Graves' Ophthalmopathy on ^{68}Ga-DOTANOC Positron Emission Tomography/Computed Tomography

Abstract

Graves' ophthalmopathy (GO) involves autoimmune activation of fibroblasts, resulting in chronic inflammatory reaction. Somatostatin receptors are expressed in the cells associated with chronic inflammation. We hereby present patients with active GO, with delayed response to the standard treatment regimen, in whom ^{68}Ga-DOTANOC positron emission tomography/computed tomography (PET/CT) was planned to evaluate the orbital inflammation. ^{68}Ga-DOTANOC PET/CT shows no physiological orbital muscle uptake. It can provide information which may possibly of utility in response assessment and also screening patients who fail to respond to conventional treatment, for newer therapies such as long-acting somatostatin analogs.

Keywords: *^{68}Ga-DOTANOC positron emission tomography/computed tomography, chronic inflammation, Graves' ophthalmopathy*

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Figure 1a-i shows ^{68}Ga-DOTANOC positron emission tomography/computed tomography (PET/CT) orbital cross-section in three different patients (control, patient 1, and patient 2) with physiologic pituitary uptake seen in all three patients (yellow arrows). Figure 1a-c shows sections in a 44-year-old male with a history of pheochromocytoma (taken as control for Graves' ophthalmopathy [GO] group). Scan shows normal extraocular muscles (EOM) with no abnormal uptake (c, white arrow). Figure 1d-f shows sections, in a 65-year-old woman with severe GO (left > right), initially managed for her thyroid eye disease with pulse intravenous methyl prednisolone (6 gm) and left orbital decompression but showed delayed response to treatment. Scan shows bulky EOM (left > right) (e and f, white arrow) with somatostatin receptor (SSTR) expression. Neck sections showed enlarged both lobes of thyroid with increased tracer uptake, with a large nodule in the left lobe (d, black arrow) and also retrosternal extension from the right lobe forming a globular mass (d, red arrow). Fine-needle aspiration cytology from the left lobe cold nodule showed benign adenomatous changes (Bethesda 2). Her thyroid profile suggested hyperthyroid status, fT4 – 2.68 ng/dl (0.9–1.7 ng/dl), fT3 – 5.6 pg/ml (2–4.4 pg/ml), and thyroid stimulating hormone (TSH) <0.005 μIU/ml. For thyroid dysfunction, she was started on antithyroid drug (tablet carbimazole 30 mg/day) which was increased to 40 mg/day. Total thyroidectomy is planned after achieving the euthyroid status. Figure 1g-i shows sections in a 38-year-old woman with severe GO initially treated with oral glucocorticoids. Orbital sections show bulky superior rectus muscle (h and i, white arrow) with SSTR expression. Neck sections showed enlarged both lobes of thyroid showing increased tracer uptake with the presence of pyramidal lobe. Her thyroid profile suggested subclinical hyperthyroid profile, total T4–5.64 μg/dl (5.1–14.1 μg/dl), total T3–151 ng/dl (80–200 ng/dl), and TSH 0.028 μIU/ml. For thyroid dysfunction, she was started on antithyroid drug (tablet carbimazole 20 mg/day).

GO is an extrathyroidal manifestation of Graves' disease.[1,2] It involves autoimmune activation of fibroblasts, through different autoantigens, commonly involving thyrotropin receptor.[3] Lymphocytes also play a crucial role. Cluster differentiation (CD4+) T-lymphocytes cause activation of fibroblasts by forming CD40–CD154 bridges.[4] Other mononuclear

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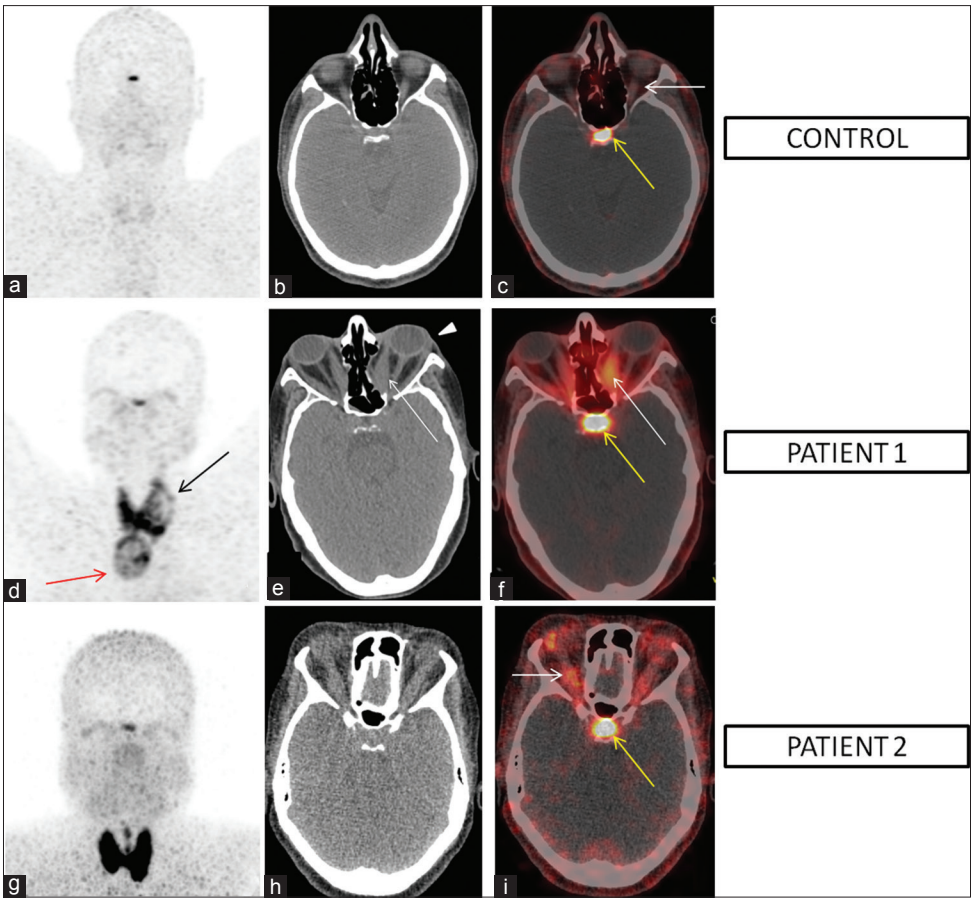

Figure 1: ^{68}Ga-DOTANOC positron emission tomography/computed tomography (control, patient 1, and patient 2). (a-c) Control (pheochromocytoma) showing normal extraocular muscles with no abnormal uptake (c, white arrow). (d-f) A 65-year-old woman with severe Graves' ophthalmopathy showing bulky extraocular muscles with somatostatin receptor expression. Neck shows enlarged thyroid with increased tracer uptake and retrosternal extension forming a globular mass (red arrow). (g-i) A 38-year-old woman with severe Graves' ophthalmopathy showing bulky extraocular muscles (white arrow) with somatostatin receptor expression. Neck sections showing enlarged both lobes of thyroid with pyramidal lobe

cells including CD8+ T-cells, B-cells, and plasma cell are also involved, resulting in chronic inflammation in orbital tissue.[5] All these factors cause hyperplasia of adipose tissue, accumulation of glycosaminoglycans resulting in expansion of EOMs, and periorbital soft tissue.[6] In a study by García-Rojas *et al*., they demonstrated, sensitivity of 18F-fluorodeoxyglucose (^{18}F-FDG) PET/CT in detecting inflammation in GO is superior to other anatomical imaging methods.[7] However, one limitation of ^{18}F-FDG PET/CT is the presence of physiological muscle uptake which can create difficulties in interpretation.[8] The molecular basis of using SSTR imaging in assessing GO is the expression of SSTRs in the cells associated with chronic inflammation in active GO.[9] Few previous studies have demonstrated SSTR expression in periorbital tissue using ^{111}In-pentetreotide scan (Octreoscan) and have also shown that intensity of uptake correlates with clinical stage of GO.[10,11] SSTR expression in active GO has also been demonstrated using ^{68}Ga-DOTANOC PET/CT.[12] This also forms the basis for using long-acting somatostatin analogs as a treatment option for refractory GO patients because these peptides inhibit lymphocyte activation, proliferation, and cytokine production.[13] ^{68}Ga-DOTANOC PET/CT shows no physiological orbital muscle uptake as shown in the control patient [Figure 1a-c]. It can also possibly provide information that can be used in response assessment of patients treated with standard therapies and screening patients who fail to respond to conventional treatment, for newer therapies such as long-acting somatostatin analogs.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: Reality and perspectives. Endocr Rev 2000;21:168-99.
2. Bahn RS. Graves' ophthalmopathy. N Engl J Med 2010;362:726-38.
3. Iyer S, Bahn R. Immunopathogenesis of Graves' ophthalmopathy: The role of the TSH receptor. Best Pract Res Clin Endocrinol Metab 2012;26:281-9.

4. Feldon SE, Park DJ, O'Loughlin CW, Nguyen VT, Landskroner-Eiger S, Chang D, *et al*. Autologous T-lymphocytes stimulate proliferation of orbital fibroblasts derived from patients with Graves' ophthalmopathy. Invest Ophthalmol Vis Sci 2005;46:3913-21.
5. Eckstein AK, Quadbeck B, Tews S, Mann K, Krüger C, Mohr CH, *et al*. Thyroid associated ophthalmopathy: Evidence for CD4(+) gammadelta T cells; de novo differentiation of RFD7(+) macrophages, but not of RFD1(+) dendritic cells; and loss of gammadelta and alphabeta T cell receptor expression. Br J Ophthalmol 2004;88:803-8.
6. Wiersinga WM, Prummel MF. Pathogenesis of Graves' ophthalmopathy – Current understanding. J Clin Endocrinol Metab 2001;86:501-3.
7. García-Rojas L, Adame-Ocampo G, Alexánderson E, Tovilla-Canales JL 18-fluorodeoxyglucose uptake by positron emission tomography in extraocular muscles of patients with and without Graves' ophthalmology. J Ophthalmol 2013;2013:529187.
8. Burrell SC, Van den Abbeele AD 2-deoxy-2-[F-18] fluoro-D-glucose-positron emission tomography of the head and neck: An atlas of normal uptake and variants. Mol Imaging Biol 2005;7:244-56.
9. Cuccurullo V, Di Stasio GD, Prisco MR, Mansi L. Is there a clinical usefulness for radiolabeled somatostatin analogues beyond the consolidated role in NETs? Indian J Radiol Imaging 2017;27:509-16.
10. Förster GJ, Krummenauer F, Nickel O, Kahaly GJ. Somatostatin-receptor scintigraphy in Graves' disease: Reproducibility and variance of orbital activity. Cancer Biother Radiopharm 2000;15:517-25.
11. Postema PT, Krenning EP, Wijngaarde R, Kooy PP, Oei HY, van den Bosch WA, *et al*. [111In-DTPA-D-phe1] octreotide scintigraphy in thyroidal and orbital Graves' disease: A parameter for disease activity? J Clin Endocrinol Metab 1994;79:1845-51.
12. Pichler R, Sonnberger M, Dorninger C, Assar H, Stojakovic T. Ga-68-DOTA-NOC PET/CT reveals active Graves' orbitopathy in a single extraorbital muscle. Clin Nucl Med 2011;36:910-1.
13. Pasquali D, Vassallo P, Esposito D, Bonavolontà G, Bellastella A, Sinisi AA, *et al*. Somatostatin receptor gene expression and inhibitory effects of octreotide on primary cultures of orbital fibroblasts from Graves' ophthalmopathy. J Mol Endocrinol 2000;25:63-71.