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Case Report

Ectopic Cushing's Syndrome Secondary to Acinic Cell Carcinoma of the Parotid Gland: A Case Report

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Cushing's syndrome · Adrenocorticotropic hormone · Acinic cell carcinoma · Parotid gland

Abstract
We present a case report of a patient with a rare high-grade transformation of an acinic cell carcinoma (ACC) of the parotid gland, who developed Cushing's syndrome (CS) as a result of ectopic secretion of adrenocorticotropic hormone by the tumour. The hypercortisolism was successfully treated with metyrapone, and the ACC was treated with local radiotherapy and a combined six cycles of gemcitabine and cisplatin, having achieved a partial response to the tumour. A multidisciplinary approach and combined medical treatment with radiotherapy and were essential for disease control and CS management. ACC should be considered in the differential diagnosis of ectopic CS.

Introduction

Ectopic secretion of adrenocorticotropic hormone (ACTH) by non-pituitary tumours is a rare cause of Cushing's syndrome (CS). The most associated tumours are small cell carcinoma of the lung and bronchial carcinoids, while thymic carcinoids, pancreatic neuroendocrine tumour, pheochromocytoma, and medullary thyroid carcinoma are

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responsible for the remaining cases [1–3]. In rare occurrences, malignant salivary gland tumours, such as acinic cell carcinoma (ACC), have been associated with ectopic ACTH production [4].

ACC is an uncommon salivary gland neoplasm, accounting for 2.5–5% of all parotid epithelial neoplasms. ACC is considered a low-grade neoplasm, usually presenting an indolent course, with a good overall prognosis [5]. However, when ACC presents with high-grade transformation (a well-differentiated ACC juxtaposed with areas of high-grade poorly differentiated adenocarcinoma, carcinoma not otherwise specified, or undifferentiated carcinoma occurs, in which the original line of differentiation is lost), it has an unpredictable clinical course, with a potential for recurrence, lymphatic, and distant metastases [6].

Herein, we report a case of a high-grade ACC, later diagnosed with ectopic CS. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530445).

Case Presentation

A 60-year-old man, with previous medical history of primary arterial hypertension and non-insulin-dependent type 2 diabetes, presented with a right latero-cervical mass. Computed tomography documented a 39 × 38 mm necrotic mass on the deep lobe of the right parotid gland and homolateral cervical lymph nodes. A PET scan revealed mediastinal, bone (right scapula, left iliac crest, left acetabulum, and right sacrum ala), and multiple pulmonary lesions. Parotid fine-needle aspiration cytology and computed tomography-guided biopsy of the lung nodule were compatible with ACC's metastasis. Histopathological analysis of the cervical mass revealed an ACC with high-grade transformation (positive for AE1/AE3, CAM5.2, DOG1, and SOX10, p40 negative), as shown in Figure 1. Discussion in multidisciplinary team agreed on parotidectomy and cervical lymph node dissection.

While waiting for parotidectomy, severe hypertension, dyslipidaemia, insulin-dependent diabetes mellitus, and hypokalaemia developed. Plasma basal ACTH (798 [<46] pg/mL), morning salivary cortisol (>101 [<15] nmol/L), and 24-urinary free cortisol (UFC) (2,392 [20–90] μg/24 h) were markedly elevated. ACTH immunohistochemistry was performed in one of the pathology specimens and immunostaining was observed, confirming the diagnosis of ACTH-dependent CS.

Hypercortisolism was managed with metyrapone (2 g/day) with early clinical response. Hypertension was initially managed with ACE inhibitor (lisinopril 20 mg bid), isosorbide mononitrate (20 mg tid), calcium channel blocker (nifedipine 60 mg bid), potassium-sparing diuretic (spironolactone 300 mg id), and β-blocker (carvedilol 25 mg bid). Hypokalaemia was treated with potassium chloride supplements (50 mEq iv + 3,600 mg oral/day) and spironolactone (300 mg/day).

Local disease progression, with skull-base involvement, precluded surgery. Radiotherapy (RT) for the parotid and cervical lesions was performed. RT was initiated 1 week after starting metyrapone, which was maintained during the RT treatment, at a dose of 2–2.5 g/day. The patient completed intensity-modulated radiation therapy with a total dose of 50 Gy/20 fractions (2.5 Gy/f) over the right parotid mass, infratemporal fossa until the skull base, and cervical adenopathy, with significant reduction of the locoregional disease. Metastatic bone lesions were treated with symptomatic RT (20 Gy/5 fractions [4 Gy/f] over the sacrum). Decrease in antihypertensive therapy, progressive discontinuation of insulin therapy, and withdrawal of potassium supplementation were noticed after RT and medical treatment. Biochemically, there was a significant reduction in UFC to 1,626 μg/24 h 2 months after initiating metyrapone.

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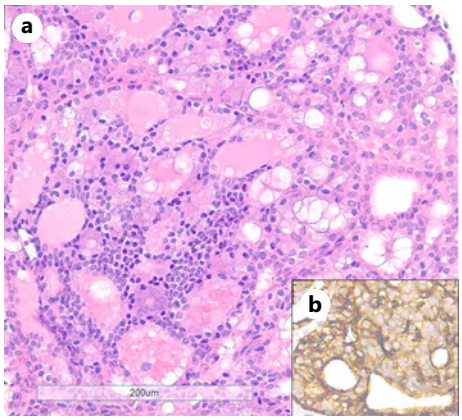

Fig. 1. Biopsy from the latero-cervical mass. **a** (H&E). Tumour presenting a microcystic and follicular pattern, with large cells with indistinct cell borders, vacuolated eosinophilic/amphophilic cytoplasm, and round to oval nuclei. Mitosis, necrosis, or relevant pleomorphism were not seen. **b** (DOG1 immunohistochemistry). The neoplastic cells are positive for DOG1, characteristic of ACC. The diagnosis of metastatic ACC was rendered.

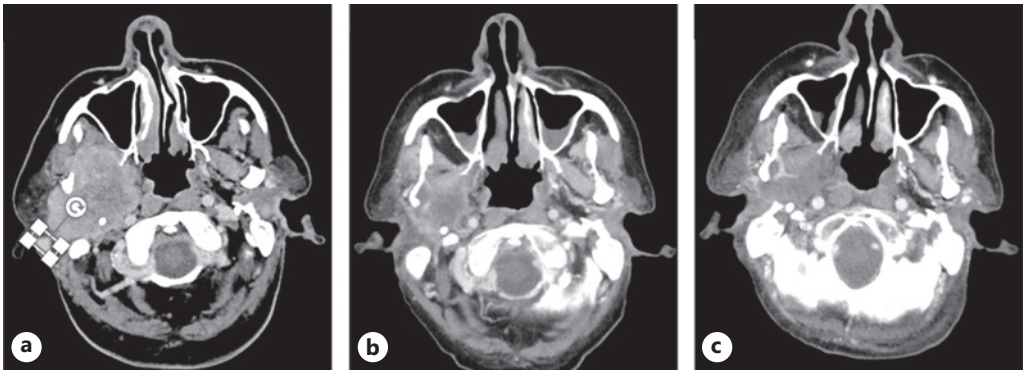

Fig. 2. Cervical computed tomography scan of the parotid mass. **a** Tumour at diagnosis, with a necrotic mass of 39 × 38 mm (arrow). **b** Tumour after completion of RT treatment. **c** Tumour after six cycles of chemotherapy.

The patient started palliative chemotherapy with gemcitabine 1,250 mg/m^2 and cisplatin 80 mg/m^2, which was reasonably tolerated, with nausea and mucositis being the most frequent adverse effects. Due to haematologic toxicity, the dose of gemcitabine was reduced to 1,000 mg/m^2 in the sixth and last cycle. Metyrapone was also maintained during chemotherapy (2–2.5 g/day) with good tolerability. UFC levels were normalized after three cycles of chemotherapy (to 45.6 μg/24 h). During chemotherapy, blood pressure and glycaemic profile were controlled without pharmacotherapy. Imagological response was favourable by the end of the treatment, as shown in Figure 2; however, clinical deterioration and progressive immunosuppression occurred, resulting in multiple hospital admissions. The patient died from a nosocomial infection 3 months after finishing chemotherapy.

Conclusion

ACC is considered a low-grade neoplasm, and most of the cases have an indolent course. However, in a minor proportion of cases, almost exclusive of the parotid gland, ACC can undergo high-grade transformation with aggressive behaviour. We describe a rare case of ectopic CS, emerging as a paraneoplastic feature of an ACC. This case shows that it is possible to diagnose salivary gland malignancy from small samples, either from fine-needle aspiration cytology or small biopsies, especially if the clinical context is adequate and paraffin material is

available for additional studies (in this case immunohistochemistry was used) [7–9]. The management of hypercortisolism with steroidogenesis inhibitors and control of tumour progression with RT and chemotherapy led to improvement in CS.

There have been only ten cases of ACTH-dependent CS secondary to ACC reported to date. Therefore, the management of this tumour and its complications were particularly challenging. The successful improvement of CS after treatment, as well as the symptomatic and imagological response, makes this a unique case report among the literature.

Statement of Ethics

The review of patient data did not require ethical approval in accordance with national guidelines. Written informed consent has been obtained from the wife of the deceased patient for publication of this case report.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pedro Miguel Antunes Meireles and Diana Pessoa drafted the manuscript. Sara Pinheiro reviewed and was responsible for the endocrinology part of the case report. Juliana Faria Filipe and Miguel Rito did the pathology revision and provided the images in this case report. Isabel Sargento was the patient's doctor in charge of all clinical information and directed patient care. All the authors participated in manuscript revision and approved the final version.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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