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Case Report

A Case of an Ectopic ACTH-Producing Tumor With Adrenal Shrinkage During Osilodrostat Administration

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Abstract

Ectopic adrenocorticotropin (ACTH)-secreting tumors are among the causes of ACTH-dependent Cushing syndrome. When surgical resection of the primary lesion is not feasible, medications such as metyrapone, mitotane, and ketoconazole have been used to control hypercortisolism. This report presents a case treated with the novel drug osilodrostat, wherein the patient's adrenal glands exhibited shrinkage following the initiation of this drug. The case involves a 68-year-old man diagnosed with small cell lung cancer and ectopic ACTH-producing Cushing syndrome. Initially, metyrapone was administered to manage hypercortisolism, but its effect proved insufficient. Subsequently, osilodrostat was initiated while gradually decreasing metyrapone, leading to full suppression of blood cortisol levels. With continued osilodrostat treatment, the adrenal glands reduced in size, suggesting the potential to reduce the osilodrostat dosage.

Key Words: ectopic ACTH-producing tumor, Cushing syndrome, osilodrostat, adrenal shrinkage

Abbreviations: 11-DOF, 11-deoxycortisol; ACTH, adrenocorticotropin; CRH, corticotropin-releasing hormone; CT, computed tomography; DOC, 11-deoxycorticosterone; POMC, proopiomelanocortin.

Introduction

Ectopic adrenocorticotropin (ACTH)-secreting tumors represent a rare cause of Cushing syndrome, with an estimated annual incidence of 2 or 3 cases per 1 000 000 (1). Cushing syndrome is categorized into ACTH-independent and ACTH-dependent forms. Ectopic ACTH-dependent Cushing syndrome arises from autonomous ACTH secretion by tumors located outside the pituitary gland, comprising approximately 15% of Cushing syndrome cases (1). Notably, small cell carcinomas of the lung are the most common cause of biochemical hypercortisolism (1). Treatment of ectopic ACTH-secreting tumors typically necessitates primary tumor removal, chemotherapy, radiation therapy, and somatostatin analogues (1). Alongside surgical intervention, medications such as metyrapone, mitotane, and ketoconazole have been employed to reduce blood cortisol levels. However, metyrapone's limitations in terms of its potency and dosing frequency have prompted the search for a more effective drug.

Osilodrostat has emerged as a promising option for managing Cushing syndrome. It inhibits the enzyme 11β-hydroxylase, which converts 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycortisol (11-DOF) to cortisol (2). Osilodrostat has a longer biological half-life than metyrapone, allowing for once-daily or twice-daily dosing. Evidently, osilodrostat possesses superior potency against 11β-hydroxylase (2). Case reports suggest that osilodrostat rapidly controls blood cortisol levels in patients with ectopic ACTH-producing tumors.

The dosage of osilodrostat typically commences at 2 mg and is gradually adjusted based on cortisol levels and patient response. Although some cases have seen an increase to more than 10 mg initially, the dosages are eventually reduced to 1 to 5 mg. This case presents a unique scenario in which the patient's adrenal glands shrank during osilodrostat treatment, enabling dosage reduction.

Case Presentation

A 68-year-old man presented to our hospital with complaints of enlarged right hilar lymph nodes, fever, back pain, dizziness, and diarrhea. His height was 171.0 cm, and his weight was 63.1 kg. His vital signs were as follows: heart rate of 102 beats/min and blood pressure of 181/86 mm Hg. He did not have any cushingoid features. A comprehensive evaluation, including blood tests and a computed tomography (CT) scan of the chest and abdomen, was conducted. His blood tests showed hypokalemia and hyperglycemia. CT revealed the presence of a tumor in the right hilar region, along with swelling of the mediastinal and right supraclavicular lymph nodes and enlargement of the bilateral adrenal glands (Fig. 1A-1C). Tumor markers such as neuron specific enolase and pro–gastrin-releasing peptide were markedly elevated; thus, small cell lung cancer was suspected (details are shown in Table 1).

Diagnostic Assessment

Although his physical findings did not include cushingoid features, the patient's severe hypokalemia, hypertension, and hyperglycemia and the existence of small cell lung cancer

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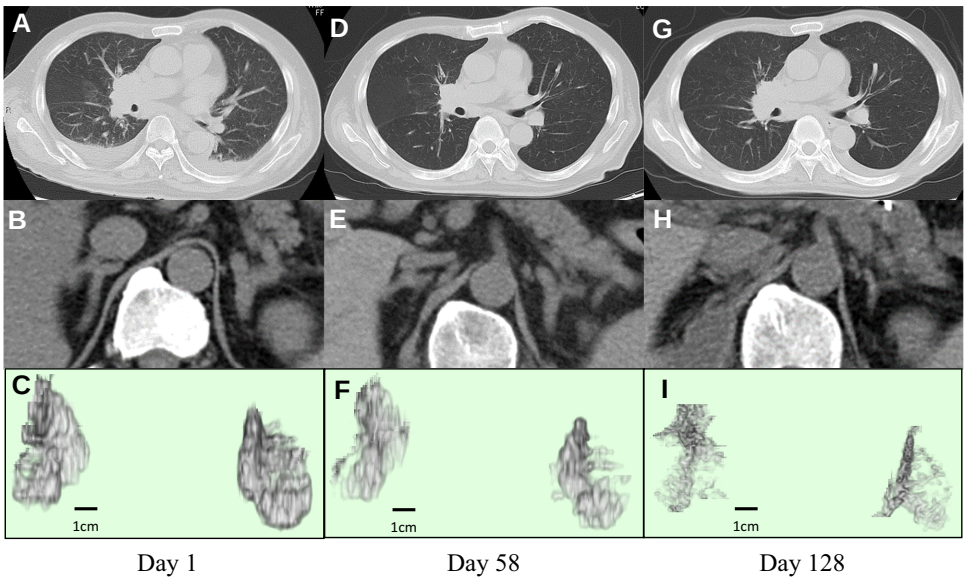

Figure 1. Progress of lung tumor and adrenal grand in computed tomography. Upper row (A, D, G): progression of small cell lung cancer. There were no changes in the progress. The density in HU of the lung cancer was 31 on day 1, 40 on day 58, and 34 on day 128. Middle row (B, E, H): progression of the size of the adrenal grand. The adrenal grand progressively shrank. Lower row (C, F, I): Each volume of the right adrenal gland was 11.7 mL on day 1, 7.5 mL on day 58, and 4.4 mL on day 128. Each volume of the left adrenal gland was 14.2 mL on day 1, 8.8 mL on day 58, and 4.9 mL on day 128. The density of the right adrenal gland was 30 HU on day 1, 13 HU on day 58, and 30 HU on day 128. The density of the left adrenal gland was 31 HU on day 1, 18 HU on day 58, and 19 HU on day 128.

indicated that he had ectopic Cushing syndrome due to small cell lung cancer. Next, we examined his plasma ACTH and serum cortisol levels. Both were markedly elevated.

Based on the CT scan and blood test data, there was a strong suspicion of ectopic ACTH-producing small cell lung cancer. Pituitary magnetic resonance imaging could not detect obvious tumors in the seller turcica within the visible range. Diagnostic tests for Cushing disease, such as the corticotropin-releasing hormone (CRH) challenge test and arginine vasopressin challenge test, are needed to definitively diagnose ectopic Cushing syndrome. However, we determined that the hypercortisolism should be corrected as soon as possible. A needle biopsy confirmed the lung tumor as small cell carcinoma on day 10. Immunohistochemical analysis revealed the tumor's negativity for chromogranin A, ACTH, and CRH but positivity for proopiomelanocortin (POMC), indicating its potential to produce pro-big ACTH and result in ectopic Cushing syndrome (Fig. 2).

Treatment

Without confirming the diagnosis, we initiated the administration of metyrapone at a dose of 500 mg per day since we were familiar with metyrapone rather than osilodrostat. The dose of metyrapone was gradually increased, reaching 2000 mg per day by day 7. An overview of the clinical course is depicted in Fig. 3. Initially, the cortisol level was extremely high, so we did not consider the replacement of any steroids. Subsequently, we used hydrocortisone with metyrapone osilodrostat from day 10. Chemotherapy with etoposide and carboplatin was also started on day 10.

As 2000 mg of metyrapone failed to sufficiently lower the patient's serum cortisol level and metyrapone needed to be taken 6 times a day, we introduced osilodrostat at a daily dose of 1 mg starting from day 25. With close monitoring of the patient's serum cortisol and plasma ACTH levels, we gradually increased the osilodrostat dose to 20 mg per day while concurrently decreasing the metyrapone dose. This approach resulted in full suppression of the serum cortisol levels, enabling the discontinuation of metyrapone 20 days after the initiation of osilodrostat.

Outcome and Follow-up

Subsequently, we gradually decreased the dose of osilodrostat while following the patient's serum cortisol levels (see Fig. 3). Sixty-six days after the initiation of osilodrostat treatment, the patient was successfully maintained on a reduced daily dose of 1 mg without any increase in serum cortisol levels. A plain CT scan conducted after 33 days of osilodrostat treatment demonstrated that the primary lung tumor had somewhat decreased in size, but the density of lung cancer ranged from 30 to 40 HU, which indicated that there was no necrotic change in his lung cancer (Fig. 1D). The scan also revealed a slight reduction in the volume of the bilateral adrenal glands compared to that on day 1 (Fig. 1E and 1F). The patient was readmitted on day 91 for chemotherapy due to small cell lung cancer. Osilodrostat administration was discontinued after day 128. However, the patient's serum cortisol level remained below 4.0 mcg/dL (110 nmol/L). A plain CT scan on day 128 showed a marked reduction in the volume of the bilateral adrenal glands (Fig. 1H and 1I). The patient died of small cell lung cancer on day 143.

We analyzed the adrenal steroid profile using residual serum samples on day 48 by liquid chromatography–mass spectrometry. Serum DOC and 11-DOF levels were elevated above the normal range (Table 2). This means that bioactive ACTH was definitely present in excess in the patient's serum, and his

Table 1. Laboratory data on administration

Blood tests	Results	Reference ranges
Red blood cell	**4.0 10^12/L** **400 10^4/mcL**	4.35-5.55 10^12/L 435-555 10^4/mcL
White blood cell	**8.7 10^12/L** **87 10^4/mcL**	3.3-8.6 10^12/L 33-86 10^4/mcL
Differential count		
Neutrophils	91.1%	
Lymphocytes	6.0%	
Eosinophils	0.0%	
BUN	6.8 mmol/L 19 mg/dL	2.9-7.1 mmol/L 8.0-20 mg/dL
Creatinine	72.5 mcmol/L 0.82 mg/dL	57.5-94.6 mcmol/L 0.65-1.07 mg/dL
eGFRCre	**72 mL/min/1.73 m^2**	>90 mL/min/1.73 m^2
Sodium	**152 mmol/L** **152 mEq/L**	138-145 mmol/L 138-145 mEq/L
Chloride	**97 mmol/L** **97 mEq/L**	101-108 mmol/L 101-108 mEq/L
Potassium	**1.6 mmol/L** **1.6 mEq/L**	3.6-4.8 mmol/L 3.6-4.8 mEq/L
Calcium	**2.00 mmol/L** **8.0 mg/dL**	2.20-2.52 mmol/L 8.8-10.1 mg/dL
Blood glucose	**15.1 mmol/L** **272 mg/dL**	3.9-6.9 mmol/L 70-125 mg/dL
HbA_{1c}	**52 mmol/mol** **6.9%**	27-44 mmol/mol 4.6%-6.2%
ACTH	**170 pmol/L** **770 pg/mL**	1.6-14.0 pmol/L 7.2-63.3 pg/mL
Cortisol	**2436 nmol/L** **88.3 mcg/dL**	196-541 nmol/L 7.1-19.6 mcg/dL
DHEA-S	**10.43 mcmol/L** **385 mcg/dL**	0.35-7.15 mcmol/L 13-264 mcg/dL
SCC	1.7 mcg/L 1.7 ng/mL	<2.3 mcg/L <2.3 ng/mL
CYFRA	**4.2 mcg/L** **4.2 ng/mL**	<3.5 mcg/L <3.5 ng/mL
Pro GRP	**147 204 ng/L** **147 204 pg/mL**	<81 ng/L <81 pg/mL
NSE	**205 mcg/L** **205 ng/mL**	<12 mcg/L <12 ng/mL

Abnormal values are shown in bold font. Values in the upper row are International System of Units (SI).

Abbreviations: ACTH, adrenocorticotropin; BUN, blood urea nitrogen; CYFRA, cytokeratin 19 fragment; DHEA-S, dehydroepiandrosterone sulfate; eGFRCre, estimated glomerular filtration rate from creatinine; HbA_{1c}, glycated hemoglobin A_{1c}; NSE, neuron specific enolase; Pro GRP, pro–gastrin-releasing peptide; SCC, squamous cell carcinoma antigen.

adrenal glands were stimulated. We also measured the plasma ACTH using test kits provided by Roche and Tosoh Corporation using residual plasma samples on day 132. The Tosoh test kit has a higher detection sensitivity for pro-ACTH than that of Roche. The ACTH levels were 924 pg/mL (203 pmol/L) and 1257 pg/mL (277 pmol/L), respectively. These results indicate that while some pro-ACTH was present in the patient's plasma, mature ACTH was also present to some extent.

Table 2. Hormone levels on day 48

Hormone tested	Results	Reference ranges
ACTH	**142 pmol/L** **646 pg/mL**	1.6-14.0 pmol/L 7.2-63.3 pg/mL
Cortisol	**41.4 nmol/L** **1.5 mcg/dL**	196-541 nmol/L 7.1-19.6 mcg/dL
DOC	**2.18 nmol/L** **0.72 ng/mL**	0.24-0.85 nmol/L 0.08-0.28 ng/mL
11-DOF	**4.34 nmol/L** **1.50 ng/mL**	0.12-3.35 nmol/L 0.04-1.16 ng/mL

Abnormal values are shown in bold font. Values in the upper row are International System of Units (SI).

Abbreviations: 11-DOF, 11-deoxycortisol; ACTH, adrenocorticotropin; DOC, 11-deoxycorticosterone.

Discussion

In our case, we observed 2 significant aspects. First, the patient's adrenal glands exhibited shrinkage despite the plasma ACTH levels not decreasing. Second, the osilodrostat dose was reduced while the adrenal glands shrank.

Our search for publications on osilodrostat and ACTH-dependent Cushing syndrome yielded 57 relevant articles as of May 23, 2023, with 47 cases of ACTH-dependent Cushing syndrome, including 38 cases of ectopic ACTH-producing tumors and 9 cases of Cushing disease (3–10). Thirty-seven out of 47 cases with ACTH-dependent Cushing syndrome were managed with osilodrostat monotherapy, while the remaining 10 patient cases received a combination of osilodrostat, ketoconazole, and cabergoline, among other drugs. In the 37 cases of osilodrostat monotherapy, 2 different strategies for initiating osilodrostat were observed: the titration strategy and the block and replacement with hydrocortisone strategy (see Fig. 4). Twenty-two of 37 cases received the titration strategy, starting with a low initial dose of 1 to 10 mg daily, with only 2 cases initially starting with a higher initial dose (20 mg daily). Twelve patients initially treated with the titration strategy transitioned to the block and replacement strategy during follow-up. On the other hand, 15 of 37 patient cases received the block and replacement strategy, with initial osilodrostat doses varying from 2 to 60 mg daily, supplemented with hydrocortisone from the outset. In our patient case, osilodrostat was initiated in combination with metyrapone but was subsequently switched to monotherapy, with the dose titrated up to 20 mg daily and then tapered to 1 mg.

Notably, none of the 47 cases of ACTH-dependent Cushing syndrome obtained from PubMed mentioned changes in adrenal gland size. Although metyrapone and osilodrostat both attenuate 11β-hydroxylase enzymatic activity, metyrapone-induced adrenal shrinkage has not been reported. Therefore, the inhibition of 11β-hydroxylase by osilodrostat is unlikely to be the cause of the adrenal gland size reduction. The mechanism by which osilodrostat reduces adrenal volume remains unknown, making it imperative to closely monitor adrenal size in patients undergoing osilodrostat treatment. As indicated in previous reports, most patients attempt dose reduction or discontinue osilodrostat successfully. Thus, if the adrenal

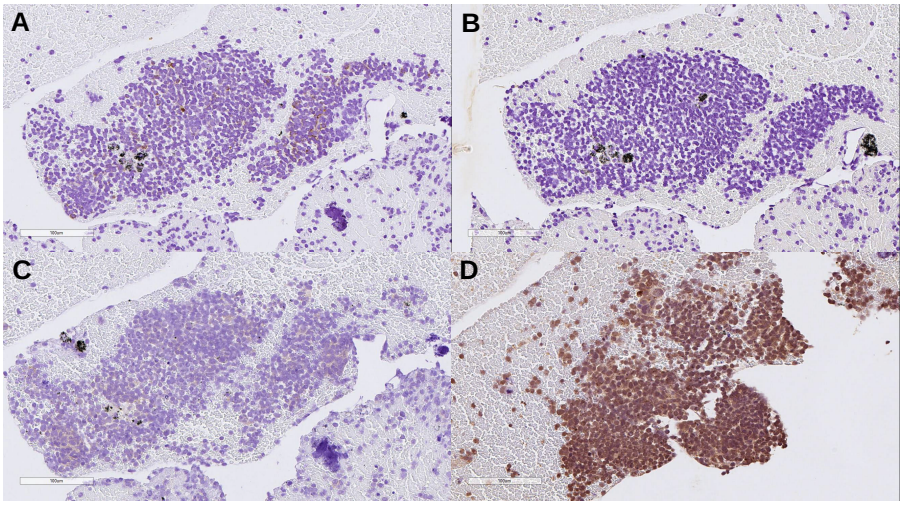

Figure 2. Immunostaining of the small cell lung cancer. Figures show each immunostaining analysis: A, chromogranin A; B, adrenocorticotropin (ACTH); C, corticotropin-releasing hormone (CRH); D, proopiomelanocortin (POMC). Chromogranin A, ACTH, and CRH are negative in small cell lung cancer, but POMC is positive. This means that small cell lung cancer produces big-ACTH and can result in ACTH-dependent Cushing syndrome.

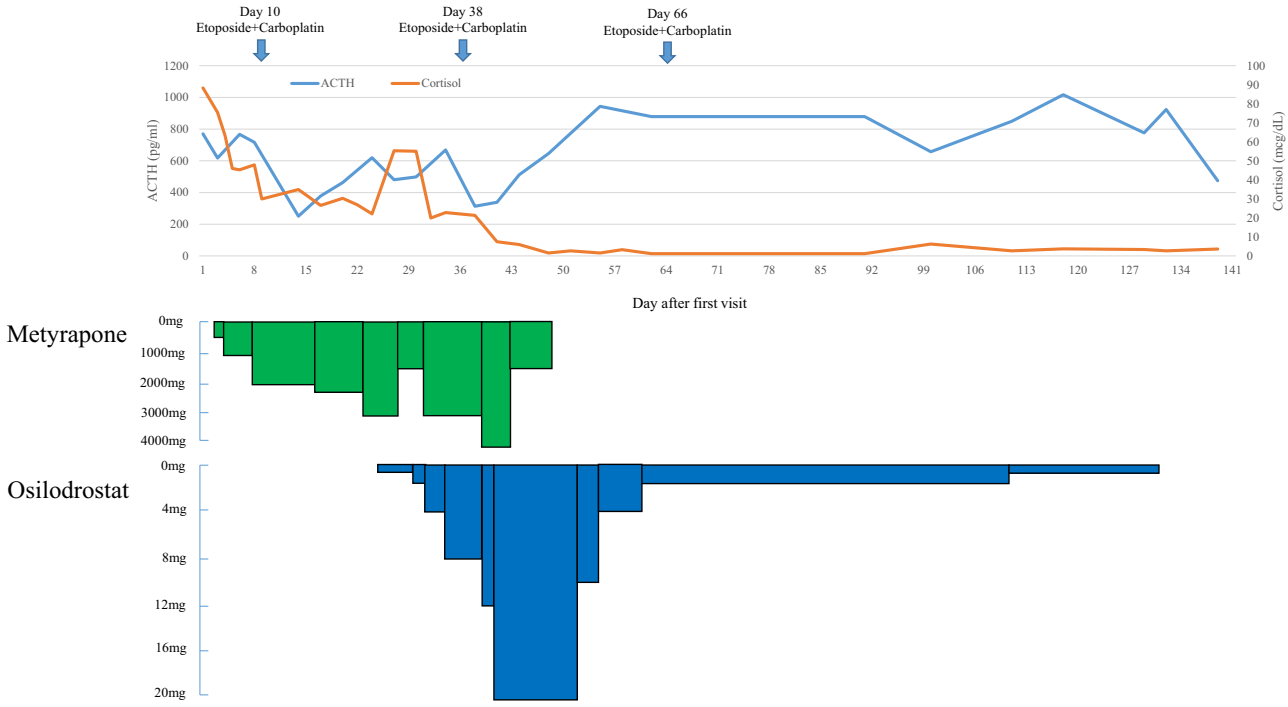

Figure 3. Changes of adrenocorticotropin (ACTH) and cortisol during metyrapone and osilodrostat, and chemotherapy. Cortisol was suppressed following an increase in the metyrapone and osilodrostat dosage. ACTH was not suppressed after chemotherapy for small cell lung cancer.

glands shrink, reducing the osilodrostat dose may be feasible without compromising blood cortisol level control. Hence, tracking adrenal size through imaging studies, such as CT and magnetic resonance imaging, in osilodrostat-treated patients becomes essential, and assessing the adrenal pathology in these individuals is equally crucial.

In addition to the former hypothesis, there is another hypothesis that the hormones produced by small cell lung cancer change from ACTH to big-ACTH, which has much less potency to increase plasma cortisol levels, due to chemotherapy or progression to undifferentiated carcinomas of small cell lung cancer. However, the CT scan after osilodrostat administration showed that the density of lung cancer did not change and ranged from 30 to 40 HU, which indicated there was no necrotic change in the patient's lung cancer. In addition, the difference in ACTH measurement results between the 2 kits suggested that bioactive ACTH was present in the plasma, and the elevation of serum DOC and 11-DOF indicated that the patient's adrenal glands were stimulated by ACTH.

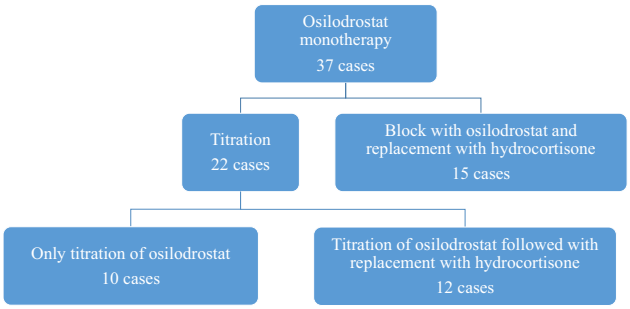

Figure 4. Reported strategy of treatment with osilodrostat. Thirty-seven patients received osilodrostat monotherapy. Twenty-two cases had a titration strategy. Twelve of 22 patient cases with a titration strategy were switched during follow-up to a block and replacement strategy. Fifteen patient cases had a block and replacement strategy initially.

We experienced a case of ectopic ACTH-dependent Cushing syndrome treated with osilodrostat. In this case, a reduction in the osilodrostat dose was needed to maintain serum cortisol levels in the appropriate range, and a concomitant reduction in adrenal gland size was observed. It is important to follow-up not only ACTH and cortisol levels but also adrenal size on imaging studies in patients treated with osilodrostat. Evaluation of the adrenal pathology in these patients is also needed.

Learning Points

- To treat ectopic ACTH-producing Cushing syndrome, osilodrostat is currently available.
- We found that osilodrostat was able to fully control the blood cortisol levels, and the dose of osilodrostat could be reduced after the patient's blood cortisol level was controlled.
- In our ectopic Cushing syndrome patient, the enlarged adrenal glands had shrunk in the course of treatment with osilodrostat.
- Through an unknown mechanism, osilodrostat decreases the size of adrenal glands; this effect enabled us to reduce the dosage of osilodrostat.

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Contributors

All authors made individual contributions to this study. F.S. was involved in the writing, submission, and preparation of tables and images. R.H. was involved in the diagnosis and management of this patient. R.K. was involved in the diagnosis and management of this patient and was responsible for overseeing the study. H.A. was responsible for the original idea and writing the first draft of the manuscript. All authors were involved in writing and reviewing the case report and approving the final draft.

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Disclosures

The authors declare no conflicts of interest.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Original data generated and analyzed during this study are included in this published article.

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