Case Reports in Oncology

Case Rep Oncol 2023;16:124–128
DOI: 10.1159/000527824
Received: May 24, 2022
Accepted: October 10, 2022
Published online: March 01, 2023

Case Report

Cushing's Syndrome in Adenocarcinoma of Lung Responding to Osilodrostat

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Keywords
Osilodrostat · Ectopic adrenocorticotropic hormone-dependent Cushing · Epidermal growth factor receptor · Case report

Abstract
Cushing's syndrome (CS), secondary to paraneoplastic syndrome, is more commonly seen in small cell lung cancer but never before reported in epidermal growth factor receptor-mutated adenocarcinoma of the lung. Here, we present a case of a patient whose symptoms of hypokalemia, hypertension, and progressive abnormal glucose levels led to further workup that revealed adrenocorticotropic hormone-dependent hypercortisolism. Her cortisol levels dropped after 1 month of osilodrostat treatment, while lung cancer was treated with osimertinib. The use of osilodrostat in paraneoplastic CS has been previously reported in only 3 patients.

Introduction

Advances in understanding the molecular pathogenesis of non-small cell lung cancer (NSCLC) have demonstrated that NSCLC is a heterogeneous group of diseases. Mutations in the epidermal growth factor receptor (EGFR) tyrosine kinase are observed in approximately 15% of NSCLC adenocarcinomas in the USA, occurring more frequently in nonsmokers [1]. The presence of an EGFR mutation confers a more favorable prognosis and strongly predicts sensitivity to EGFR thyrosine kinase inhibitors (TKIs). TKIs have become the standard treatment of EGFR-mutated lung cancer in the metastatic [2] and adjuvant settings [3]. Cushing's syndrome (CS), secondary to paraneoplastic syndrome, is reported in 1% of small cell lung cancer (SCLC) and less frequently in large cell neuroendocrine carcinoma and

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carcinoid tumors of the lung. It is uncommonly seen in NSCLC [1]. Here we present, for the first time, a case of CS related to an EGFR-mutant adenocarcinoma of the lung.

Our patient presented with symptoms of hypokalemia, hypertension, and progressive abnormal glucose levels that led to further workup and revealed adrenocorticotropic hormone (ACTH)-dependent hypercortisolism. Her cortisol levels dropped after 1 month of osilodrostat treatment, a cortisol biosynthesis inhibitor, while lung cancer was treated with osimertinib. We are publishing this case because the use of osilodrostat in paraneoplastic CS has been previously reported in only 3 patients.

Case Report

A 69-year-old Asian female, never smoker, with a medical history of rheumatoid arthritis and pulmonary fibrosis, likely secondary to chronic use of methotrexate, was diagnosed with stage IIIA infiltrating adenocarcinoma (lepidic and acinar pattern) in the right upper lung. She was started on neoadjuvant chemotherapy with cisplatin, docetaxel, and nintedanib for 3 cycles as part of the clinical phase 2 protocol [4] followed by right upper lung lobectomy and lymph node dissection. Her pathologic stage was pT2aN2M0, and adjuvant radiotherapy was given to a total dose of 50 Gy in 25 fractions (200 cGy per fraction). After 48 months following surgery, she had a CT scan that showed disease recurrence (Fig. 1). Given her baseline diagnosis of pulmonary fibrosis, her high risk for pneumothorax, and the low yield for lung biopsy, we proceed with liquid biopsy [5, 6]. She was started on osimertinib 80 mg/day based on the EGFR L858R mutation that was detected. After 6 months of treatment, she started to exhibit severe fatigue, facial and leg edema, unsteady gait, and labile hypertension with no evidence of disease progression. Laboratory tests revealed a potassium level of 2.8 mEq/L and elevated HbA1c of 6.9% (5.9% on previous testing). Endocrinology workup showed cortisol levels of 50.3 μg/dL (range; 5.0–25.0 μg/dL), urine free cortisol of 3,760 μg/24 h (range; 4.0–50.0 μg), ACTH of 153 pg/mL (range; 7.2–63 pg/dL), and dehydroepiandrosterone of 506 μg/dL (NR; 26–460 μg/dL). There was a non-suppressed cortisol with ACTH of 153 pg/mL after administration of 1 mg of dexamethasone, and a high-dose (8 mg) dexamethasone suppression test showed a cortisol level of 35.8 pg/mL with ACTH levels of 56 pg/mL, a mild drop from 119 pg/mL, reinforcing the diagnosis of an ectopic ACTH-dependent hypercortisolism. MRI of the brain was negative for pituitary abnormalities, ruling out CS related to pituitary disease. Adrenal glands were also unremarkable on abdominal CT.

She continued on with the use of osimertinib and started use of osilodrostat 2 mg twice a day, a cortisol inhibitor. After 1 month of treatment, her hypercortisolism symptoms improved, and 24-h urine free cortisol dropped from 2,835 μg/24 h to 53 μg/24 h (range; 4.0–50.0 μg). Osimertinib was used for 9 months and changed to erlotinib due to progressive pulmonary fibrosis. One more time, there was no tumor progression. Her disease remained stable for more 2 months after starting erlotinib treatment, on her last follow-up (Fig. 2). The patient was also diagnosed with pulmonary embolism (PE) during treatment, which is a well-known complication of CS and lung cancer. On our case report writing, we used the CARE guidelines (see www.karger.com/doi/10.1159/000527824).

Discussion/Conclusion

CS due to ectopic ACTH syndrome is an uncommon paraneoplastic phenomenon in non-small cell lung cancer. This case shows, for the first time, a CS related to an EGFR-mutant adenocarcinoma of the lung. According to the Surveillance, Epidemiology, and End Results

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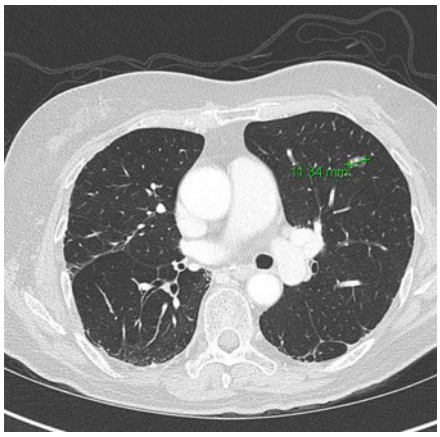

Fig. 1. CT image showing recurrence of the lung adenocarcinoma.

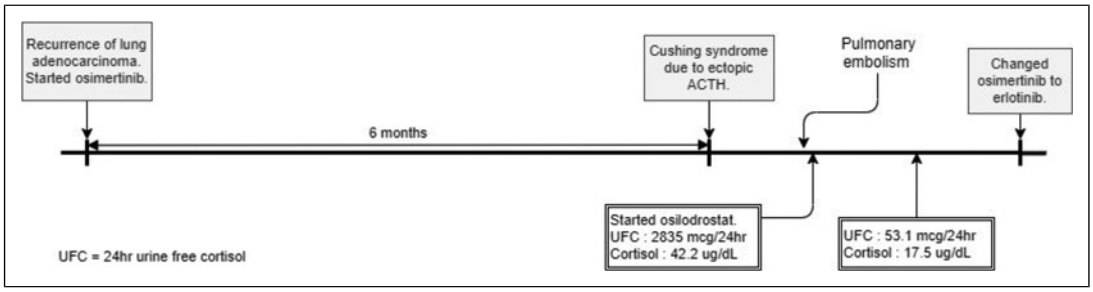

Fig. 2. Timeline of patient's treatment regime.

(SEER) database, ectopic ACTH syndrome is diagnosed in approximately 1 per million person-years in the USA. It is more frequent in SCLC, males, and the elderly population, paralleling that of lung carcinoma. CS secondary to ectopic ACTH syndrome is the third most common cause of CS responsible for 10–15% of the cases. ACTH-dependent syndrome related to pituitary dysfunction represents 65–70%, with adrenal adenoma/carcinoma represents nearly 20% of the CS incidence [7].

Establishing the diagnosis of CS is often difficult because few of the symptoms or signs are pathognomonic of the syndrome in isolation. Some of them (such as obesity, hypertension, and glucose intolerance) are common in individuals who do not have adrenal hyperfunction, especially in an oncologic patient, in whom use of steroids and other medications is common. In our case, what call our attention to order specific tests to establish this diagnosis was the severe fatigue and the facial pletora associated with hypokalemia and hypertension [8]. The use of hydrochlorothiazide and previous use of steroids were confounding factors in this case.

Ectopic ACTH production in SCLC is associated with poor prognosis, poor response to chemotherapy, short overall survival, and higher complication rate. Currently, there is no prognostic data available for CS with adenocarcinoma [9]. Although, the risk of venous thromboembolism event increases up to 10 times in CS, even in the absence of malignant disease [10]. Even though our patient was classified as low risk for venous thromboembolism event according to the Khorana score, she developed PE. The cancer itself is already a risk factor for PE, and there is a possibility that the presence of CS may have increased her risk.

The patient was treated with osilodrostat which inhibits 11β-hydroxylase, an enzyme that catalyzes the last step in the biosynthesis of endogenous cortisol (Fig. 3). This drug was recently approved for use in patients with CS for whom pituitary surgery is not an option or

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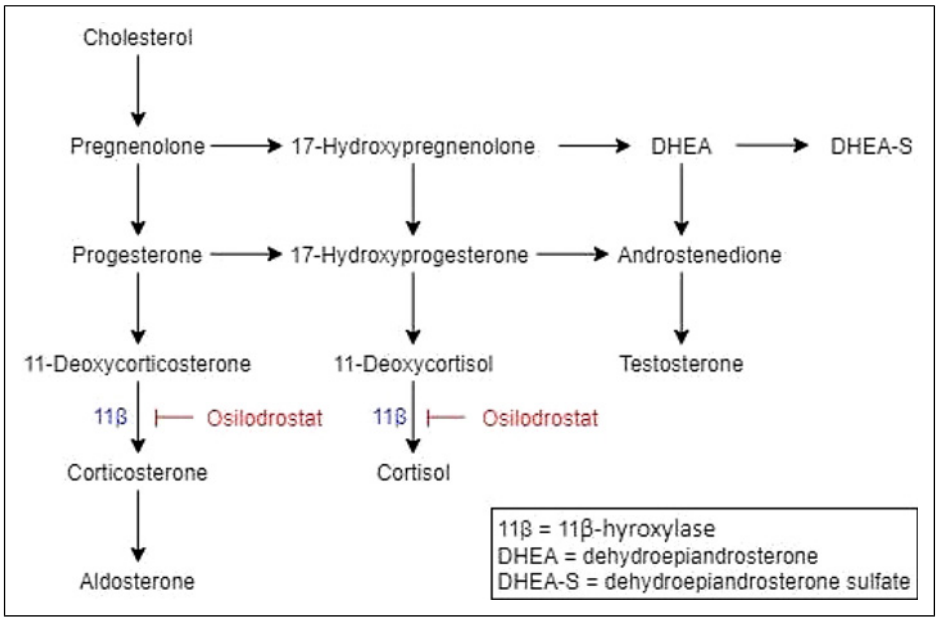

Fig. 3. The steroidogenic pathway for aldosterone and steroids.

for whom surgical removal has not been curative. In this setting, osilodrostat showed an efficacy of 86% in maintaining a normal cortisol level, but its use in ectopic ACTH syndrome is much more limited and studies are scarce. There is only one publication reporting its use in 2 patients with SCLC and 1 patient with adrenal adenoma/carcinoma [11]. In this case series, all patients had their cortisol levels under control. Here we report the first case which osilodrostat was used to control paraneoplastic CS in NSCLC. For the very first time, we present a case of ectopic ACTH-dependent CS in a patient with EGFR-mutated adenocarcinoma of the lung. The patient was successfully managed with osilodrostat and TKI. Osimertinib was used for 9 months, and it was changed to erlotinib, another TKI, due to side effects.

Statement of Ethics

A written informed consent was obtained from the patient for publication of details of his medical case, including images, for a case report in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare no conflict of interest from the point of the view of financial involvement and or nonfinancial relationships (personal, political, or professional) that may potentially influence the writing of the manuscript.

Funding Sources

This research received no external funding from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contributions

Caio Heleno had a major role in writing the original draft preparation, review, and editing. Seung Pyo D. Hong, Hyung-Gyo Cho, Min Jeong Kim, and Yeonggyeong Park were involved in the original draft preparation, review, and editing. Young Kwang Chae was involved in the supervision and project administration. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this trial. All data are available at Northwestern University, Feinberg School of Medicine, Chicago, IL, under care of Dr. Chae Kwang Chae. Further inquiries can be directed to the corresponding author.

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