Unveiling the Hidden Enemy: Ectopic Cushing Syndrome-Induced Cardiomyopathy in Small Cell Lung Carcinoma

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Abstract

Ectopic Cushing Syndrome (CS) is a paraneoplastic syndrome encountered in 1-5% of Small Cell Lung Carcinoma (SCLC) cases (1,2). It usually presents with weight gain or loss, muscle wasting, hypertension and hypokalemic metabolic alkalosis, whereas the typical Cushingoid phenotype is usually absent (2). Cardiomyopathy associated with Cushing syndrome is an exceedingly rare presentation (3). We report a case involving a middle-aged woman who experienced confusion, fatigue and progressive difficulty in walking for the past week. An electrocardiogram (ECG) revealed a new-onset Left Bundle Branch Block (LBBB), and a Transthoracic Echocardiogram (TTE) demonstrated severe systolic dysfunction with a reduced Left Ventricular Ejection Fraction (LVEF), findings indicative of dilated cardiomyopathy. A coronary angiogram did not reveal any critical stenoses, excluding common cardiac pathologies as a cause. Concurrently, laboratory tests identified an ectopic source of adenocorticotropic hormone (ACTH) expression, whereas imaging studies identified a lung lesion suspicious for malignancy, along with multiple liver and bone-lytic lesions suggestive of metastases. A CT-guided biopsy of the lung nodule was performed, and histopathological analysis confirmed the diagnosis of small cell lung cancer (SCLC), thereby supporting the diagnosis of ectopic CS-associated cardiomyopathy.

Keywords: Cushing Syndrome; Ectopic Secretion; Cardiomyopathy; Case Report.

Introduction

Cushing Syndrome (CS), defined by prolonged exposure to elevated levels of cortisol, is an uncommon condition with an estimated global annual incidence of 2-2.7 per million.[1,2] Elevated glucocorticoid levels can result from direct production by a tumor or hyperplasia in the adrenal glands, from increased ACTH production by a pituitary gland tumor, or through ectopic ACTH secretion by various malignancies as part of a paraneoplastic syndrome.[3,4] Ectopic ACTH production is a rare occurrence, accounting for 12-17% of all CS cases.[5] Following the metabolic disturbance induced by hypercortisolism, complications such as diabetes, hypertension, immunosuppression, osteoporosis, cardiac and psychiatric disorders may develop.[1,6] Cardiomyopathy, a less frequently reported manifestation of ectopic Cushing Syndrome,[7] often presents with new-onset systolic and diastolic dysfunction, reduced Left Ventricular Ejection Fraction (LVEF), various arrhythmias, or thromboembolic events.[4] Prompt

treatment aimed at lowering cortisol levels is essential and can potentially reverse myocardial damage.[1,8,9] This case hopes to shed light on one of the most underrecognized complications of Cushing Syndrome, particularly as a paraneoplastic manifestation, that carries significant implications for patient outcome.

Case Report

A 63-year-old female presented with fatigue, progressive difficulty in walking and confusion over several days. Her medical history was significant for major depressive disorder and long-term smoking, but she had no known history of hypertension, diabetes, alcohol or drug abuse. Upon examination, the patient demonstrated prominent skin hyperpigmentation, and her vital signs were recorded as follows: temperature 36°C, blood pressure 148/86 mmHg, heart rate 78 beats per minute, oxygen saturation (SpO2) 96%, and respiratory rate (RR) 12 breaths per minute. Clinical examination revealed an ill-appearing disoriented patient with diminished muscle strength, rated as 2^{+}/5 in the lower limbs.

Arterial Blood Gas (ABG) revealed metabolic alkalosis (*Table 1*). Laboratory examinations showed mild hypokalemia (Potassium - K: 3 mEq/L), significant hyperglycemia and elevated Liver Function Tests (LFT) (*Table 2*). The patient was started on intravenous fluids with potassium replacement, an insulin pump, aspirin, captopril, and a statin, and was subsequently admitted for further evaluation. Persistent marked hypokalemia, hyperglycemia, muscle wasting and hypertension led to additional workup, that revealed markedly elevated free serum cortisol, 24-hour urinary free cortisol and ACTH, indicating ACTH-dependent cortisol overproduction (*Table 3*). Renin and aldosterone levels were within normal limits. Low and high-dose dexamethasone suppression test indicated failure to suppress serum cortisol levels (*Table 3*). The patient was initiated on broad-spectrum antibiotic therapy due to her increased susceptibility to infection, with specific coverage for pneumocystis jirovecii (PCP), ketoconazole 1200mg per day as a steroid synthesis inhibitor, and spironolactone.

Table 1: Arterial Blood Gas (ABG) of the patient on admission.

ABG (FiO_2 21%)	**Patient's Values**	**Reference Range**
SpO_2	95%	>93%
pH	7.52	7.35-7.45
pCO_2	34.1	35-45 mmHg
pO_2	79.1	60-100 mmHg
HCO_3^-	28.2	18-24 mEq/L
Lactate	0.9	<1 mmol/L

Table 2: Laboratory Examinations of the patient on admission.

Laboratory Exam	**Patient's Values**	**Reference Range**
White Blood Cells	10.1	4-10 K/µL
Neutrophil	9.2	1.5-7 K/µL
Hemoglobin	15.1	12-16 gr/dL
Hematocrit	44	36-46%
Platelets	229	140-440 K/µL
Prothrombin Time	10.6	10-15 sec
INR	0.9	0.85-1.15
Glucose	217	75-110 mg/dL
HbA1c	11.7	5.5-6.5%
Serum Osmolarity	310	285-295 mOsm/L
Blood Urea Nitrogen	46	15-54 mg/dL
Creatinine	0.89	0.55-1.2 mg/dl
SGOT	29	5-40 IU/L
SGPT	121	5-45 IU/L
γGT	398	10-40 IU/L
Potassium (K)	3	3.5-5.5 mEq/L
Sodium (Na)	137	137-150 mEq/L
Calcium (Ca)	8.5	8.1-10.4 mg/dL
Magnesium (Mg)	2.5	1.5- 2.5 mg/dL
Phosphorus (P)	2.2	2.5-5 mg/dL
C-Reactive Protein	4.8	0-10 mg/L
Troponin I	38.5	0-47.8 pg/mL
Myoglobin	83	10-92 ng/mL

Creatine Kinase-MB	3.5	0-3.6 ng/mL
BNP	20603	0-300 pg/mL
Lipoprotein (a)	11.2	<30 mg/dL
Creatine Phosphokinase	38	10-170 IU/L

INR: International Normalized Ratio. AST: Aspartate Aminotransferase. ALT: Alanine Aminotransferase. γGT: Gamma-Glutamyl Transpeptidase. BNP: pro-B type Natriuretic Peptide.

Table 3: Hormonal profile of the patient during hospitalization.

Laboratory Exam	**Patient's Values**	**Reference Range**
Serum free cortisol	96.1	3.7-19.4 μg/L
24-hour urine cortisol	4920	4.3-176 μg/24h
Renin	2.2	2-20 pg/mL
Aldosterone	101.5	29-160 pg/mL
ACTH	150.2	<40 pg/mL
Low-dose Dexamethasone Suppression Test	79.5 (POSITIVE)	3.7-19.4 mg/dL
D-4 Androstenedione	6.8	0.24-3.44 ng/mL
TSH	0.45	0.35-4.94 μiu/mL

An electrocardiogram (ECG) revealed new-onset Left Bundle Branch Block (LBBB), raising the concern for an acute myocardial infarction (AMI). To further evaluate this possibility and assess cardiac function, a transthoracic echocardiogram (TTE) was performed. The TTE demonstrated impaired systolic function, evidenced by a severely reduced left ventricular ejection fraction (LVEF) of 20%, and global hypokinesis of the myocardial walls. Fractional shortening was measured at 16%. The left ventricle was dilated (left ventricular end-diastolic diameter [LVDd]: 57 mm, left ventricular end-systolic diameter [LVDs]: 45 mm), while the interventricular septum thickness (IVSt) was normal at 10 mm. The left atrium and right ventricle dimensions were increased (42 mm and 32 mm, respectively). No pericardial effusion or significant valvular disease was observed. A subsequent coronary angiogram showed patent vasculature with no critical stenoses. These findings are consistent with dilated cardiomyopathy.

A full-body imaging workup was conducted to locate the source of the ectopic ACTH excretion. CT scan of the brain revealed the absence of pituitary lesions, whereas chest and abdominal CT scans with intravenous contrast demonstrated multiple lesions in the left lower lung lobe suspicious of a primary lung tumor *(Figure 1 – panel A)*, along with left hilar lymphadenopathy. Notably, in the thoracic spine, there were pathologic fractures associated with bone-lytic lesions *(Figure 1 – panel B)*. Further, the abdominal CT scan disclosed multiple hypodense hepatic lesions, which are suggestive of metastatic spread *(Figure 2)*.

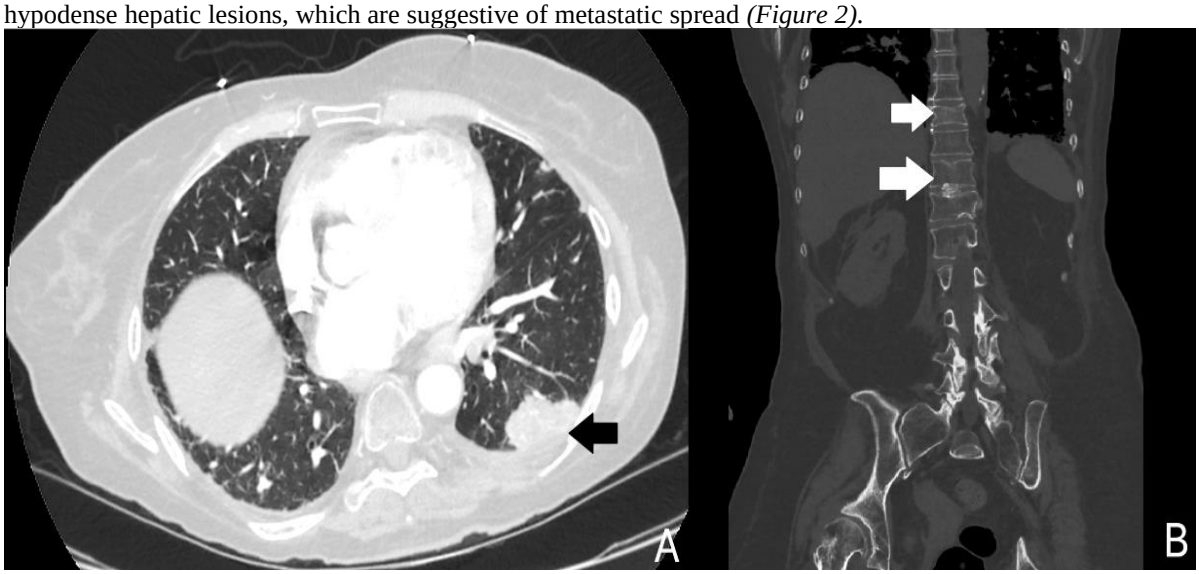

Figure 1. Axial CT scan of the chest displaying a lesion in the lower lobe of the left lung, abutting the pleura (panel A - black arrow), suggestive of a primary lung neoplasm. Additionaly, pathologic fractures are visible in the thoracic spine (panel B - white arrows) consistent with bone lytic metastases.

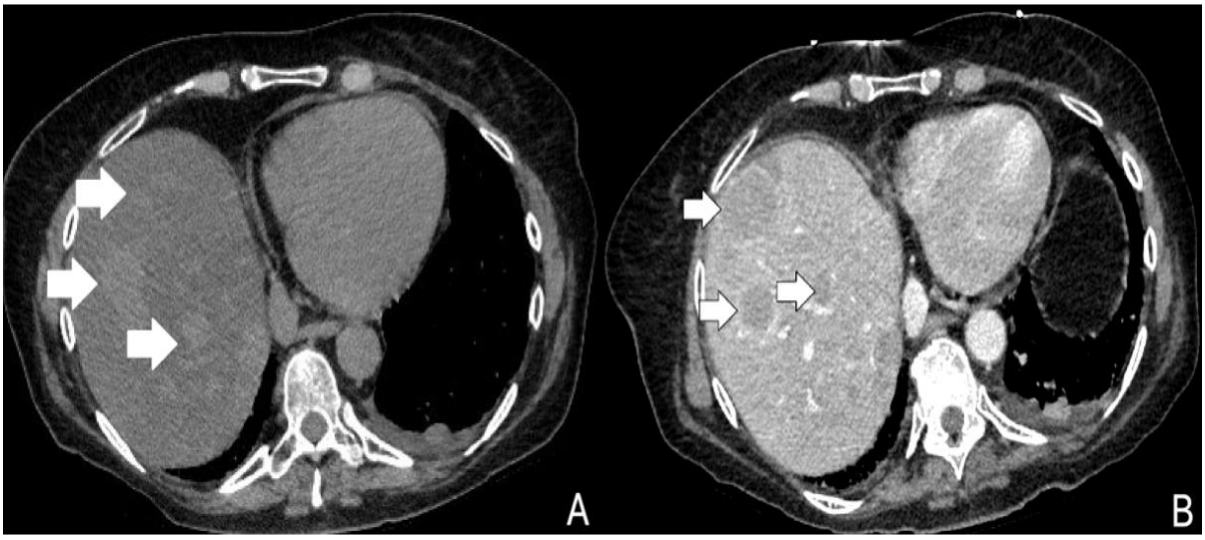

Figure 2. Axial computed tomography (CT) scan of the abdomen with intravenous contrast, revealing multiple hyperdense lesions within the liver, suspicious for hepatic metastases (panel A-white arrows). Post-contrast administration, these lesions show no enhancement (as shown in panel B with white arrows).

A CT-guided biopsy of the lung nodule was performed, and histopathological examination revealed characteristic features of small cell lung carcinoma (SCLC). The tumor consisted of small cells with minimal cytoplasm and a high nuclear-to-cytoplasmic ratio, along with focal necroses *(Figure 3 – panel A).* Immunohistochemical analysis showed positive staining for cytokeratin-7 (CK-7), thyroid transcription factor-1 (TTF-1), synaptophysin, and chromogranin, as well as islet-1 (ISL1/ISMN-1) *(Figure 3 – panel B),* along with negative staining for Napsin-A and p63. The proliferation index, indicated by Ki67 staining, was measured at 85%. The tumor cells stained negative for ACTH.

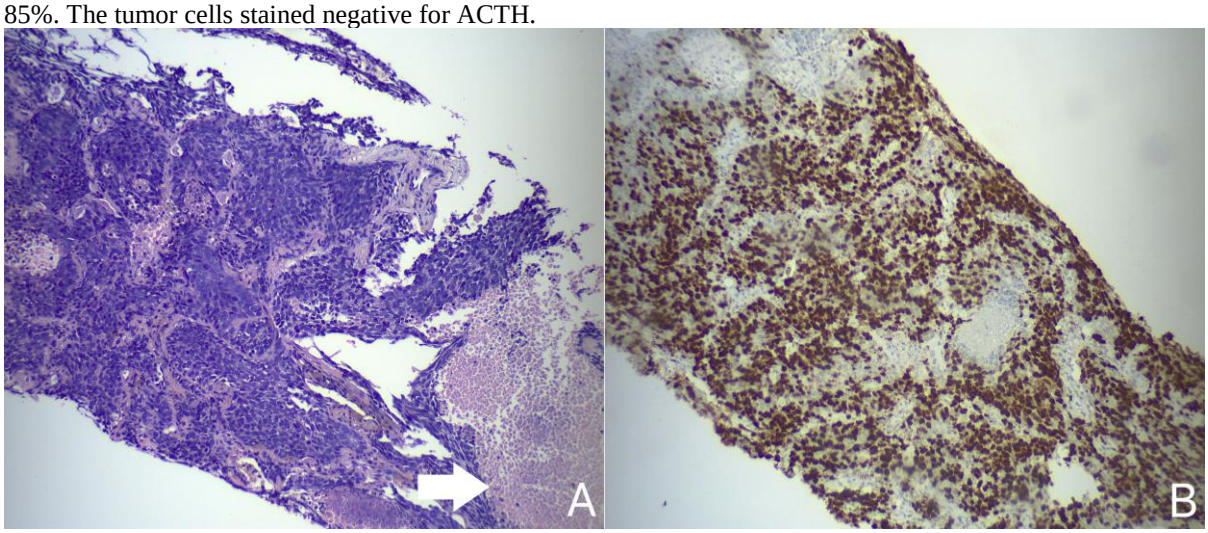

Figure 3. Histopathologic examination demonstrates the presence of small sized cells with lack of nucleoli and a high nuclear-to cytoplasmic ratio, as well as focal necroses (panel A - identified by white arrow, x10 magnification). Immunohistochemical analysis reveals positive staining for islet-1 (ISL1/ISMN-1), a nuclear marker specific of neuroendocrine differentiation (panel B, x10 magnification).

These findings, coupled with the lack of an alternative explanation for the patient's sudden deterioration in cardiac function, led to the diagnosis of cardiomyopathy induced by ectopic Cushing Syndrome. Hospital course was notable for refractory hypokalemia, hyperglycemia, significant weight loss and muscle wasting. Regrettably, the patient's condition deteriorated, marked by the abrupt onset of dyspnea and chest pain. Clinical examination revealed an ill-appearing patient, with bilateral rales upon auscultation. Despite comprehensive medical interventions, the patient's health continued to decline, culminating in her demise after 15 days of hospitalization.

Discussion

Cushing Syndrome (CS) is characterized by elevated cortisol production, which can occur directly due to adrenal adenoma or hyperplasia, through increased ACTH secretion from a pituitary adenoma, or via ectopic ACTH production as part of a paraneoplastic manifestation.[3,4] Ectopic ACTH secretion from non-pituitary tumors was first described by Liddle in 1963,[5,10] and it is most commonly associated with SCLC, occurring in 1-5% of SCLC cases.[3,7,10,11] Additionally, ectopic CS has reportedly been linked to neuroendocrine tumors of the pancreas, carcinoids, pheochromocytoma, medullary thyroid carcinoma, and olfactory neuroblastoma, among others.[5,10,12-14]

The clinical presentation of ectopic CS may be subtle, as most patients lack the distinctive phenotypic characteristics of Cushing syndrome, which includes symptoms such as skin hyperpigmentation, striae, buffalo hump and truncal obesity.[7,11,15] Instead, patients may experience severe weight fluctuations, muscle wasting, osteoporosis that can lead to pathologic fractures, immunosuppression, menstrual irregularities and mental health disorders.[5,7,11,13] Furthermore, metabolic issues like hyperglycemia and hyperlipidemia are frequently observed.[6,16,17] Our patient exhibited solely skin hyperpigmentation, lacking the additional typical features of a Cushingoid phenotype.

Unlike these extensively reported manifestations of CS, cardiomyopathy stands out as a comparatively rare and less recognized consequence of ectopic ACTH syndrome. Its clinical presentation varies widely, from being completely asymptomatic to exhibiting severe arrhythmias, thromboembolism, myocardial ischemia, or non-ischemic cardiac failure.[16,18,19] There are documented cases where cardiomyopathy emerged as the initial manifestation of CS, with the abrupt presentation of dyspnea and cardiac dysfunction prompting investigations that revealed an ACTH-secreting tumor as the source of glucocorticoid overproduction.[20-23]

On a cellular level, glucocorticoid excess contributes to the development of cardiomyopathy by inducing pressure overload by upregulation of both glucocorticoid and mineralocorticoid receptors.[8] This process promotes cardiomyocyte hypertrophy[24] and enhances myocardial cells' responsiveness to angiotensin-II.[6,16] Moreover, this hormonal surplus further induces myofibrillolysis by upregulating the FOXO transcription factor, leading to increased atrogin-1 and ubiquitin expression.[7,16,24] Concurrently, fibroblast activity is stimulated, leading in myocardial tissue remodeling and fibrosis.[24]

In ectopic Cushing's Syndrome, laboratory examinations often reveal hyperglycemia, hypokalemic metabolic alkalosis, hyperlipidemia, and abnormal coagulation parameters.[16] Hormonal assessment of the pituitary-adrenal axis typically shows increased levels of cortisol in both serum and urine.[13,25] Cortisol levels typically fail to suppress during both low- and high-dose dexamethasone suppression tests.[13,25] The Corticotropin-Releasing Hormone (CRH) stimulation test can be instrumental in distinguishing between pituitary and ectopic ACTH production.[13,14] In the context of cardiomyopathy, elevated cardiac enzymes or abnormalities in an electrocardiogram (ECG) may prompt suspicion of cardiac involvement.[4] Imaging studies, such as CT or Magnetic Resonance Imaging (MRI) scans, are particularly useful for locating the primary tumor.[14] A biopsy is often essential for definitive diagnosis, and ACTH positive staining on tumor cells identifies the tumor as the source of the ectopic ACTH secretion.[26] In our case, ACTH staining was negative, yet the clinical presentation, laboratory findings, and absence of an alternative diagnosis led to the conclusion of ectopic CS.

In CS associated cardiomyopathy, echocardiographic evaluations typically reveal a spectrum of abnormalities, including both systolic and diastolic dysfunction.[6] These dysfunctions are frequently evidenced by a significantly reduced left ventricular ejection fraction (LVEF) and diminished Fractional Shortening.[6] Furthermore, left ventricular hypertrophy (LVH) is a common observation, manifesting as increased LV mass and wall thickness,[6,16] while right ventricular hypertrophy may also occur. Cardiac MRI may reveal reduced ejection fractions in the left ventricle, right ventricle, and left atrium, along with an increase in left ventricular mass.[21] Collectively, these findings are consistent with dilated cardiomyopathy, which is the most prevalent pattern of cardiac failure observed in CS.

The differential diagnosis of cardiomyopathy associated with CS includes a range of endocrine disorders, including hypothyroidism, hyperthyroidism, pheochromocytoma, acromegaly, and growth hormone deficiency.[24] Moreover, myocarditis, which can be induced by inherited, viral, autoimmune, or ethanol-related factors, should also be considered.[16] Additionally, Takotsubo cardiomyopathy, especially in the setting of cancer, is an important consideration in the differential diagnosis.[7,16]

Effective management of Cushing's Syndrome primarily involves lowering glucocorticoid levels and addressing the underlying cause.[1,8] Treatment options include steroid synthesis inhibitors such as ketoconazole, metyrapone, mitotane, mifepristone, and aminoglutethimide.[3,11,13] In some cases, bilateral adrenalectomy may be considered.[11] Addressing the primary malignancy, through surgery, chemotherapy or radiotherapy, is a crucial step in management.[11] t's noteworthy that myocardial damage in CS is more closely linked to the duration of hypercortisolism rather than the degree of cortisol elevation and is highly reversible.[1,8,27] A study by Frustachi et al., highlighted significant recovery of myocardial tissue and function 1 year after cortisol levels normalisation.[9] Moreover, the use of cardioprotective agents, such as Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), beta-blockers, potassium-sparing diuretics, along with thromboprophylaxis and cardiac monitoring, can be crucial for patient survival.[3,15]

Ectopic CS is usually associated with bulky disease with metastases in at least three organs.[7] Prognosis of metastatic SCLC associated with ectopic Cushing Syndrome is particularly poor, with an estimated life expectancy of about 3 to 6 months.[3,11] Steroid-induced immunosuppression, hyperglycemia, osteoporosis, pro-coagulation and muscle wasting, among others, confer a deleterious effect on patients' survival.[11,16] Furthermore, it is hypothesized that hypercortisolism may induce resistance to chemotherapy and radiotherapy by mediating epigenetic modifications in crucial genes associated with therapeutic response.[11]

To the best of our knowledge, this is the 5th case of ectopic Cushing Syndrome-associated cardiomyopathy reported in literature.[4,6,7] Our case prompted further investigation for hypercortisolism syndromes due to the persistent hypertension and hypokalemia, as well as muscle wasting and new-onset hyperglycemia. The significant impairment in systolic function, notably diverging from a normal cardiologic evaluation (LVEF: 60% two years prior), as well as the absence of critical coronary stenoses, pointed towards the excessive glucocorticoids' impact on myocardial tissue as the most likely contributor to the patient's rapidly deteriorating condition.

Conclusion

Ectopic Cushing Syndrome is a well-recognized paraneoplastic manifestation of various solid tumors, particularly SCLC. Cardiomyopathy due to excess glucocorticoid secretion is exceedingly rare. Therefore, physicians should be highly vigilant for signs of this condition, particularly in new-onset cardiac dysfunction in the context of hypercortisolism syndrome. Prompt initiation of treatment aimed at normalizing glucocorticoid levels and addressing the underlying malignancy is crucial, in order to potentially alter the ominous prognosis of these patients.

Conflicts of Interest

No conflicts of interest to disclose.

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