ENDOCRINOLOGY RESEARCH AND PRACTICE

SOCIETY OF ENDOCRINOLOGY AND METABOLISM OF TÜRKİYE

CASE REPORT
Endocrinol Res Pract. 2024;28(4):229-232

Lymph Node ACTH Washout: New Assistant Method for Localizing the Source of Ectopic ACTH Secretion in a Case of Metastatic Medullary Thyroid Carcinoma

ABSTRACT

In ACTH-dependent Cushing syndrome, identifying the source of ACTH can be challenging. A 23-year-old male presented with Cushingoid symptoms and signs to other clinics. Laboratory tests confirmed ACTH-dependent Cushing's syndrome. Imaging revealed a suspicious adenoma in the pituitary, a hypoechoic nodule in the thyroid, and pathological-appearing lymph nodes in the neck. Following a fine needle aspiration cytological examination, medullary thyroid carcinoma was diagnosed. A total thyroidectomy and lymph node dissection were subsequently performed. The pathology report confirmed medullary thyroid carcinoma. When the patient was admitted to our hospital, disease recurrence was considered, and lymph node ACTH washout was performed as an unusual method to identify the source of ACTH. The washout sample yielded a very high value of 958 pg/mL. We describe a patient who was hospitalized with severe symptoms of Cushing's syndrome resulting from medullary thyroid cancer. We employed a novel method involving lymph node ACTH washout to identify the source of ACTH production. Lymph node ACTH washout can be an effective diagnostic option to determine the origin of ACTH.

Keywords: Cushing, diagnosis, ectopic ACTH syndrome, lymph node, ACTH washout, medullary thyroid carcinoma

Introduction

According to the literature, ectopic ACTH syndrome can result from 0.7% of medullary thyroid carcinoma (MTC) cases, with MTCs accounting for 2.2%-7.5% of all cases of this syndrome.[1] Most (80%-85%) of ACTH-dependent Cushing's syndrome (CS) cases originate from the pituitary gland, while fewer cases are related to ectopic ACTH secretion.[2] Inferior petrosal sinus sampling (IPSS) is the gold standard for determining the source of hypercortisolism in ACTH-dependent CS.[3] However, IPSS is an operator-dependent application requiring experience and carries risks such as complications (e.g., transient hypotension, vascular injury, stroke, and subarachnoid hemorrhage) and failure. Therefore, it may be challenging to determine the source of ACTH.[4] We present a case of ACTH-dependent Cushing's disease where ACTH hypersecretion was localized using a unique method: collecting an ACTH washout sample from the cervical lymph node.

Case Presentation

A 23-year-old male patient sought medical attention due to complaints of gaining approximately 40 kg of weight in the past 2 years. At the time of attendance at another medical center, the patient showed a Cushingoid appearance, including centripetal obesity, moon face, buffalo hump, supraclavicular fat, purple striae on the abdomen, and acanthosis nigricans in the axillary region. A palpable nodule was detected in the right lobe of his thyroid gland.

In different measurements, cortisol in 24-hour urine was measured at 554 µg/day (3.6-45) and 223 µg/day (5.8-40.3). Serum ACTH (at 8 : 00) was found to be 80 ng/L (0-46), and serum cortisol (at 8:00) was 26.75 ng/L (6.70-22.6). Serum cortisol value was 12 µg/dL after the 2-day 2 mg dexamethasone suppression test. In the overnight 8 mg dexamethasone suppression test, the serum cortisol value was 16.8 µg/dL before the test and 12.5 µg/dL after the test. These results suggested ACTH-dependent Cushing's syndrome. There was a suspicious lesion on the pituitary magnetic resonance imaging (MRI) that could be indicative of a 4 mm adenoma or cyst (Figure 1).

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Received: April 17, 2024
Revision Requested: May 23, 2024
Last Revision Received: June 23, 2024
Accepted: July 3, 2024
Publication Date: August 26, 2024

Cite this article as: İşler AO, Şendur SN, Gönül İremli B, et al. Lymph node ACTH washout: new assistant method for localizing the source of ectopic ACTH secretion in a case of metastatic medullary thyroid carcinoma. *Endocrinol Res Pract.* 2024;28(4):229-232.

DOI: 10.5152/erp.2024.457

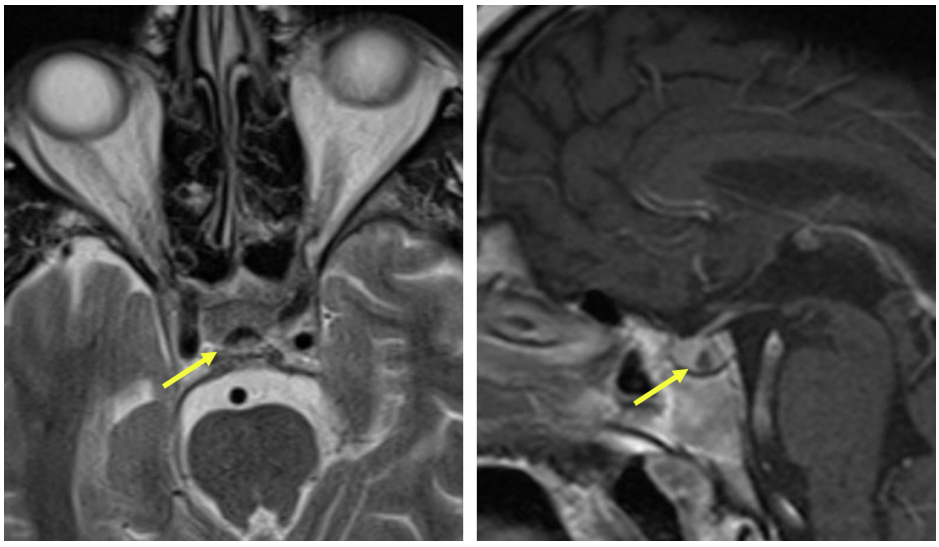

Figure 1. In the pituitary MRI, a 4 mm lesion suspicious of adenoma or cyst is seen at the tip of the arrow.

The results of the neck ultrasound showed a solid nodule, 24 × 20 mm in the right lobe of the thyroid gland with lobulated hypoechoic borders and punctate calcification areas, and it was classified as TIRADS 5 according to the ACR system. In addition, lymph nodes with a pathological appearance were found in the right level 6 and right cervical levels 2, 3, and 4 regions. The positron emission tomography (PET)/computed tomography (CT) scan revealed pathological involvement in the right thyroid lobe, with a SUVmax of 4.62. Pathological involvement was also observed in the right levels 3, 4, and 6 (Figure 2). Fine needle aspiration cytology of the thyroid nodule revealed medullary thyroid cancer. The serum calcitonin value was 6528 ng/L, and the CEA value was 12.3 ng/mL.

The patient subsequently underwent a total thyroidectomy along with central and right cervical lymph node dissection. The pathology report confirmed that the patient had metastatic medullary thyroid cancer. The tumor had a mitosis rate of 2/mm^2, and the Ki-67 index was 2%-3%.

After these evaluations, the patient was referred to our center for further diagnosis and treatment. In the initial evaluation, cervical ultrasonography revealed the presence of cervical pathological lymph nodes and a solid mass of 18 × 13 mm in the right thyroid area. A Gallium-68 DOTA PET/CT scan revealed increased involvement in retropharyngeal, bilateral cervical level 2-4, right level 3, bilateral central, and bilateral lower cervical lymph nodes. These results confirmed the presence of residual and metastatic disease.

To diagnose ectopic ACTH-secreting medullary thyroid cancer and determine the source of ACTH, calcitonin washout and ACTH washout were performed on the right level 4 lymph node. The ACTH washout procedure was similar to other washout methods (such as thyroglobulin and calcitonin). The aspirate in the needle was washed with 1 mL of isotonic solution, and the washout sample was transferred to a tube containing EDTA. It was sent to the laboratory in an ice container, following cold chain rules.

The calcitonin washout value was found to be very high at 133 262 pg/mL, and the ACTH washout value was 958 pg/mL, which is approximately 12 times the upper serum limit. This procedure confirmed the diagnosis of ectopic ACTH-secreting medullary thyroid cancer, thereby eliminating the need for IPSS, which is an invasive procedure. At the same time, ACTH staining was performed on pathology preparations brought from the other center. ACTH showed patchy positive staining. ACTH staining was present in 6% of neoplastic cells (Figure 3).

Before receiving permanent treatment, metyrapone (1 g/day PO) was started to reduce the adverse effects of excess cortisol. Before starting metyrapone, the 24-hour urinary-free cortisol level was 858 µg/day (58-403). The initiation of metyrapone led to a decrease in 24-hour urinary-free cortisol levels below the normal range (3.97 µg/day). Prednisolone 7.5 mg/day was added to metyrapone as part of a block-and-replace treatment approach.

The patient underwent complementary thyroidectomy and neck dissection to treat a recurring mass and lymph node metastases. Due to progressive disease, the patient underwent several further surgeries, including cervical lymph node dissection, lung wedge resection, partial decortication, and bilateral mediastinal lymph node dissection.

Following these surgeries, calcitonin decreased to 810 ng/L. A tyrosine kinase inhibitor, cabozantinib, was administered at 40 mg/day orally. He has now been followed up with cabozantinib treatment for 4 months. A partial response was observed with cabozantinib according to RECIST criteria, and calcitonin levels decreased to 257 ng/L. Treatment of hypercortisolism was achieved through the treatment of the primary disease and metyrapone; bilateral adrenalectomy was not required, and the patient was doing well at the time of this writing.

MAIN POINTS

- Medullary thyroid carcinoma is an uncommon cause of ectopic ACTH syndrome.
- Identifying the source of ACTH can be problematic in ACTH-dependent Cushing's syndrome.
- ACTH washout from a suspicious lymph node or lesion can help diagnose the source of ACTH such in a case of medullary thyrıid carcinoma.

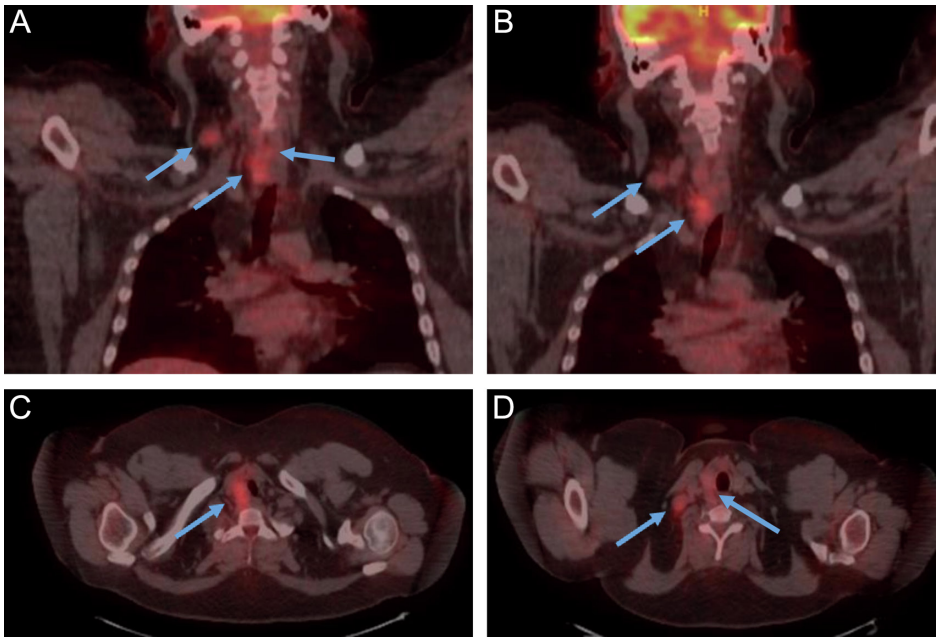

Figure 2. PET CT images in the diagnostic evaluation of the patient. Pathological involvement was observed in the right thyroid lobe (SUVmax : 4.62), right levels 3 and 4, and right level 6. (A, B) Coronal image. (C, D) Transverse image.

Discussion

Diagnosing hypercortisolism and ACTH-dependent Cushing's syndrome can be challenging, especially when pituitary adenomas and neuroendocrine tumors (e.g. medullary thyroid cancer or pulmonary nodules) co-occur.[5] In our case, a suspicious lesion measuring 4 mm in the pituitary gland was detected. IPSS was supposed to be performed at the previous center but could not be performed due to technical reasons. To confirm the source of ACTH, we conducted an ACTH washout from one of the metastatic lymph nodes. The result was significantly higher than the serum value, confirming the ectopic

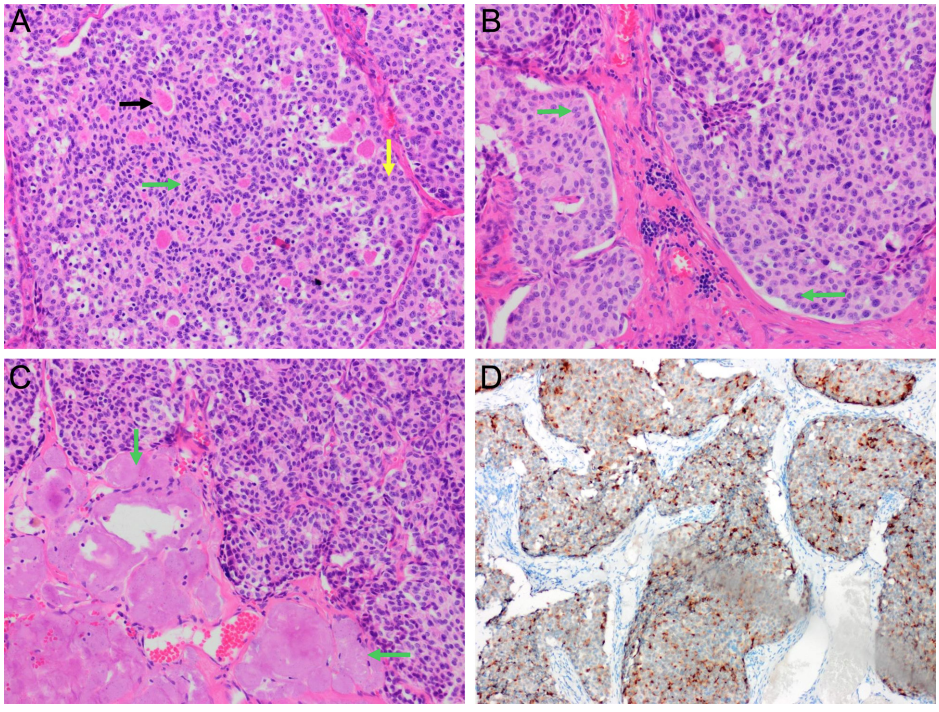

Figure 3. Pathological examination of thyroidectomy material brought from the other center. (A) Uniform, round (yellow arrow), and spindle cells (green arrow) in nests and amyloid deposits (black arrow). (B) Cells have finely stippled chromatin and indistinct nucleoli, eosinophilic granular cytoplasm. (C) Stroma has pink amorphous deposits (positive with Congo red). (D) Immunohistochemical ACTH staining is positive.

ACTH source without requiring IPSS. This is a less invasive procedure, avoiding the risks of false positivity or negativity associated with IPSS.

Increased secretion in medullary thyroid cancer that ectopically secretes ACTH may reduce ACTH stores, and some medullary thyroid cancer cells may not stain positive for ACTH by immunohistochemistry.[6] In rare cases of cancer-related ectopic ACTH syndrome, the primary tumor causing the syndrome may not be correctly localized or cannot be accessed because of the anatomic localization. These conditions make histopathological diagnosis difficult.

The particular case we presented had aggressive clinical characteristics. Despite multiple procedures, the disease recurred. Studies suggests that 51% of patients with medullary thyroid carcinoma and ectopic ACTH syndrome have severe hypercortisolism and metastatic disease at diagnosis.[7]

Conclusion

We suggest that if the source of the ectopic ACTH is uncertain, an ACTH washout from available and accessible metastatic tissue can be performed to identify the source of the ectopic ACTH.

Availability of data and materials: Dataset regarding the patient's evaluation may be obtained from the corresponding author upon reasonable request.

Informed Consent: Informed consent has been obtained from the patient for the publication of the case report and accompanying images.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Ş.N.Ş.; Data Collection and/or Processing – A.O.İ., O.P., Z.K., A.O.; Analysis and/or Interpretation – A.O.İ.; Literature Search – A.O.İ., A.G.; Writing Manuscript – A.O.İ., Ş.N.Ş., O.P., U.Ü., A.G.; Critical Review – A.O.İ., Ş.N.Ş., B.G.İ, Ö.C., A.B.D., S.U., O.P., Z.K., A.O., U.Ü., A.G.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This study received no funding.

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