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Case report

Ectopic ACTH syndrome complicated by hypercortisolism-associated urolithiasis. A case report

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ABSTRACT

Introduction: We present an elusive case of an ectopic Cushing's syndrome mimicking an autoimmune syndrome induced by adjuvants (ASIA), complicated by rapidly progressive urolithiasis.
Case presentation: A 30-year-old female with recent breast augmentation presented for easy bruising, night sweats, nocturia, fatigue, and weight gain. After fulfilling diagnostic criteria for ASIA, she underwent explantation, nonetheless, the patient worsened. Workup revealed an ACTH-dependent Cushing's syndrome with a neuroendocrine tumor in the right lung, confirmed by immunostaining after VAT-FNA. Management was complicated by urolithiasis and COVID-19 infection. She was rendered stone-free and subsequently underwent open lobectomy and mediastinal lymphadenectomy.
Conclusion: Pathology confirmed an atypical ACTH-secreting pulmonary carcinoid tumor. She received radiotherapy and was free of recurrence at follow-up.

1. Introduction

Nephrolithiasis is a frequent and underestimated complication of Cushing's syndrome (CS), reported to occur in 15 % of patients compared to 1–5 % of the general population in industrialized countries [1]. This prevalence soars up to 50 % in adult patients with active CS, and 25 % in cured patients. As some patients with cured CS are left with residual abnormalities that contribute to stone recurrence, the prevalence of nephrolithiasis will always be significantly higher than in the general population [2].

Ectopic ACTH secretion (EAS) is a less common cause of Cushing syndrome and is seen in 5 to 10 % of cases with endogenous hypercortisolemia [3]. Sudden and dramatic onset of CS often suggests an ectopic ACTH-secreting tumor [1]. The mean time to diagnosis of CS is 14 months [4]. More than 50 % of ectopic ACTH-secreting tumors are located in the chest (45 % pulmonary NETs, 6.5 % thymic NETs). 68Ga-DOTATOC PET/CT provides a high sensitivity (88–93 %) and specificity (88–95 %) for the diagnosis of carcinoid tumors, which are often non-metastatic and well-differentiated NETs [6]. Lung NETs generally present similarly to other lung neoplasms with symptoms such as dyspnea, cough, or hemoptysis, but can also be found incidentally as an asymptomatic pulmonary nodule [7].

The mainstay of treatment for early-stage typical carcinoid (TC) and atypical carcinoids (AC) is surgical resection with post-operative active surveillance. A negative resection margin offers excellent PFS rates of 97 % and 80 % in TC and AC patients, respectively. Surgical resection generally follows non-small-cell lung carcinoma (NSCLC) guidelines with lobectomy and mediastinal node sampling being the standard of care [7]. The utility of adjuvant treatment is not as well-established. Using an aggressive treatment regimen is important, as local-regional recurrence remains an important mode of treatment failure. The treatment of advanced tumors requires a multidisciplinary approach. Tumor-directed therapy can include somatostatin analogs, systemic chemotherapy, interferon-α, chemoembolization, radiofrequency ablation, and radiation therapy (RT) [8]. ESMO advises that adjuvant treatment consisting of chemotherapy with or without RT may be considered in patients at high risk of recurrence, such as AC N2 patients [7]. Results from a recent open-label, phase III RCT concluded that post-operative radiotherapy (PORT) cannot be recommended for all patients with stage II and III NSCLC with mediastinal nodal involvement. Potential benefits of adjuvant PORT were offset by a predominantly higher risk of cardiopulmonary toxicities [9]. All groups call for an individualized

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approach and shared clinical decision-making [7]. This case highlights the underrecognized association of nephrolithiasis in patients with CS as well as the multidisciplinary approach required in EAS.

2. Case report

A 30-year-old female with an unremarkable past medical history, family history and psychosocial history presented to the ER complaining of easy bruising, peripheral edema, insomnia, night sweats, nocturia, fatigue, and weight gain after breast augmentation surgery. The patient denied COVID-19 vaccination, breast pain or any other local inflammatory symptoms. No striae were noted. Although silicone implant incompatibility syndrome had been dismissed by several plastic surgeons in the previous six months, she fulfilled diagnostic criteria for ASIA syndrome, or Shoenfeld's syndrome, and agreed to explantation. Postoperatively, the patient worsened with hirsutism, buffalo hump, facial plethora, supraclavicular fullness, hair loss, dyspnea, hypertension, and menstrual abnormalities (Fig. 1). Initial diagnostic workup revealed polycystic ovaries. Blood tests for PCOS reported severe hypercortisolism. Urinary free cortisol (UFC) confirmed hypercortisolemia. High levels of plasma ACTH with a positive CRH test were noted. Imaging studies were performed revealing bilateral renal microlithiasis with no suspicious lesions in the brain or adrenals. A chest X-ray showed a 16 mm lung nodule in the right lung (Fig. 2), which was confirmed

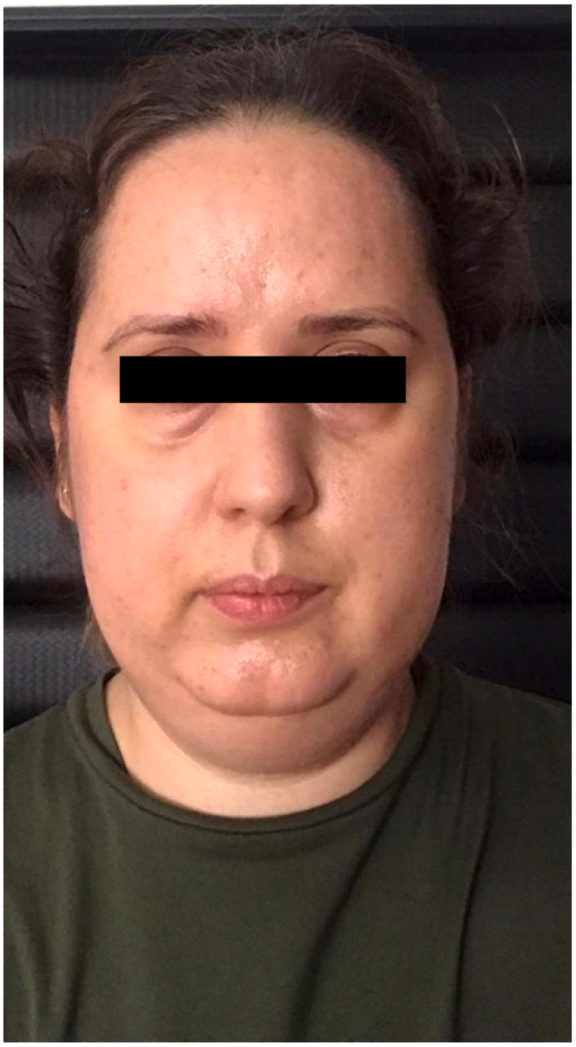

Fig. 1. Female pattern hair loss with facial plethora, acne, hirsutism and supraclavicular fullness.

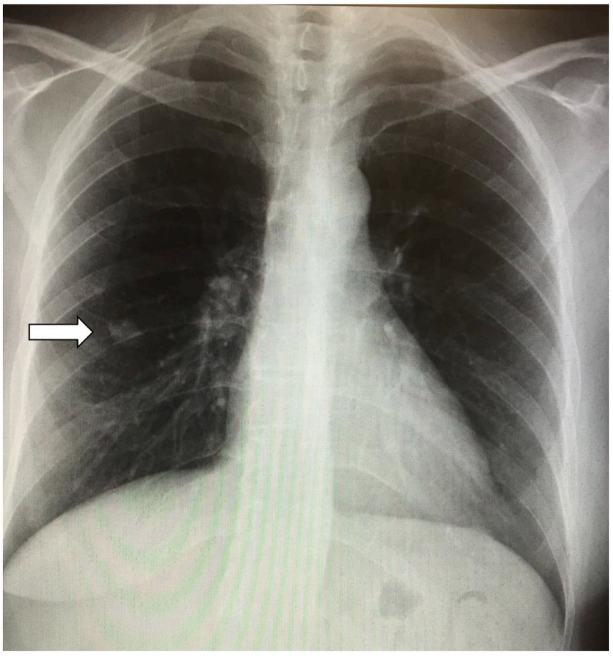

Fig. 2. Chest radiograph demonstrating a 16 mm pulmonary nodule in the right lung.

with a CECT chest scan. The patient underwent VAT-FNA with frozen section analysis revealing an atypical carcinoid tumor of the lung (Fig. 3) with positive immunostaining for CD56, synaptophysin, cytokeratin and Ki67 (low index), but no reactivity for TTF-1 or CD45. A 99mTc-HYNIC-TOC scan showed radiopharmaceutical uptake of two pulmonary nodules in the superior segment of the right lower lobe, right mediastinum, and thyroid gland. Thyroid FNAC reported a follicular adenoma. While waiting for scheduled surgery she presented renal colic and underwent emergency double-J stenting due to an 8 mm stone lodged at the right ureterovesical junction. After being successfully rendered stone-free by ureteroscopy and laser lithotripsy, infrared spectroscopy results showed calcium oxalate composition, and a stone-specific metabolic evaluation revealed no abnormalities. Shortly after, open lobectomy and mediastinal lymphadenectomy were performed. Histological examination confirmed PT1a,N2,Mx disease with negative surgical margins. The patient initiated glucocorticoid replacement therapy and was discharged 4 days after surgery. A week after she presented fever, malaise, arthralgias and weakness. Early post-lobectomy complications and steroid withdrawal syndrome were ruled out. A diagnostic nasopharyngeal swab was performed testing positive for SARS-CoV-2. She progressed well with a mild case of COVID-19

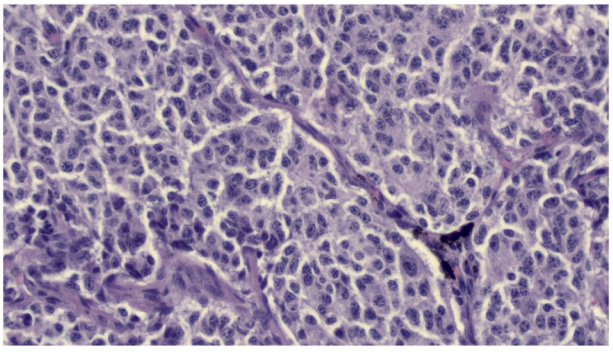

Fig. 3. Large nests of cells with eosinophilic cytoplasm and ovoid nuclei containing granular chromatin and inconspicuous nucleoli. Scattered mitoses are present (H&E, 10×).

without having to suspend glucocorticoid therapy. The patient received adjuvant stereotactic ablative body radiotherapy (SABR) for locoregional control of nodal disease. On follow-up, abnormal endocrine levels were normalized, and all clinical signs and symptoms had abated. One year after surgery, the patient remains well with no evidence of tumor or stone recurrence.

3. Discussion

The association of hypercalciuria and nephrolithiasis has been clearly established. There is paucity of literature on the pathogenesis of nephrolithiasis in CS, especially in patients with no discernible metabolic disturbances in the stone-specific evaluation, such as this patient. Regarding management and treatment of cortisol-dependent comorbidities, the Endocrine Society's guidelines on Cushing's syndrome makes no reference to nephrolithiasis. Likewise, there is no information in any urological clinical practice guideline (AUA, CUA, EAU, NICE and UAA) in relation to management of this particular subset of patients with glucocorticoid-induced nephrolithiasis; nor are there any available recommendations on screening for nephrolithiasis in CS. Bearing in mind that half of patients with CS have kidney stones and are considered high-risk stone formers, follow-up in glucocorticoid-induced nephrolithiasis should be tailored to the type of stone, severity of the disease, patient comorbidities and available resources. Not only should patients with biochemical “cure” of CS warrant follow-up for recurrent calculi, but screening and preventative strategies for nephrolithiasis should also be implemented in all patients with chronic hypercortisolism. Enrolling stone patients with CS in a prevention program can reduce the risk of stone recurrence, with the potential for substantial health-care savings.

While surgical resection should be considered for early-stage disease, the role of adjuvant therapy is not as clear. Treatment of presumed residual microscopic disease in NSCLC has been the rationale for the use of post-operative radiation therapy (PORT). There is limited data on the effectiveness of adjuvant therapy in the literature and treatment beyond surgery is controversial. Guidelines from different organizations vary, citing a lack of trials to support a high-level recommendation. This represents an unmet need in the treatment for lung NETs and prospective studies are warranted, however, the rarity of this tumor makes RCTs difficult to conduct. Multiples studies show a detrimental effect of adjuvant therapy in ACs and should be avoided outside of a clinical trial.

We hope this paper leads towards future research and new insights to provide decision makers with much-needed evidence-based recommendations in the management of this special group and conditions. In this manner, urologists and neuroendocrinologists can maximize efficiency through multidisciplinary and preventative clinical practice.

4. Methods

The current case report was written following the SCARE 2020 guidelines criteria [10].

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None.

Ethical approval

Ethical approval has been exempted by our institution, Tecnologico de Monterrey.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of a standard consent form is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Emilio de León Castorena: He is a PGY-5 urology resident. He led the work recollecting data and wrote the manuscript.

Dulce María López Sotomayor: She is a PGY-4 pathology resident. She helped obtain the images and descriptions of them. She helped with the final edition as well.

Luis Edwin Gaona Garza: He is a PGY-2 family medicine resident. He checked the manuscript and helped with the outline of the paper.

Mario Alberto Treviño Aguillón: He is a medical student. He helped organize the manuscript and helped with the final edition.

Alejandro Talamas Mendoza: He is a PGY-3 urology resident. He helped organize the manuscript and helped with the final edition.

Registration of research studies

Not applicable.

Guarantor

Emilio de León Castorena.

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Declaration of competing interest

None.

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