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Case Report

Remission of Ectopic Cushing Syndrome Secondary to Medullary Thyroid Cancer With Vandetanib and Selpercatinib

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Abstract

Medullary thyroid cancer (MTC) is a neuroendocrine tumor associated with activating mutations of the rearranged during transfection (*RET*) proto-oncogene. These tumors may rarely secrete adrenocorticotropin or corticotropin-releasing hormone, resulting in a paraneoplastic ectopic Cushing syndrome (ECS). Paraneoplastic ECS carries a high risk of mortality, and management is difficult due to the lack of response to antiadrenal therapies. We report on a 37-year-old man who was diagnosed with metastatic MTC and reported symptoms of cortisol excess with laboratory testing in keeping with ECS. He began treatment with vandetanib, a multitargeted tyrosine kinase inhibitor, which resulted in decreased tumor burden as well as clinical and biochemical resolution of ECS. Due to progressive structural disease 10 months later, he was switched to the selective RET inhibitor selpercatinib, which was followed by a rapid reduction of cortisol nearing the threshold of adrenal insufficiency. Tumor markers were also improved, and repeat imaging showed decreased tumor burden. Our case highlights the efficacy of tyrosine kinase inhibitors in the management of paraneoplastic ECS. Selective RET inhibitors may emerge as preferred targeted treatment options due to better efficacy and toxicity profiles compared to multitargeted inhibitors. Clinicians should monitor for adrenal insufficiency with the use of selective RET inhibitors.

Key Words: medullary thyroid cancer, MTC, ectopic Cushing syndrome, treatment, tyrosine kinase inhibitors, RET inhibitors, vandetanib

Abbreviations: ACTH, adrenocorticotropin; CEA, carcinoembryonic antigen; CRH, corticotropin-releasing hormone; CT, computed tomography; ECS, ectopic Cushing syndrome; MTC, medullary thyroid cancer; RET, rearranged during transfection; TKIs, tyrosine kinase inhibitors.

Introduction

Medullary thyroid cancer (MTC) is a rare neuroendocrine tumor originating from the parafollicular cells of the thyroid gland, and accounts for 3% to 5% of all thyroid cancers. These cancers are associated with activating mutations of the rearranged during transfection (*RET*) proto-oncogene, which encodes a transmembrane receptor tyrosine kinase, in all inherited cases and in up to 60% of sporadic cases. MTCs may secrete calcitonin, carcinoembryonic antigen, prostaglandins, and serotonin, and can rarely secrete adrenocorticotropin (ACTH) or corticotropin-releasing hormone (CRH), resulting in a paraneoplastic ectopic Cushing syndrome (ECS) (1). At least 96 cases of ECS secondary to MTC have been reported in the literature (1).

To date, management of ECS due to MTC has been primarily surgical given the lack of response to medical treatments for hypercortisolism (1). Multitargeted tyrosine kinase inhibitors (TKIs) used in the management of MTC have been shown to reverse the biochemical and clinical manifestations of paraneoplastic ECS (2). Newer, selective *RET* inhibitors are approved as treatment options for *RET*-mutant advanced MTC, and may be promising treatment options for associated ECS, but evidence supporting their use in treatment of paraneoplastic ECS is limited to case series (3-5).

Here we report a case of MTC complicated by ECS with good response to the sequential use of the multitargeted TKI vandetanib and to the selective *RET* inhibitor selpercatinib, and discuss the use of selective *RET* inhibitors as emerging treatment options for paraneoplastic ECS. Department of Medicine, University of Alberta, Edmonton, AB, T6G 2R7, Canada

Case Presentation

A previously healthy 37-year-old man presented with a primary complaint of upper abdominal discomfort over the previous 9 months. Associated symptoms included increased frequency of bowel movements (3 episodes/day), 25-pound (11.4 kg) weight gain, irritability, and a new rash on his torso and upper extremities. His past medical history was positive for gastroesophageal reflux disease for which he took pantoprazole 40 mg daily. There was no family history of endocrine disorders.

Diagnostic Assessment

On examination the patient had a cushingoid appearance with truncal obesity, facial erythema, and pedal edema. He had a bulky thyroid gland with left cervical lymphadenopathy.

Thyroid ultrasound revealed a large 50×38 mm mass in the left lobe with calcifications (Fig. 1A), Thyroid Imaging

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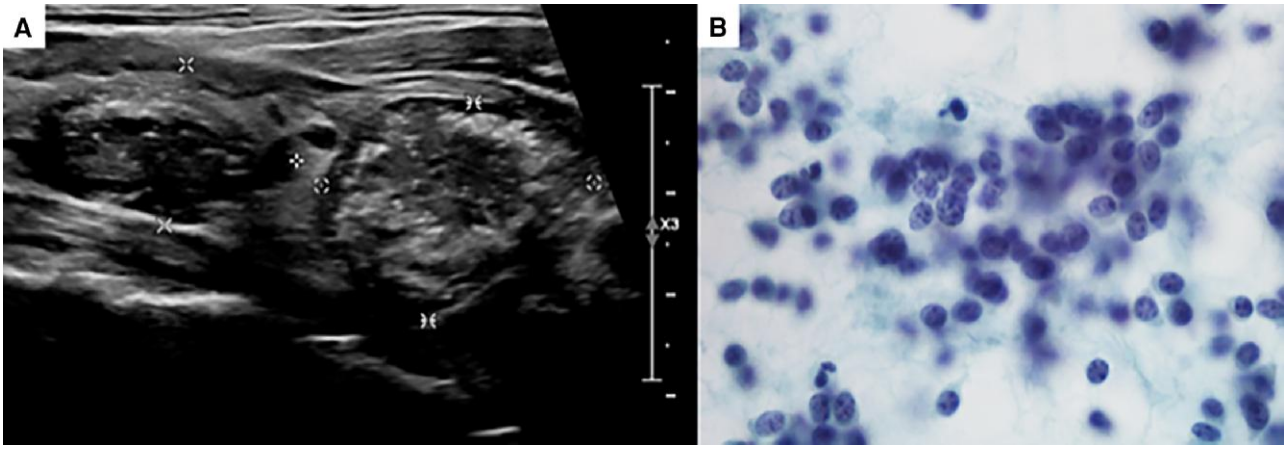

Figure 1. A, Thyroid ultrasound revealing a large 50 × 38 mm mass in the left lobe of the thyroid with calcifications, Thyroid Imaging Reporting and Data System 4; and B, fine-needle biopsy of the left neck mass demonstrating metastatic medullary thyroid carcinoma: Papanicolaou stain demonstrating clusters of cells with polygonal and spindle cell morphology associated with polarized nuclei and dispersed chromatic pattern with granular cytoplasm (magnification 1000×).

Reporting and Data System 4, associated with multiple abnormal appearing lymph nodes in the left neck, measuring up to 19 × 14 mm. Fine-needle aspiration biopsy of the left neck mass and nodes was consistent with metastatic MTC (Fig. 1B). Computed tomography (CT) with contrast enhancement revealed a 50 × 30 mm ill-defined nodule arising from the left lobe of the thyroid (Fig. 2), peripherally enhancing lesions within superior mediastinal lymph nodes (a conglomerate of nodes measuring 70 × 70 mm), liver (multiple lesions, largest measuring 60 × 60 mm), and spleen (2 lesions, each measuring 9 mm). Liver biopsy was consistent with metastatic MTC (Fig. 3), staining positive for pankeratin, TTF-1, synaptophysin, chromogranin, and calcitonin.

Initial laboratory investigations included elevated calcitonin (23 530 ng/L, normal <18 ng/L; 23 530 pg/mL) and carcinoembryonic antigen (CEA) (2798 µg/L, normal <5 µg/L; 2798 ng/mL) with normal calcium and parathyroid hormone levels. Additional investigations revealed an elevated random cortisol of 837 nmol/L (85-620 nmol/L; 30.34 µg/dL), elevated ACTH (35.1 pmol/L, 1.6-13.9 pmol/L; 159.4 pg/mL), and elevated 24-hour urine cortisol (4385 nmol/d, normal <230; 1587 µg/24 h). Dynamic testing revealed a lack of cortisol suppression after administration of high-dose dexamethasone, in keeping with an ectopic source of ACTH or CRH. Altogether, these investigations were consistent with a diagnosis of metastatic MTC with ECS. Genetic testing was negative for a germline *RET* pathogenic variant and positive for a somatic *RET* pathogenic variant (RET_ [p.M918T; c.2753T > C], variant allele frequency 15.6%).

Treatment

First-line treatment was with vandetanib 300 mg daily, a TKI that is publicly funded in Canada. No additional treatment was initiated for hypercortisolism given his excellent functional status and stable blood pressure and electrolytes.

Outcome and Follow-up

Two weeks following the initiation of vandetanib, the patient's 24-hour urine cortisol had decreased to 998 nmol/d (361 µg/24 h). In the following months, continued biochemical and clinical resolution of ECS was noted. Repeat imaging

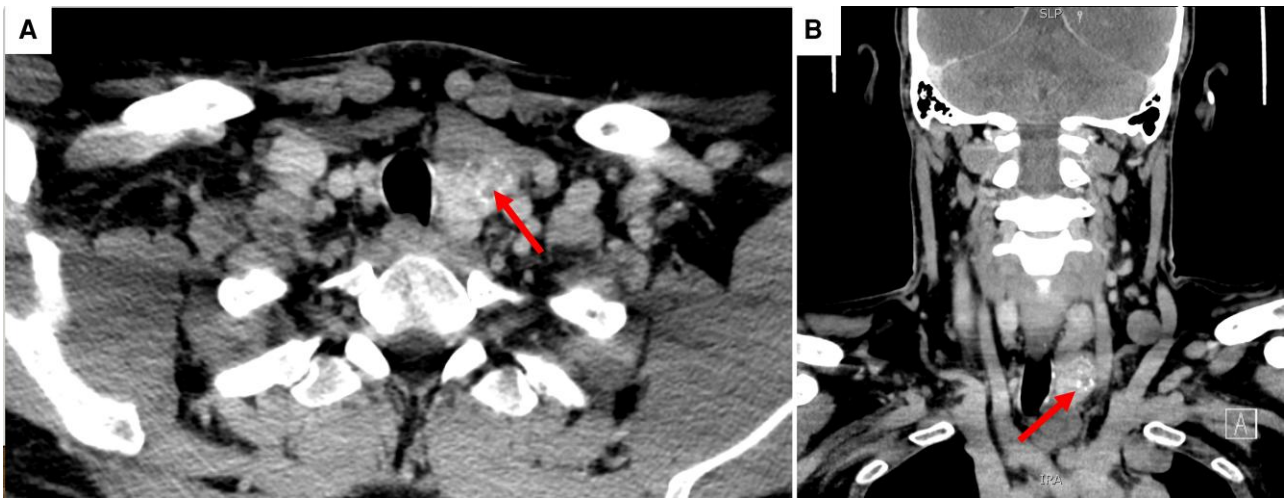

Figure 2. Computed tomography images demonstrating A, axial and B, coronal views of left neck mass.

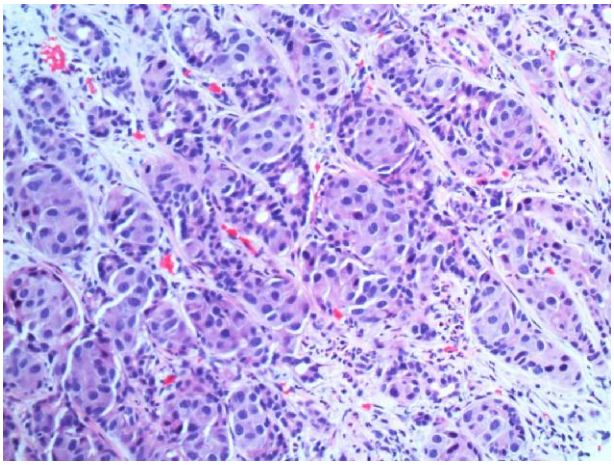

Figure 3. Histopathologic analysis of hepatic metastases consistent with metastatic medullary thyroid carcinoma (magnification 200×).

performed 7 months following treatment initiation revealed a decrease in the size of the thyroid mass and associated metastatic lesions. Observed side effects of vandetanib included diarrhea, hypertension, proteinuria, hypoglycemia, and grade I hand-foot syndrome.

Approximately 10 months following the initiation of vandetanib, an increase in the size of his liver metastases was noted associated with elevations in calcitonin, CEA, and cortisol. These findings were sustained with repeat investigations 3 months later. There was no associated change to cervical, intrathoracic, or splenic lesions. Given the evidence of progressive disease, vandetanib was discontinued and the selective RET inhibitor selpercatinib was initiated. This was followed by a rapid decrease in calcitonin (753 ng/L, normal <18 ng/L; 753 pg/mL) and CEA (479 µg/L, normal <5 µg/L; 479 ng/mL) after 5 weeks. Rapid corrections in random cortisol (173 nmol/L, 85-620 nmol/L; 6.23 µg/dL) and 24-hour urine cortisol (18 nmol/d, normal <230 nmol/d; 6.52 µg/24 h) were also noted within this period (Fig. 4). At the subsequent follow-up he noted worsening fatigue, and his morning cortisol was 220 nmol/L (120-620 nmol/L; 7.92 µg/dL). He started hydrocortisone (20 mg total daily dose in 3 divided doses) with an improvement in his fatigue. By 3 months following selpercatinib initiation, there was a decrease in the size of his hepatic and splenic lesions as well as his cervical and mediastinal lymphadenopathy (Fig. 5). At 6 months there was further reduction in tumor burden on imaging, and an improvement in calcitonin (282 ng/L, normal <18 ng/L; 282 pg/mL), CEA (299 µg/L, normal <5 µg/L; 299 ng/mL), and ACTH (19.8 pmol/L, 1.6-13.9 pmol/L; 89.9 pg/mL). At his most recent follow-up visit 10 months after the initiation of selpercatinib, his morning cortisol level (after holding hydrocortisone for 24 hours) was 280 nmol/L (120-620 nmol/L; 10.15 mcg/dL), and 24-hour urine cortisol was 52 nmol/d (normal <230 nmol/d; 18.8 mcg/24 h). He continues hydrocortisone 10 mg in the morning, and occasionally takes a second dose in the afternoon prior to exercise.

Discussion

Paraneoplastic ECS affects a spectrum of malignancies and occurs following neuroendocrine differentiation of the primary tumor, which results in hypercortisolism through ectopic secretion of ACTH or CRH (1). ECS has been reported in 0.7% of people with MTC and is often associated with advanced metastatic disease and a more limited prognosis (1). The increased mortality reflects the secondary effects of hypercortisolism and underscores the importance of recognizing and treating ECS within this population. Antiadrenal therapies such as ketoconazole, mitotane, and metyrapone have limited efficacy in treating paraneoplastic ECS, and up to 50% of reported cases have required surgical management with bilateral adrenalectomy (1).

TKIs are targeted therapies that act by inhibiting TK-dependent oncogenic pathways. MTC is driven by mutations in the *RET* proto-oncogene in all inherited cases and up to half of sporadic cases (6). Accordingly, TKIs with activity against RET have demonstrated efficacy in the management of both MTC and hypercortisolism due to paraneoplastic ECS (2-5).

Vandetanib and cabozantinib are multitargeted TKIs that have been approved as first-line agents for the management of MTC in many countries. Consistent with our findings, there are various reports of biochemical and clinical improvement of paraneoplastic ECS following the use of vandetanib and other multitargeted TKIs (2). With these agents, the control of hypercortisolism has been shown both in adolescent and adult populations, and in cases of treatment-resistant hypercortisolism. The control of cortisol persisted regardless of the interval progression of MTC (2).

Despite the demonstrated efficacy of these multitargeted TKIs, their use is limited by adverse events, thought to be primarily due to their broad activity against multiple kinases, in particular vascular endothelial growth factor receptors. These adverse events include diarrhea, rash, nausea, hypertension, and hand-foot syndrome. In one study investigating vandetanib and cabozantinib, dose reductions in up to 79% and discontinuation of therapy in up to 16% were noted due to drug toxicity (7). Furthermore, TKIs are limited by the development of resistance, which occurs independent of the specific TKI used or the molecular profile of the primary tumor (6).

Selpercatinib is a recently approved RET-specific inhibitor that has shown promise in overcoming the limitations of nonspecific TKIs. Selpercatinib inhibits various *RET* alterations comprising both mutations and fusions, including the *RET* V804M pathogenic variant known to confer resistance to other TKIs (8). Owing to the focused spectrum of activity, toxicities associated with selective RET inhibitors are mild and often limited to hypertension and diarrhea (8). Resistance remains an issue with selective RET inhibitors, mainly due to activation of downstream oncogenic pathways through the amplification of the MET kinase (9). Emerging evidence has shown that the combination of selpercatinib and the MET inhibitor crizotinib is able to overcome resistance owing to *MET* amplification (9).

Selective RET inhibitors have been proposed as emerging treatments in the management of paraneoplastic ECS; however, studies surrounding their use in this context are limited. Selpercatinib has shown efficacy in managing ECS in limited series, and there are currently no reports showing similar benefits with pralsetinib, another selective RET inhibitor (3-5). In the 3 cases reporting resolution of ECS following selpercatinib use, side effects were limited to grade I headache and fatigue, and remission was sustained beyond 34 months in 1 report (3-5).

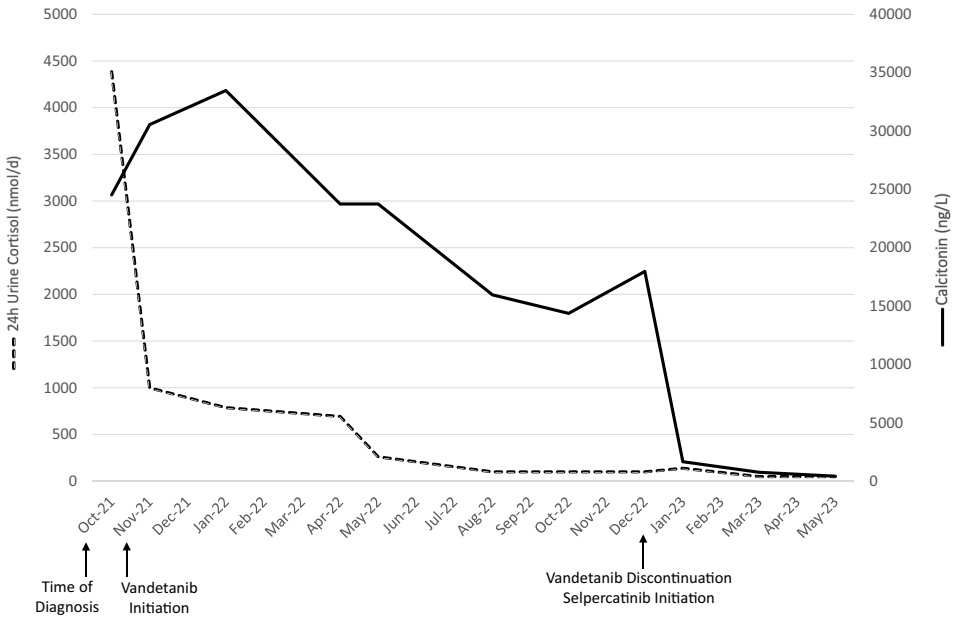

Figure 4. Rapid resolution of 24-hour urine cortisol and calcitonin levels following initiation of vandetanib and selpercatinib.

Our case highlights the need to monitor for adrenal insufficiency following TKI use. One study revealed subclinical adrenal insufficiency in 29 of 55 (52.7%) of those receiving treatment with nonspecific TKIs (10). Of the 3 cases reporting selpercatinib use in the management of paraneoplastic ECS, 2 reported adrenal insufficiency despite no adrenalectomy (3, 5).

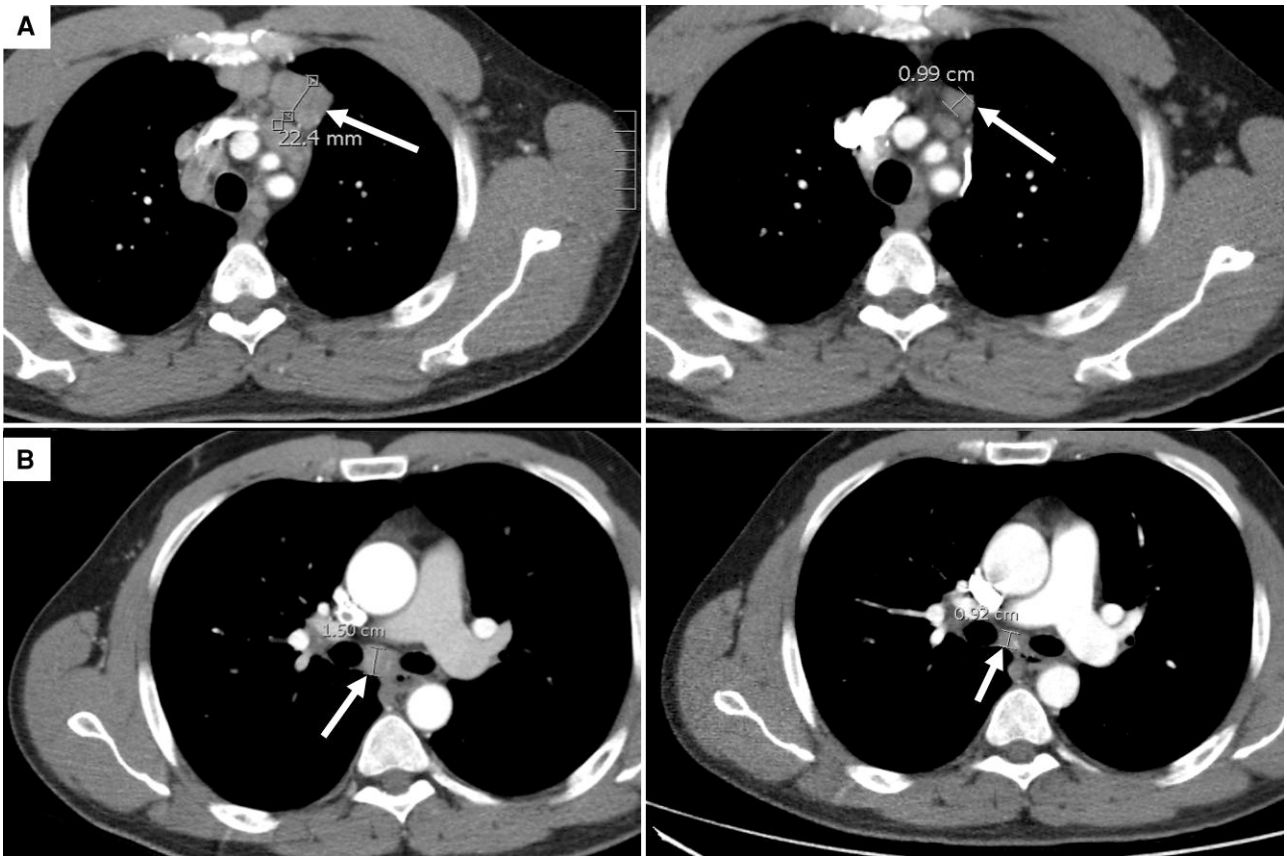

Figure 5. Decrease in tumor burden following initiation of selpercatinib. A, Computed tomography (CT) imaging demonstrating metastases to the left upper prevascular nodes prior to selpercatinib initiation (2.24 cm) and 3 months following selpercatinib initiation (0.99 cm). B, CT imaging demonstrating metastases to subcarinal lymph nodes prior to selpercatinib initiation (1.50 cm) and 3 months following selpercatinib initiation (0.92 cm).

Though the exact mechanisms of adrenal insufficiency following TKI therapy remain poorly understood, it has been suggested that TKIs may induce adrenal damage through alteration of vascular endothelial growth factor–mediated physiologic angiogenesis (10). Alternatively, this may represent a secondary adrenal insufficiency due to hypothalamic-pituitary-adrenal axis suppression caused by longstanding hypercortisolism. It has been recommended that patients undergo periodic ACTH stimulation testing every 6 to 8 months to test for subclinical adrenal insufficiency within this population (10).

In summary, our case provides further evidence supporting the use of TKIs as efficacious and tolerable agents that may reduce the need for invasive surgical interventions in the management of paraneoplastic ECS complicating MTC. Selective RET inhibitors may emerge as important options where treatment is otherwise limited by toxicity or disease progression; however, ongoing research is needed to further evaluate the safety and efficacy of these therapies.

Learning Points

- Multitargeted tyrosine kinase inhibitors have been shown to reverse paraneoplastic ECS associated with MTC, though use is limited by side effects and development of resistance.
- Newer, selective RET inhibitors may overcome the limitations of multitargeted inhibitors, though data regarding their efficacy in reversing paraneoplastic ECS are limited.
- Clinicians should monitor for adrenal insufficiency following treatment of paraneoplastic ECS with multitargeted tyrosine kinase inhibitors or selective RET inhibitors.

Contributors

All authors made individual contributions to authorship. A.J. prepared the initial draft and was involved in manuscript revision; O.A. was involved in the diagnosis and management of this patient and manuscript revision; and J.J. was involved in the diagnosis and management of the patient, manuscript submission, and revision. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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