Case Report

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^{68}Ga DOTATOC PET-CT and ^{123}I-mIBG scan discordances in a refractory case of pediatric neuroblastoma: implications for patient management

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ABSTRACT

High-risk and refractory neuroblastomas carry poor overall survival, and novel approaches must be explored to improve global outcome. With better knowledge of underlying molecular patterns and growing radioligand portfolio, nuclear medicine physicians can test new strategies for disease assessment and therapy. For decades, meta-iodobenzylguanidine (mIBG) has been used to evaluate disease extent when coupled with iodine-123 due to the high expression of noradrenaline transporter (NAT) in neuroblastoma cells. In recent years, ^{68}Ga-DOTATOC has emerged as a new PET-CT tool to screen for somatostatin receptor subtype 2 (SSTR-2) overexpression, opening the way to internal radiotherapy mediated by ^{177}Lu-DOTATATE. We report the case of a 6-year-old patient with refractory neuroblastoma and extensive bone involvement after three lines of chemotherapy. Dual exploration with ^{123}I-mIBG scintigraphy and ^{68}Ga-DOTATOC PET-CT was performed to evaluate the more appropriate therapeutic strategy. We observed significant mismatches regarding bone lesions, some overexpressing NAT and/or SSTR-2. This rare presentation highlights the phenotypic heterogeneity of metastases after various lines of chemotherapy. With more than half of lesions with no or weak SSTR-2 expression, ^{177}Lu-DOTATATE internal therapy was ruled out. Further investigations are needed to better comprehend this tumor mismatch and its prognostic implications. Screening of molecular targets using complementary nuclear imaging techniques is an interesting option to guide treatment of refractory neuroblastomas.

Keywords: Neuroblastoma; ^{123}I-mIBG; ^{68}Ga-DOTATOC; PET-CT; Imaging Biomarkers

Introduction

Neuroblastoma is a severe condition in youth population, affecting mainly children before five and representing up to 10% of solid pediatric tumors [1]. Overall survival remained poor despite significant advances in therapies. Deriving from cells originating from peripheral sympathetic nervous system, this extracranial malignancy is divided into three groups of different prognoses (low-, intermediate- and high-risk groups) according to various criteria (age, stage, molecular patterns). High-risk patients are prone to metastatic osteo medullar spreading. 5-year overall survival can exceed 60% with modern treatment protocols [2], but the exploration of new diagnostic and therapeutic strategies is needed to reduce the mortality of metastatic children.

During the last decades, neuroblastoma imaging assessment relies primarily on computed tomography (CT) and Magnetic Resonance Imaging (MRI) for local exploration, while iodine-123 meta-iodobenzylguanidine (^{123}I-mIBG) scintigraphy allows for whole-body evaluation. Imaging in neuroblastoma is chosen upon the International Neuroblastoma Response Criteria (INRC) which have been revised in 2017 [3] under the validation of international groups such as International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) group, with dedicated scoring systems for the metastatic spread assessment and for the evaluation of treatment response. The International Neuroblastoma Risk Group (INRG) designed the INRG Staging System (INRGSS) to stratify patients at initial diagnosis prior to treatment.

The high sensitivity of ^{123}I-mIBG to identify both tissue and bone metastases is correlated to the overexpression of noradrenaline transporter (NAT) in neuroblastoma cells, leading to the high uptake of the radiopharmaceutical inside tumor. This exam can also be used to screen patients who may benefit from ^{131}I-mIBG therapy [4]. In addition, it has been shown that neuroblastoma may also express somatostatin receptor subtype 2 (SSTR-2) in up to 90% of neuroblastoma cells [5-7]. Tumor abundance of somatostatin receptor is currently assessed in nuclear medicine for diagnostic and therapeutic strategies, mainly for mid-gut neuroendocrine malignancies using radiolabeled somatostatin analogues (e.g., ^{68}Ga-DOTATOC for diagnostic and ^{177}Lu-DOTATATE for therapy). Neuroblastoma patients with high levels of SSTR-2 expression on ^{68}Ga-DOTATOC positron emission tomography-computed tomography (PET-CT) may beneficiate from ^{177}Lu-DOTATATE therapy, with recently demonstrated safety on few case reports and clinical trials [8,9].

Case Presentation

We present the case of a 6-year-old patient diagnosed with left adrenal neuroblastoma with synchronous plurifocal metastatic bone involvement. Induction chemotherapy was performed using GPOH protocol (six alternating courses, N5 (vindesine, cisplatin, etoposide) and N6 (vincristine, dacarbazine, ifosfamide, doxorubicin) [10], but disease response was considered insufficient after six months. Consequently, a new induction chemotherapy was initiated with a combination of irinotecan and temozolomide (VERITAS protocol). After three cycles, a dissociated response was observed: partial response of lower limbs and sacrum metastases, and progression of a secondary cranial lesion. Local radiotherapy was performed on the cranial metastasis, and chemotherapy with irinotecan and temozolomide was pursued. After a total of six cycles, progressive disease was confirmed. According to current guidelines, therapeutic strategy was switched to topotecan-cyclophosphamide in combination with dinutuximab (anti-GD2 antibody). Progressive disease was observed after six cycles of the above-mentioned therapy on ^{123}I-mIBG imaging (whole-body SPECT/CT acquisition 20h after 146 MBq of ^{123}I-mIBG administration; VERITON-CT, Spectrum Dynamics Medical, Israel) (Figure 1A).

International Society of Pediatric Oncology European Neuroblastoma (SIOPEN) classification is used for assessing disease extension in neuroblastoma. Scoring is evaluated using the following criteria. Skeleton is divided in 12 anatomical segments with grading related to the involvement of each segment: 0, no lesion; 1: one discrete lesion; 2: two discrete lesions; 3: three discrete lesions; 4: more than three discrete lesions or diffuse involvement below 50%; 5: diffuse involvement between 50% et 95%; 6: whole segment involvement. With ^{123}I-mIBG scintigraphy, a value of 19/72 was reached in this patient, with identification of various bone foci. Ten days later, to assess the feasibility of metabolic radiation therapy using radiolabeled somatostatin analogues, a whole-body ^{68}Ga-DOTATOC PET-CT was performed (Discovery Omni Legend PET-CT system (GE Healthcare), 2-min/FOV) 50 minutes after intravenous administration of 37 MBq of ^{68}Ga-DOTATOC (according to BMI and pediatric guidelines [11]). SIOPEN scoring reached a value of 34/72 (Figure 1B).

^{68}Ga-DOTATOC PET-CT was indeed able to identify more lesions than ^{123}I-mIBG scintigraphy: e.g., median skull, upper left humerus, distal left femur and right tibia foci. However, some lesions were remarkably visible only on ^{123}I-mIBG scan, with no or very low uptake on ^{68}Ga-DOTATOC PET-CT: e.g., right skull, right humerus, right acetabulum. Consequently, a significant mismatch of bone lesions was identified in this patient (Figures 1C-1H), with suspected underlying tumoral heterogeneity. As there were more than 50% of lesions with weak to moderate SSTR-2 expression and uptake lower than liver, it was decided that the patient should not be treated with ^{177}Lu-DOTATATE.

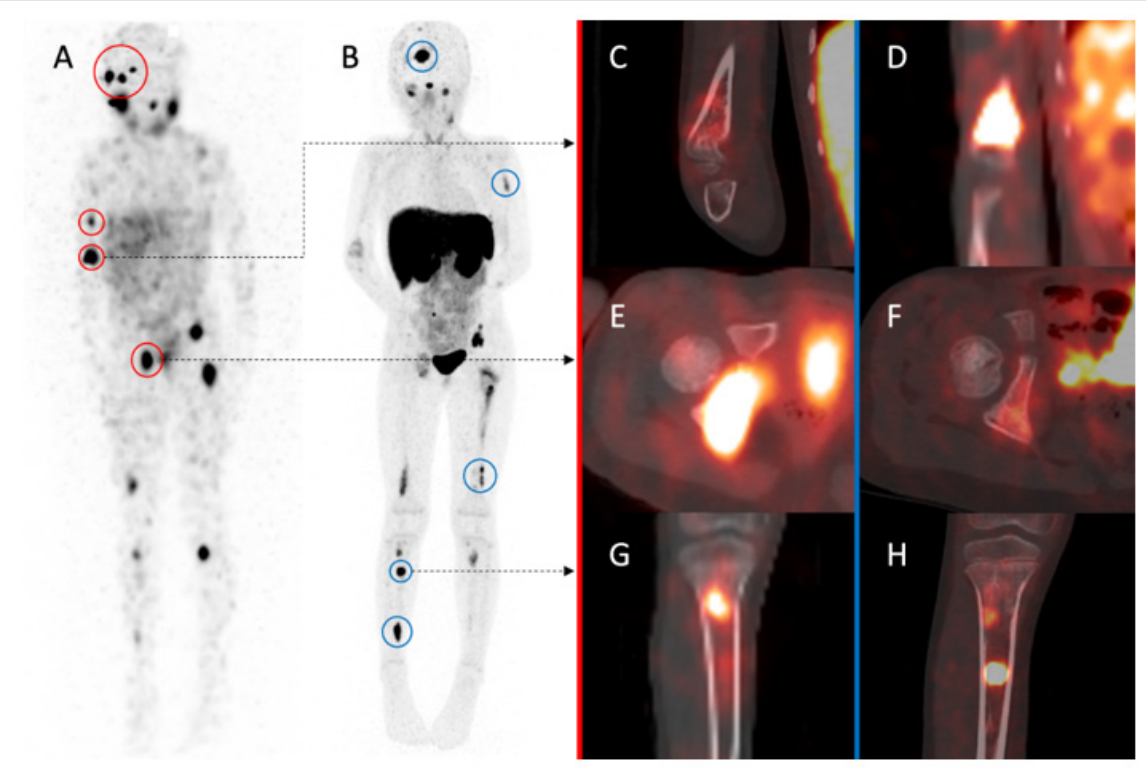

Figure 1: Anterior planar view of ^{123}I-mIBG scintigraphy (A) and maximum intensity projection of ^{68}Ga-DOTATOC PET-CT (B) revealing bone foci mismatch, some lesions presenting with high ^{123}I-mIBG uptake but lower than liver ^{68}Ga-DOTATOC uptake (red circles), while others presented with no or low ^{123}I-mIBG uptake and high ^{68}Ga-DOTATOC uptake (blue circles). Fused ^{123}I-mIBG SPECT/CT (red lined column) and ^{68}Ga-DOTATOC PET-CT (blue lined column) displaying noticeable mismatch on right distal humerus (C and D respectively, coronal view), right acetabulum (E and F respectively, axial view) and right tibia (G and H respectively, coronal view).

Discussion

This case report highlights the tumoral heterogeneity in a patient with refractory neuroblastoma with bone metastases after three lines of chemotherapy. Imaging of both NAT and SSTR-2 receptors allows for extensive knowledge of molecular targets. While ^{177}Lu-DOTATATE internal radiotherapy data remains scarce, there has been several studies assessing the role and the efficacy of ^{131}I-mIBG in the population of refractory neuroblastoma, able to induce disease response in a significant proportion of patients [12-15]. In the past years, ^{177}Lu-DOTATATE has emerged as a new treatment of metastatic but well-differentiated neuroendocrine malignancies, and its effectiveness for disease control has been demonstrated in a large randomized clinical trial [16]. Given the high mortality rate of children with refractory neuroblastoma, there is a need for new therapeutic approaches, and ^{177}Lu-DOTATATE could be an additional line aside chemotherapy, anti-GD2 immunotherapy and ^{131}I-mIBG therapy.

Dual exploration with ^{123}I-mIBG planar scintigraphy and ^{68}Ga-DOTATOC PET maximum intensity projection (MIP) has been performed by Gains and al. in 2020 in a cohort of 42 patients with neuroblastoma (including 13 patients with refractory disease and 26 patients with relapsed disease), to evaluate and compare the distribution of these radiopharmaceuticals [17]. ^{68}Ga-DOTATOC MIP was able to detect pathological foci in all patients (42/42), while ^{123}I-mIBG scintigraphy missed bone and/or soft-tissue disease in 2/42 patients. As 36/42 patients had bone disease, ^{123}I-mIBG scintigraphy was positive for 29/36 patients, thus underperforming ^{68}Ga-DOTATOC MIP having a positivity rate of 35/36, but the difference was non-significant ($p = 0.07$). It is noteworthy that 7/36 patients had positive bone lesions with ^{68}Ga-DOTATOC MIP and negative with ^{123}I-mIBG scintigraphy, while only 1/36 patient had positive bone lesions with ^{123}I-mIBG scintigraphy and negative with ^{68}Ga-DOTATOC MIP. Discordances between the two imaging techniques were observed in 26/42 patients for skeletal disease and 15/42 for soft-tissue disease. Similarly, to our case report, a mismatch in disease extent was observed in 2/42 patients.

In 2018, the same team carried out an analysis of NAT and SSTR-2 immunohistochemical expression in neuroblastoma tissue samples of 75 patients [18]. They reported a marked intensity and heterogeneity

regarding the expression of both molecular targets. Moreover, only a weak correlation was seen between the expression of NAT and SSTR-2 (correlation coefficient = 0.23, p = 0.05), including in patients with stage 4 disease. Patients without MYCN amplification seem to have higher SSTR-2 expression, suggesting a more severe disease. It was also highlighted that expression of both NAT and SSTR-2 tend to increase in refractory patients compared to baseline. Increased SSTR-2 expression as assessed by immunohistochemistry seems to be related to lesions that are more aggressive. Finally, no relation to age, sex, stage, or overall survival was found. These data contrast with an earlier study on a cohort of 49 patients suggesting that primary neuroblastoma with high levels of SSTR-2 expression measured by RT-PCR is associated with better cumulative survival [19].

This case report shows that there is biological heterogeneity in the expression of noradrenaline and somatostatin receptors, so that both imaging methods are complementary and useful to guide on the choice of the most adequate molecular radiotherapy. Heterogeneous clonal evolution related to genomic instability might be responsible for the mismatch seen in this patient. Biopsies and molecular analysis of tumors could be performed to assess molecular profile. It is interesting to notify that this almost complete mismatch between ^{68}Ga-DOTATOC PET and ^{123}I-mIBG scintigraphy is extremely rare. Moreover, these findings suggest that molecular radiotherapy targeting either NAT or SSTR-2 alone may not treat all the disease. Combined treatments with both ^{131}I-mIBG and ^{177}Lu-DOTATATE may have an advantage over either radiopharmaceutical used as a single agent; however, feasibility and safety need to be explored on prospective clinical trials.

Conclusion

We highlight the molecular discordance of NAT and SSTR-2 receptors expression revealed by dual exploration with ^{123}I-mIBG scintigraphy and ^{68}Ga-DOTATOC PET-CT respectively in a patient with neuroblastoma-related extensive bone involvement, thus ruling out internal therapy with radiolabeled somatostatin analogues. This case confirms the phenotypic heterogeneity of metastatic disease and illustrates the importance of comprehensive target screening using nuclear imaging modalities.

References

1. Irwin MS, Park JR (2015) Neuroblastoma: Paradigm for precision medicine. Pediatr Clin North Am 62: 225-256.
2. Chung C, Boterberg T, Lucas J, Panoff J, Valteau Couanet D, et al. (2021) Neuroblastoma. Pediatr Blood Cancer 68(2): e28473.
3. Park JR, Bagatell R, Cohn SL, Pearson AD, Villablanca JG, et al. (2017) Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement from the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 35(22): 2580 2587.
4. Bar Sever Z, Biassoni L, Shulkin B, Kong G, Hofman MS, et al. (2018) Guidelines on Nuclear Medicine Imaging in Neuroblastoma. Eur J Nucl Med Mol Imaging 45(11): 2009-2024.
5. O Dorisio MS, Chen F, O Dorisio TM, Wray D, Qualman SJ (1994) Characterization of somatostatin receptors on human neuroblastoma tumors. Cell Growth Differ 5(1): 1-8.
6. Albers AR, O Dorisio MS, Balster DA, Caprara M, Gosh P, et al. (2000) Somatostatin Receptor Gene Expression in Neuroblastoma. Regul Pept 88(1-3): 61-73.
7. Georgantzi K, Tsolakis AV, Stridsberg M, Jakobson Å, Christofferson R, et al. (2011) Differentiated Expression of Somatostatin Receptor Subtypes in Experimental Models and Clinical Neuroblastoma: Expression of Somatostatin Receptors in Neuroblastoma. Pediatr Blood Cancer 56: 584 589.
8. Kong G, Hofman MS, Murray WK, Wilson S, Wood P, et al. (2016) Initial Experience with Gallium-^{68} DOTA-Octreotate PET/CT and Peptide Receptor Radionuclide Therapy for Pediatric Patients with Refractory Metastatic Neuroblastoma. J Pediatr Hematol Oncol 38: 87-96.
9. Gains JE, Bomanji JB, Fersht NL, Sullivan T, D Souza D, et al. (2011) ^{177} Lu-DOTATATE Molecular Radiotherapy for Childhood Neuroblastoma. J Nucl Med 52(7): 1041-1047.
10. Berthold F, Faldum A, Ernst A, Boos J, Dilloo D, et al. (2020) Extended Induction Chemotherapy Does Not Improve the Outcome for High-Risk Neuroblastoma Patients: Results of the Randomized Open-Label GPOH Trial NB2004-HR. Ann Oncol 31(3): 422-429.
11. Abongwa C, Mott S, Schafer B, McNeely P, Abusin G, et al. (2017) Safety and Accuracy of 68Ga-DOTATOC PET/CT in Children and Young Adults with Solid Tumors. Am J Nucl Med Mol Imaging 7(5): 228-235.
12. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, et al. (2007) Phase II Study on the Effect of Disease Sites, Age, and Prior Therapy on Response to Iodine-^{131}-Metaiodobenzylguanidine Therapy in Refractory Neuroblastoma. J Clin Oncol 25: 1054-1060.
13. Hutchinson RJ, Sisson JC, Miser JS, Zasadny KR, Normolle DP, et al. (1991) Long-term results of [^{131}I]metaiodobenzylguanidine treatment of refractory advanced neuroblastoma. J Nucl Biol Med 35: 237-240.
14. Lashford LS, Lewis IJ, Fielding SL, Flower MA, Meller S, et al. (1992) Phase I/II Study of Iodine 131 Metaiodobenzylguanidine in Chemoresistant Neuroblastoma: A United Kingdom Children's Cancer Study Group Investigation. J Clin Oncol 10: 1889-1896.
15. DuBois SG, Matthay KK (2008) Radiolabeled Metaiodobenzylguanidine for the Treatment of Neuroblastoma. Nucl Med Biol 35(1): 35-48.
16. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, et al. (2017) Phase 3 Trial of ^{177} Lu-Dotatate for Midgut Neuroendocrine Tumors ». N Engl J Med 376: 125-135.
17. Gains JE, Aldridge MD, Mattoli MV, Bomanji JB, Biassoni L, et al. (2020) ^{68}Ga-DOTATATE and ^{123}I-MIBG as Imaging Biomarkers of Disease Localisation in Metastatic Neuroblastoma: Implications for Molecular Radiotherapy. Nucl Med Commun 41: 1169-1177.
18. Gains JE, Sebire NJ, Moroz V, Wheatley K, Gaze MN (2018) Immunohistochemical Evaluation of Molecular Radiotherapy Target Expression in Neuroblastoma Tissue. Eur J Nucl Med Mol Imaging 45: 402-411.
19. Orlando C, Raggi CC, Bagnoli L, Sestini R, Briganti V, et al. (2001) Somatostatin receptor type 2 gene expression in neuroblastoma, measured by competitive RT-PCR, is related to patient survival and to somatostatin receptor imaging by indium-111-pentetreotide. Med Pediatr Oncol 36: 224-226.

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