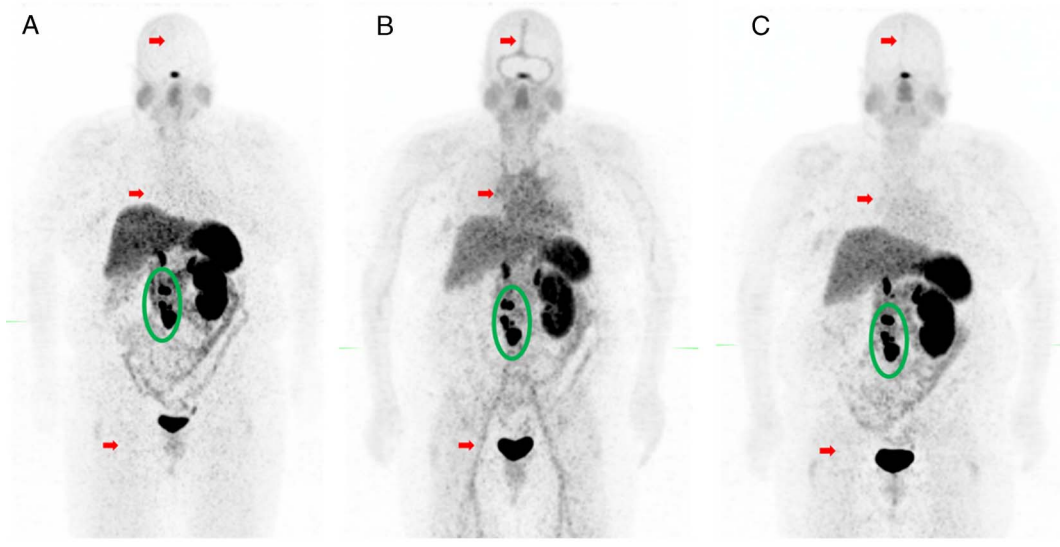

FIGURE 1. MIP images of serial ^{68}Ga-DOTATATE PET studies of a woman with biopsy-proven metastatic well-differentiated neuroendocrine tumor (WHO grade 1). Initial time point (**A**) demonstrates ^{68}Ga-DOTATATE–avid retroperitoneal nodal disease (green circle) and typical low blood pool activity (red arrows). Follow-up ^{68}Ga-DOTATATE PET (**B**) after commencement of lanreotide therapy demonstrates interval increased blood pool uptake (red arrows) and interval decreased uptake in the liver, spleen, and retroperitoneal lymph nodes (green circle). Subsequent ^{68}Ga-DOTATATE PET (**C**) demonstrated interval resolution of blood pool uptake (red arrows) and increased ^{68}Ga-DOTATATE uptake in retroperitoneal lymph nodes (green circle). As seen here, physiologic biodistribution of ^{68}Ga-DOTATATE includes the pituitary and salivary glands, liver, spleen, kidney, adrenals, pancreas, and some gastrointestinal and marrow uptake.[1,2] Increased blood pool component has been described for ^{67}Ga-citrate but not for ^{68}Ga-DOTATATE,[3] and ^{68}Ga-DOTATATE has been shown to have high in vitro and in vivo stability at many time points.[4,5] However, informal communications with the manufacturer and unpublished work from our radiochemistry department have confirmed that ^{68}Ga can have suboptimal binding to the DOTA cage and may bind to blood products such as transferrin.[6] The high blood pool ^{68}Ga uptake in this patient is believed to be unbound ^{68}Ga, as DOTA conjugated ^{68}Ga clears rapidly from the blood.[7] The probability of unbound ^{68}Ga is most likely independent of the production of ^{68}Ga, whether via generator or cyclotron.[8,9] Preclinical studies demonstrates that ^{177}Lu-DOTATATE has similar binding stability to ^{68}Ga-DOTATATE,[10] and thus although rare, incomplete binding of ^{177}Lu-DOTATATE could in theory result in suboptimal treatments.

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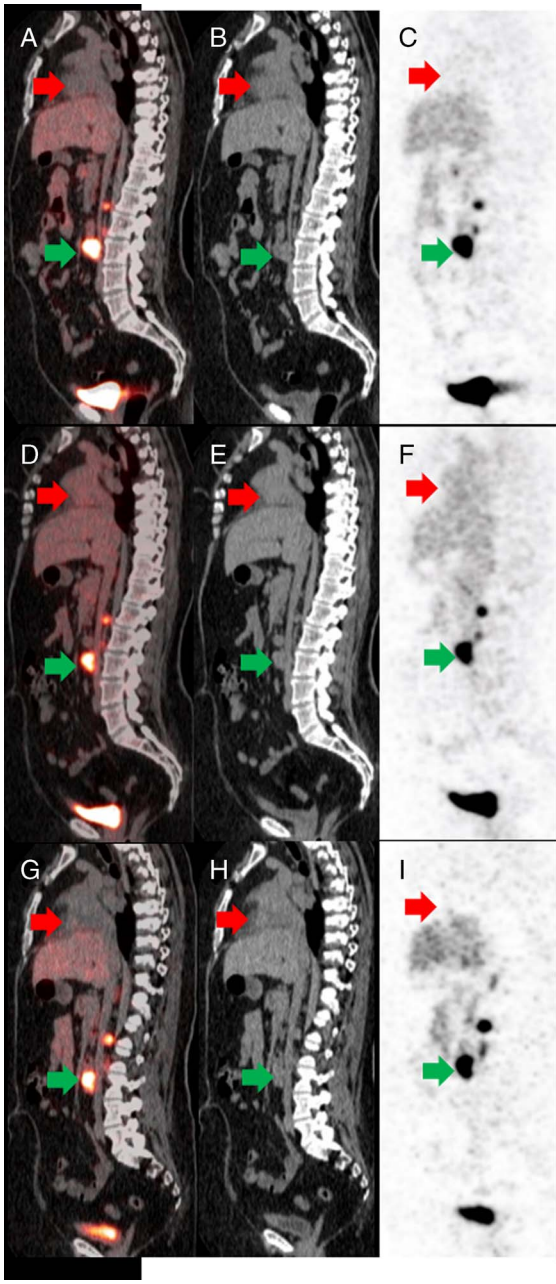

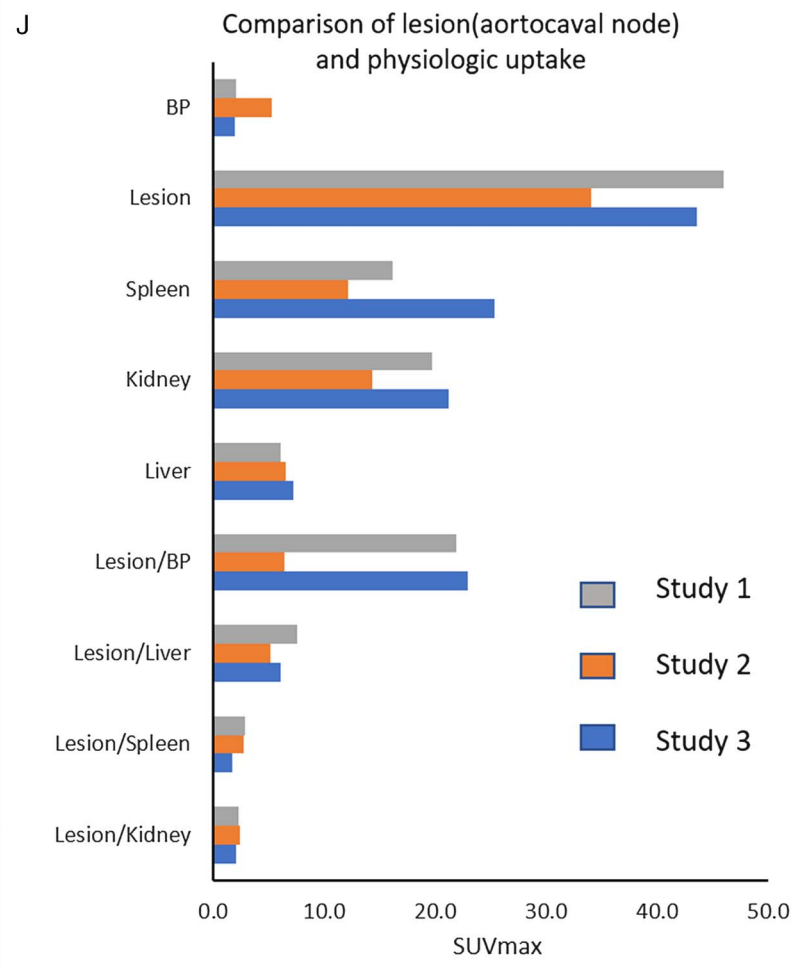

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	Study 1	Study 2	Study 3
Lesion (SUVmax)	43.6	34.1	46.0
Lesion (size in cm)	2.1x1.9	2.3x2.1	2.4x2.1
Blood Pool (BP)	1.9	5.3	2.1

FIGURE 2. Sagittal images from serial ^{68}Ga-DOTATATE PET/CT show inverse relationship between nodal disease and blood pool uptake. Initial time point ^{68}Ga-DOTATATE sagittal fused (**A**), CT (**B**), and PET (**C**) demonstrate low blood pool uptake (red arrows; SUV_{max}, 1.9) and high ^{68}Ga-DOTATATE uptake in a dominant aortocaval lymph node (green arrows; SUV_{max}, 43.6). Sagittal fused (**D**), CT (**E**), and PET (**F**) of 2 months' follow-up ^{68}Ga-DOTATATE show high blood pool SUV values (red arrows; SUV_{max}, 5.3) and corresponding drop in ^{68}Ga-DOTATATE uptake in the aortocaval lymph node (green arrows; SUV_{max}, 34.1), which returned to baseline values on subsequent ^{68}Ga-DOTATATE imaging with fused (**G**), CT (**H**), and PET (**I**) with low blood pool uptake (red arrows; SUV_{max}, 2.1) and high lymph node uptake (green arrows; SUV_{max}, 46). In this case, the lesion and blood pool uptake showed greater variability than in liver, spleen, and kidney (**J**). There was no substantial change in lymph node sizes between the 3 studies on CT images (**K**).

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