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CASE REPORT Open Access

Suspicious cold thyroid nodule with intense focal 68Ga-DOTATATE uptake: a case report

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Abstract

A 51-year-old male was found with bilateral thyroid nodules on ultrasonography neck imaging. The largest nodule, measuring 23 × 26 × 35 mm, was located in the left lobe and was classified as EU-TIRADS 4. Thyroid function tests were normal, as were serum levels of parathormone, Chromogranin A, carcinoembryonic antigen and calcitonin. The nodule was cold on thyroid scintigraphy. Fine-needle aspiration of the nodule did not demonstrate cellular atypia. High focal uptake was found on both ^{111}In-DTPA-octreotide scintigraphy and ^{68}Ga-DOTATATE PET/CT. Histopathological analysis showed a microfollicular adenoma without malignancy. Immunohistochemical staining did not suggest neuroendocrine neoplasia or C cell hyperplasia. However, high expression of somatostatin receptor 2 (SSTR2) was observed in the microfollicular adenoma compared to the surrounding healthy tissue, with predominant localization in the endothelial cells and at the secretory pole of the thyroid epithelial cells in contact with blood vessels. High focal thyroid uptake on ^{68}Ga-DOTATATE PET/CT can be observed in benign thyroid nodules due to an overexpression of SSTR by endothelial cells. However, incidental focal thyroid uptake on SSTR imaging requires further investigations to rule out thyroid malignancy.

Keywords: Thyroid nodule, Somatostatin receptor, ^{68}Ga-DOTATATE PET/CT

Introduction

Somatostatin receptor (SSTR) imaging methods, such as ^{111}In-DTPA-octreotide scintigraphy and ^{68}Ga-DOTATATE PET/CT, are mainly indicated for the workup of neuroendocrine tumors (NET) (Özgüven et al. 2021). As this imaging modality is becoming increasingly used, incidental focal uptake in benign tissues or organs has been described (e.g., inflammatory lymph nodes, pituitary adenoma and meningioma). We present a case of a patient with intense and focal SSR expression in a cold thyroid nodule.

Case report

A 51-year-old male presented with significant weight loss and fatigue for several months with a history of hypertension and gastroesophageal reflux disease. Clinical examination revealed a left palpable thyroid nodule. All routine blood tests, including a complete hemogram, renal function and liver function, were normal. Thyroid

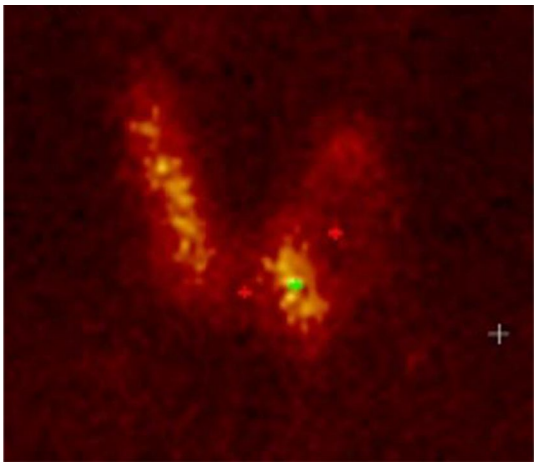

Fig. 1. ^{99m}Tc planar thyroid scan showing a cold left thyroid nodule

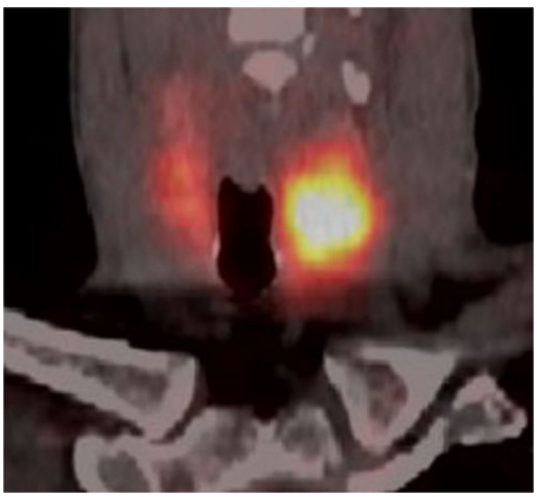

Fig. 2. ^{68}Ga-DOTATATE PET/CT coronal fusion image showing high uptake in the left thyroid nodule and mild and diffuse physiological uptake in the right lobe

function tests were within the normal range as were serum levels of parathormone (PTH), Chromogranin A (CgA), carcinoembryonic antigen (CEA) and calcitonin. Ultrasonographic neck imaging showed bilateral intermediate-risk EU-TIRADS 4 thyroid nodules. The largest nodule, measuring $23 \times 26 \times 35$ mm, was located in the left lobe. Thyroid scintigraphy using technetium-99 m pertechnetate showed a cold nodule located in the left lobe (Fig. 1). Fine-needle aspiration biopsy (FNAB) of the nodule did not demonstrate cellular atypia (Bethesda category II). For unknown reasons, ^{111}In-DTPA-octreotide scintigraphy was requested by the treating physician and displayed a high focal uptake in the left nodule. The same findings were observed on the ^{68}Ga-DOTATATE PET/CT, with a SUV_{max} of 13.8 (Fig. 2). No other sites of pathological uptake were detected. The patient was discussed at the multidisciplinary

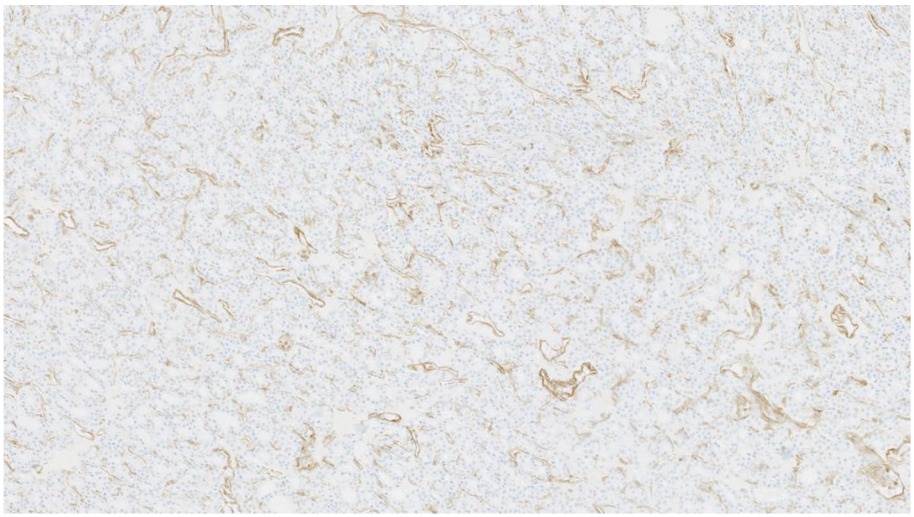

Fig. 3 SSTR2 immunohistochemistry staining in the adenomatous nodule showing prominent immunostaining in the endothelial cells

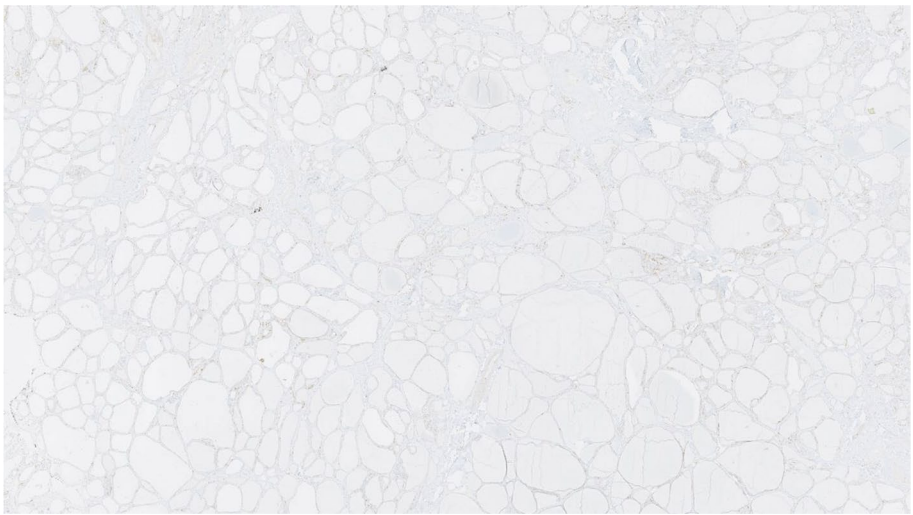

Fig. 4 SSTR2 IHC staining of healthy surrounding thyroid tissue

tumor board meeting. Given the presence of bilateral thyroid nodular lesions, the decision was to perform a near-total thyroidectomy associated with a prophylactic neck dissection of level VI. Histopathological findings revealed a multinodular goiter containing a microfollicular adenoma without malignancy. Immunohistochemical analysis of calcitonin, CgA, synaptophysin and somatostatin receptor subtype 2 (SSTR2) expression was performed. Results did not suggest neuroendocrine neoplasia or C cell hyperplasia. Higher expression of SSTR2 was observed in the microfollicular adenoma compared to the surrounding healthy tissue, with predominant localization in the endothelial cells and at the secretory pole of the thyroid epithelial cells in contact with blood vessels (Figs. 3, 4).

Discussion

The prevalence of thyroid nodules in the general adult population is up to 60%. Thyroid malignancy accounts for approximately 1–10% of incidental thyroid nodules (Fisher and Perrier 2018; Durante et al. 2018). Ultrasonography allows the assessment of various morphological features suggesting malignancy. European Thyroid Imaging and Reporting Data System (EU-TIRADS) features include irregular margins, non-oval shape, microcalcifications and hypoechogenicity (Russ et al. 2017). Thyroid scintigraphy is used to determine the functional status of a nodule as non-functioning nodules are associated with a 10 to 20% risk of malignancy, while most hyperfunctioning nodules are benign (Maia and Zantut-Wittmann 2012). Both morphological and functional features help to select nodules for US-guided FNAB. However, results are inaccurate in approximately 10 to 30% of cases (Maia and Zantut-Wittmann 2012).

SSTR are highly expressed at the surface of neuroendocrine cells and can be found in many tissues, including normal thyroid tissue (Özgüven et al. 2021). Beyond expression in NETs, expression of SSTR was also demonstrated in other tumors such as lymphoma, small cell lung carcinoma and prostate cancer or benign lesions such as sarcoid granulomas (Banerjee and Pomper 2013). SSTR expression can be detected by scintigraphy and PET/CT using radiolabeled somatostatin analogues such as 111In-octreotide and 68Ga-DOTATATE, respectively.

Increased thyroid uptake on SSTR imaging has been described in various thyroid disorders such as Hashimoto's thyroiditis, papillary thyroid cancer and medullary thyroid cancer (Lincke et al. 2009). In a retrospective study, thyroid uptake was evaluated in 237 patients who underwent ^{68}Ga-DOTATATE PET/CT to localize unknown primary and metastatic neuroendocrine tumors (Nockel et al. 2016). Among fourteen patients with incidental focal thyroid uptake, three (21%) had papillary thyroid cancer. No malignancy was detected among the remaining eleven patients, including six patients (42%) with adenomatous nodules and one patient (7%) with lymphocytic thyroiditis.

In the present case, the incidental finding of a high focal thyroid uptake with a SUV_{max} of 13.8 as detected by ^{68}Ga-DOTATATE PET/CT raised suspicion for thyroid malignancy. Histopathological and immunohistochemical analyses revealed a benign adenomatous nodule with overexpression of SSTR2. Remarkably, the high density of SSTR2 was predominantly localized in endothelial cells. High endothelial expression of SSTR has been reported in both malignant and benign lesions such as lymphoma, hemangioma and thymoma (Ruuska et al. 2018; Brogsitter et al. 2014; Ferone et al. 2001). The presence of SSTR on endothelial cells is thought to contribute to tissue growth, however, precise clinical significance remains unclear (Watson et al. 2001).

Conclusion

High focal thyroid uptake on ^{68}Ga-DOTATATE PET/CT can be observed in benign thyroid nodules due to an expression of SSTR by endothelial cells. However, incidental focal thyroid uptake on SSTR imaging requires further investigations to rule out thyroid malignancy.

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Authors' contributions
RM and IDD performed original writing—draft. MQ treated the patient. PD performed examination and interpretation of microscopic and macroscopic tissue. IK performed imaging diagnosis. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Verbal informed consent was obtained from the patient.

Competing interests
As corresponding author of the manuscript, I declare that all authors have no conflict of interest to disclose, and I confirm that neither the manuscript nor any part of its content is currently under consideration or published in another journal.

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References

Banerjee SR, Pomper MG (2013) Clinical applications of Gallium-68. Appl Radiat Isot 76:2–13
Brogsitter C, Hofmockel T, Kotzerke J (2014) (68)Ga DOTATATE uptake in vertebral hemangioma. Clin Nucl Med 39(5):462–463
Durante C, Grani G, Lamartina L, Filetti S, Mandel SJ, Cooper DS (2018) The diagnosis and management of thyroid nodules a review. JAMA J Am Med Assoc 319:914–924
Ferone D, Kwekkeboom DJ, Pivonello R, Bogers ADJJ, Colao A, Lamberts SWJ et al (2001) In vivo and in vitro expression of somatostatin receptors in two human thymomas with similar clinical presentation and different histological features. J Endocrinol Invest 24(7):522–528
Fisher SB, Perrier ND (2018) The incidental thyroid nodule. CA Cancer J Clin 68(2):97–105
Lincke T, Singer J, Kluge R, Sabri O, Paschke R (2009) Relative quantification of indium-111 pentetreotide and gallium-68 DOTATOC uptake in the thyroid gland and association with thyroid pathologies. Thyroid 19(4):381–389
Maia FFR, Zantut-Wittmann DE (2012) Thyroid nodule management: clinical, ultrasound and cytopathological parameters for predicting malignancy. Clinics 67:945–954
Nockel P, Millo C, Keutgen X, Klubo-Gwiezdzinska J, Shell J, Patel D et al (2016) The rate and clinical significance of incidental thyroid uptake as detected by Gallium-68 DOTATATE positron emission tomography/computed tomography. Thyroid 26(6):831–835
Özgüven S, Filizoğlu N, Kesim S, Öksüzoğlu K, Şen F, Öneş T et al (2021) Physiological biodistribution of 68 Ga-dota-tate in normal subjects. Mol Imaging Radionucl Ther 30(1):39–46
Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L (2017) European thyroid association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. Eur Thyroid J 6:225–237
Ruuska T, Ramírez Escalante Y, Vaittinen S, Gardberg M, Kiviniemi A, Marjamäki P et al (2018) Somatostatin receptor expression in lymphomas: a source of false diagnosis of neuroendocrine tumor at 68Ga-DOTANOC PET/CT imaging. Acta Oncol (Madr) 57(2):283–289
Watson JC, Balster DA, Gebhardt BM, O'Dorisio TM, O'Dorisio MS, Espenan GD et al (2001) Growing vascular endothelial cells express somatostatin subtype 2 receptors. Br J Cancer 85(2):266–272

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