Dušan Ilić[1], Sanja Ognjanović, Bojana Popović, Valentina Elezović Kovačević, Milica Opalić Palibrk, Lena Radić, Katarina Krstić, Đuro Macut

MEDULLARY THYROID CARCINOMA WITH ACTH-DEPENDENT CUSHING'S SYNDROME: THERAPEUTIC POSSIBILITIES

Case Report

In August 2016, a 61-year-old female patient underwent total thyroidectomy with central and functional left-sided neck dissection due to multinodular goitre and elevated baseline calcitonin levels (37.2 pg/mL). Pathohistologically and immunohistochemically, a medullary thyroid carcinoma (30 mm) with dissemination to regional lymph nodes (T3N1b(3/5)Mx) was verified. Postoperatively, the patient developed left-sided vocal cord paralysis and iatrogenic hypoparathyroidism. Replacement therapy with l-thyroxine, calcitriol, and calcium was initiated. Postoperative MSCT scans of the neck and chest in October 2016 and May 2017 confirmed disease progression in the thyroid bed with tumour recurrence/rest, left para-pharyngeal and supraclavicular lymphadenopathy, micronodules in both lungs and increased calcitonin concentration (752.4 pg/mL). Somatostatin receptor scintigraphy verified radiopharmaceutical uptake in the thyroid bed and mediastinum (grades II-III). In contrast, DMSA scintigraphy was positive in the thyroid bed on the left and the left lung. In May 2017, redissection of the left side of the neck confirmed medullary thyroid carcinoma metastases. Local radiotherapy was proposed but was not conducted because of distant disease dissemination. Two months after neck re-dissection, an 18FDG-PET/CT scan confirmed tumour recurrence in the thyroid bed with jugular and paratracheal deposits and in both lung lobes and the liver. The brain's MR, including the sellar region, was without pathological alterations, while secondary deposits were verified left para-pharyngeal. In October 2017, due to a worsening general condition, the patient was hospitalised. On admission, she appeared to be a moderately ill patient (PS 2), well nourished, eumetabolic, and with average body proportions. Due to muscle weakness and severe headaches, she took an antalgic position in bed, with therapy including opioid anal-

[1] Dušan Ilić, Clinic for Endocrinology, Diabetes, and Metabolic Diseases, UKCS

gesics and SSRIs. Blood pressure was well controlled by antihypertensive treatment. Routine biochemical analyses showed hypokalemia (K 3.2 mmol/L) with hyperkaliuria and metabolic alkalosis. There were no disturbances in glycoregulation, and the lipid profile was normal. Calcitonin (346.8 pg/mL) and CgA (487.6 ng/mL) levels were elevated, while CEA levels were normal. A disrupted daily cortisol secretion rhythm (8h 1013.6 nmol/L, 24h 620.7 nmol/L) was confirmed, with no suppression during dexamethasone suppression tests (DEXI 435.4 nmol/L, DEXII 729.4 nmol/L). ACTH values were unavailable for technical reasons. Due to the absence of the primary thyroid tumour specimen, additional immunohistochemical staining for ACTH on the extirpated lymph nodes obtained after the second surgery was performed, which was negative. Direct sequencing did not reveal a germline mutation in the RET proto-oncogene gene. A control MSCT scan of the neck, chest, and abdomen verified further disease progression, with enlargement of all previously noted findings, new findings in the head of the pancreas, and nodularities in the left adrenal gland with the characteristic of an adenoma. Catecholamine excess was excluded. To control hypercortisolemia, metyrapone was introduced, and vandetanib was started due to the rapid progression of the underlying disease. Shortly after initiating therapy, the patient showed dramatic subjective and objective improvements, leading to discontinuation of analgesic treatment. After three months of therapy, a control MSCT scan showed partial remission of all previously described neck, lung, liver, and pancreas findings. Hypercortisolemia and hypokalemia were corrected. The patient felt subjective well until February 2018, when she had a seizure followed by a disturbance of consciousness and retrograde amnesia lasting five days. MR brain scans showed no focal alterations, and due to suspected reversible posterior leukoencephalopathy syndrome, vandetanib was temporarily discontinued. ACTH values of 60.7 ng/L were measured, indicating ACTH-dependent Cushing's syndrome. A follow-up appointment was planned to decide on further treatment, which the patient did not attend.

Discussion

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumour originating from the parafollicular C cells, accounting for 1-2% of all thyroid cancers (1). In 75-80% of cases, it occurs sporadically, while in the remaining 20-25%, it is an autosomal dominant inherited disease and is part of the multiple endocrine neoplasia type 2A (MEN 2A) and type 2B (MEN 2B) syndromes (1). Nearly all individuals with these hereditary syndromes have a germline mutation in the RET proto-oncogene, whereas two-thirds of sporadic MTCs have a somatic mutation, most commonly in codon 918 (M918T) (2). In 10-70% of sporadic MTCs without a somatic RET proto-oncogene mutation, there is a somatic mutation in the HRAS, KRAS, or, less frequently, NRAS genes (2). Sporadic MTC most commonly occurs in the fourth or sixth decade of life

(1). Unlike hereditary MTC, which is mainly multicentric and bilateral, sporadic MTC typically appears as a solitary unilateral thyroid tumour (1). Approximately 70% of patients with a palpable thyroid nodule have metastases in the regional lymph nodes of the neck, whereas 10% have distant metastases (1). MTC most commonly metastasises to the mediastinal lymph nodes, lungs, liver, and bones and, less frequently, to the skin and brain (1). The ten-year survival rates for patients with stages I, II, III, and IV were 100%, 93%, 71%, and 21%, respectively (1).

Thyroid gland C cells secrete several hormones and biogenic amines. The most significant are calcitonin and carcinoembryonic antigen (CEA), the concentrations of which are directly proportional to the mass of C cells and are used as markers of tumour progression (3). Additionally, C cells can secrete adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), β-melanocyte-stimulating hormone, chromogranin, histamine, neurotensin, and somatostatin (3). Ectopic secretion of ACTH or CRH can lead to Cushing's syndrome. MTC is responsible for 2.2-7.5% of all cases of ectopic Cushing's syndrome, while approximately 0.7% of patients with MTC have ectopic Cushing's syndrome (4). To date, approximately 50 cases of ectopic Cushing's syndrome in patients with MTC have been described in the literature (4). Despite evidence of tumour production, negative immunohistochemical staining for ACTH may be due to reduced amounts of deposited ACTH in tumour cells owing to its abundant secretion (5). Another reason could be a disorder in the translation and processing of pro-opiomelanocortin (POMC) mRNA and the tumour secretion of CRH (5). Hormone secretion profiles can also differ between primary tumours and metastases in the same patient (5). The occurrence of Cushing's syndrome in patients with advanced MTC is a poor prognostic sign and is associated with a short survival period (6). Control of hypercortisolemia and related clinical manifestations can be achieved by removing or reducing metastases using ketoconazole, mifepristone, metyrapone, mitotane, or bilateral adrenalectomy (6). There are reports of symptoms and signs of regression of Cushing's syndrome after vandetanib administration (7). In our patient, a disrupted daily cortisol secretion rhythm was verified in the absence of suppression during the dexamethasone suppression tests. Owing to technical reasons, ACTH values were not immediately available, and given the patient's severe general condition, metyrapone was introduced into therapy with a favourable therapeutic response. Later, the ACTH values confirmed the presence of ACTH-dependent Cushing's syndrome, which is likely ectopic. However, the possibility of Cushing's disease cannot be entirely excluded, which raises the question of a multi-tumor syndrome. Hypokalemic metabolic alkalosis, which is more common in ectopic Cushing's syndrome than in Cushing's disease (57% vs. 10%), supports the diagnosis of ectopic ACTH secretion. Although higher ACTH values are expected in ectopic Cushing's syndrome, there may be some overlap with values more commonly observed in Cushing's disease. On two occasions, MR scans of the brain described the sellar region as normal, and

for technical reasons, targeted MR scans of the pituitary and petrosal sinus sampling were not performed.

Total thyroidectomy with neck lymph node dissection is the standard treatment for patients with sporadic or hereditary diseases.

References

1. Wells SA, Jr., Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610.
2. Sahakian N, Castinetti F, Romanet P. Molecular Basis and Natural History of Medullary Thyroid Cancer: It is (Almost) All in the RET. Cancers (Basel). 2023;15(19).
3. Kim GY, Park CY, Cho CH, Park JS, Jung ED, Jeon EJ. A Calcitonin-Negative Neuroendocrine Tumor Derived from Follicular Lesions of the Thyroid. Endocrinol Metab (Seoul). 2015;30(2):221-5.
4. Pivovarova AI, Patrick S, Reddy PJ. Sporadic Medullary Thyroid Carcinoma with Paraneoplastic Cushing Syndrome. Case Rep Endocrinol. 2019;2019:6414921.
5. Choi HS, Kim MJ, Moon CH, Yoon JH, Ku HR, Kang GW, et al. Medullary thyroid carcinoma with ectopic adrenocorticotropic hormone syndrome. Endocrinol Metab (Seoul). 2014;29(1):96-100.
6. Koehler VF, Fuss CT, Berr CM, Frank-Raue K, Raue F, Hoster E, et al. Medullary thyroid cancer with ectopic Cushing's syndrome: A multicentre case series. Clin Endocrinol (Oxf). 2022;96(6):847-56.
7. Forde HE, Mehigan-Farrelly N, Ryan K, Moran T, Greally M, Duffy AG, et al. Metastatic medullary thyroid carcinoma presenting as ectopic Cushing's syndrome. Endocrinol Diabetes Metab Case Rep. 2021;2021.
8. Kim M, Kim BH. Current Guidelines for Management of Medullary Thyroid Carcinoma. Endocrinol Metab (Seoul). 2021;36(3):514-24.
9. Dabelić N, Jukić T, Fröbe A. Medullary Thyroid Cancer - Feature Review and Update on Systemic Treatment. Acta Clin Croat. 2020;59(Suppl 1):50-9.
10. Maghsoomi Z, Emami Z, Malboosbaf R, Malek M, Khamseh ME. Efficacy and safety of peptide receptor radionuclide therapy in advanced radioiodine-refractory differentiated thyroid cancer and metastatic medullary thyroid cancer: a systematic review. BMC Cancer. 2021;21(1):579.
11. Trimboli P, Castellana M, Virili C, Giorgino F, Giovanella L. Efficacy of Vandetanib in Treating Locally Advanced or Metastatic Medullary Thyroid Carcinoma According to RECIST Criteria: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2018;9:224.
12. Schlumberger M, Elisei R, Müller S, Schöffski P, Brose M, Shah M, et al. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Ann Oncol. 2017;28(11):2813-9.

13. Subbiah V, Velcheti V, Tuch BB, Ebata K, Busaidy NL, Cabanillas ME, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol. 2018;29(8):1869-76.
14. Subbiah V, Gainor JF, Rahal R, Brubaker JD, Kim JL, Maynard M, et al. Precision Targeted Therapy with BLU-667 for RET-Driven Cancers. Cancer Discov. 2018;8(7):836-49.