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REVIEW ARTICLE

Ectopic adrenocorticotropic hormone syndrome due to olfactory neuroblastoma: A case report and literature review

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Abstract Ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is a cause of Cushing's syndrome usually associated with neuroendocrine tumors. Olfactory neuroblastoma (ONB) is a rare malignant neoplasm of the olfactory epithelium. This is the case of a 56-year-old woman with an ONB presenting with EAS. After initiating metyrapone, she developed a *Pneumocystis jirovecii* pneumonia. Following successful treatment of the infection, she underwent surgical tumor excision and radiotherapy, which has been in remission for the past 3 years. The authors provide a literature review of the 30 previously published cases of ONB presenting with EAS. Most were reported in middle-aged men, with a recurrence rate of 15.6% (3 patients eventually died). A total of 9.5% of all reported had an infection after starting corticosteroid-blocking therapy. ONB is a very rare cause of EAS with poor prognosis and a relapsing course. In the presence of severe hypercortisolism, chemoprophylaxis for common opportunistic agents must be considered.

PALABRAS CLAVE
Síndrome de Cushing;
Estesioneuroblastoma;
Producción ectópica de ACTH;
Infección oportunista

Síndrome de secreción ectópica de hormona adrenocorticotrópica secundario a un neuroblastoma olfativo: reporte de un caso y revisión de la literatura

Resumen El síndrome de secreción ectópica de hormona adrenocorticotrópica (SEA) es una causa de síndrome de Cushing habitualmente asociada a tumores neuroendocrinos. El neuroblastoma olfativo (NO) es un tumor maligno raro del epitelio olfativo. Se describe el caso de

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una mujer de 56 años con SEA secundario a NO. Tras empezar con metirapona, la paciente tuvo una neumonía por *Pneumocystis jirovecii*. La infección fue tratada, el tumor fue extirpado quirúrgicamente, y recibió radioterapia. La paciente se ha mantenido en remisión durante los 3 últimos años. Se presenta una revisión de los 30 casos de SEA secundario a NO reportados previamente. La mayoría fue en hombres de mediana edad, con una tasa de recurrencia del 15,6% (3 pacientes murieron). El 9,5% de estos casos tuvieron una infección tras empezar el control del hipercortisolismo. El NO es una causa rara de SEA con mal pronóstico y elevada recurrencia. En presencia de hipercortisolismo, se debe considerar quimioprofilaxis para agentes oportunistas frecuentes.

Case description

Production of adrenocorticotropic hormone (ACTH) from nonpituitary tumors – known as ectopic ACTH syndrome (EAS) – is the cause of ACTH-dependent hypercortisolism in up to 18% of all cases of Cushing's syndrome.[1] EAS is more commonly associated with neuroendocrine tumors located in the chest, namely small-cell lung carcinoma, bronchial carcinoids and thymic neuroendocrine tumors.[2] These are followed less frequently by breast, colon, gastric, pancreatic and prostate cancers.[2–6] Olfactory neuroblastoma (ONB), or esthesioneuroblastoma, is a rare malignant neoplasm that develops from the olfactory neuroepithelium and has a neuroblastic differentiation.[7] Approximately 1000 cases of ONBs have been reported worldwide and 30 cases presented with EAS.[8–10] It usually has an indolent and recurrent progression, metastasizing via hematogenous and lymphatic routes.[7,11–13] This is the case of a patient with EAS-related Cushing's syndrome due to an underlying ONB.

The patient was a 56-year-old woman who presented to our hospital with a 3-month history of bilateral oedema of the lower limbs, polyuria, polydipsia and an involuntary weight loss of 8 kg. She had been previously diagnosed with hyperlipidemia, controlled with atorvastatin. She did not have any other relevant previous medical and family history. On physical examination at admission, she exhibited mild hirsutism, slight facial hyperpigmentation and exuberant oedema involving the lower limbs up to her thighs. Lab test results included metabolic alkalosis, severe hypokalaemia (potassium levels of 2.6 mmol/L) and a casual blood glucose level of 527 mg/dL. She was put on potassium chloride, spironolactone 200 mg/day and insulin glargine titrated to 18 units daily.

This presentation suggested Cushing's syndrome. The morning serum cortisol (90.4 mcg/dL; reference levels 4.82–19.5 mcg/dL), 24-h urinary cortisol (23,062 mcg/24 h; reference levels 124–581 mcg/24 h), salivary cortisol at night-time (26.60 ng/dL; reference levels 3–10 ng/dL) and ACTH levels (760 pg/mL; reference levels 4.7–48.8 pg/mL) were all elevated. Furthermore, there was no cortisol suppression after the low and high-dose dexamethasone suppression tests (with 1 mg and 8 mg, respectively). These findings confirmed the hypothesis of Cushing's syndrome, most likely due to an EAS.

A cranioencephalic computed tomography (CT) scan revealed the presence a solid mass in the frontal area with invasion of the ethmoidal labyrinth and left orbital cavity. The full body CT-scan showed atraumatic vertebral fractures of the lumbar spine, with no other abnormalities. A cranioencephalic magnetic resonance image (MRI) confirmed the presence of a solid mass in the olfactory bulb with invasion of surrounding structures (Fig. 1). Reviewing previous symptoms with the patient, she mentioned a several-month history of anosmia and epistaxis of unclear origin, requiring local cauterization at least twice. A biopsy of the lesion through a nasal approach revealed respiratory mucosa tissue infiltrated with intermediate sized neoplastic cells, with round and oval-shaped nuclei and chromatin with a ''salt and pepper'' pattern. Immunohistochemical staining showed positivity for CD56, chromogranin, synaptophysin, S100p (peripherally and with a sustentacular pattern) and, focally, ACTH. These aspects confirmed the diagnosis of ONB with positive immunostaining for ACTH.

Optimal medical therapy was initiated, considering the severe Cushing syndrome with multiple complications. She was put on metyrapone (maximum dose of 250 mg every 6 h), which allowed the control of the serum potassium levels and improved the peripheral oedema. Morning serum and urinary cortisol levels 5 days into metyrapone were 14.3 mcg/dL and 1118 mcg/24 h, respectively.

Seven days into metyrapone therapy, the patient progressed to fever, indolent hypoxemia and an increase in inflammatory parameters. Chest radiography showed a diffuse bilateral lung infiltrate (Fig. 2). Blood and sputum cultures all tested negative, but the bronchoalveolar lavage confirmed the diagnosis of *Pneumocystis jirovecii* pneumonia. The patient was put on non-invasive ventilation and was admitted to the intensive care unit due to progressive respiratory failure. She completed 21 days of therapy with trimethoprim–sulfamethoxazole with the resolution of the respiratory failure. She maintained chemoprophylaxis with trimethoprim–sulfamethoxazole ever since.

Surgical excision of the mass was performed once the infection was resolved. The postoperative cranioencephalic MRI still revealed the presence of a small lesion in the

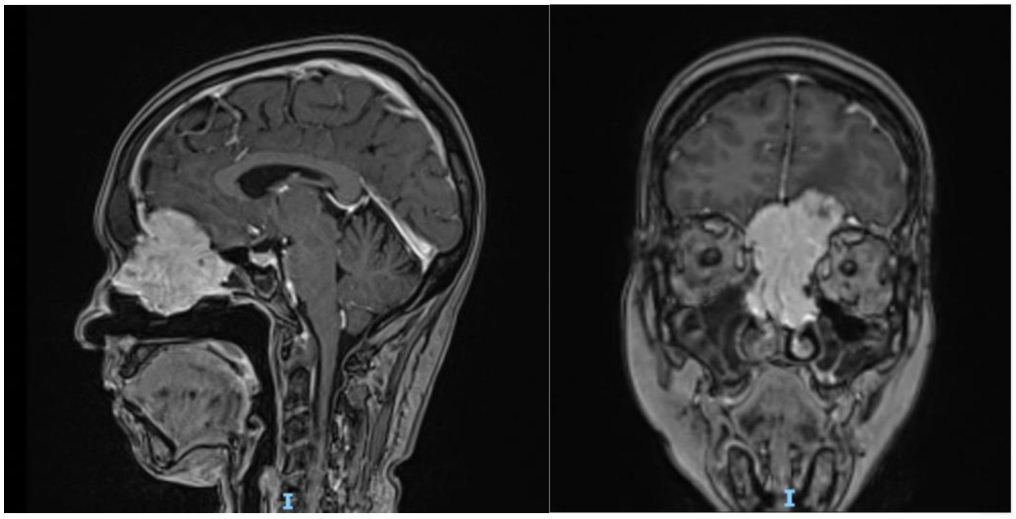

Figure 1 Brain MRI (T1-weighted; contrasted with gadolinium; sagittal and coronal planes) showing a large solid mass in the olfactory bulb with invasion of surrounding structures.

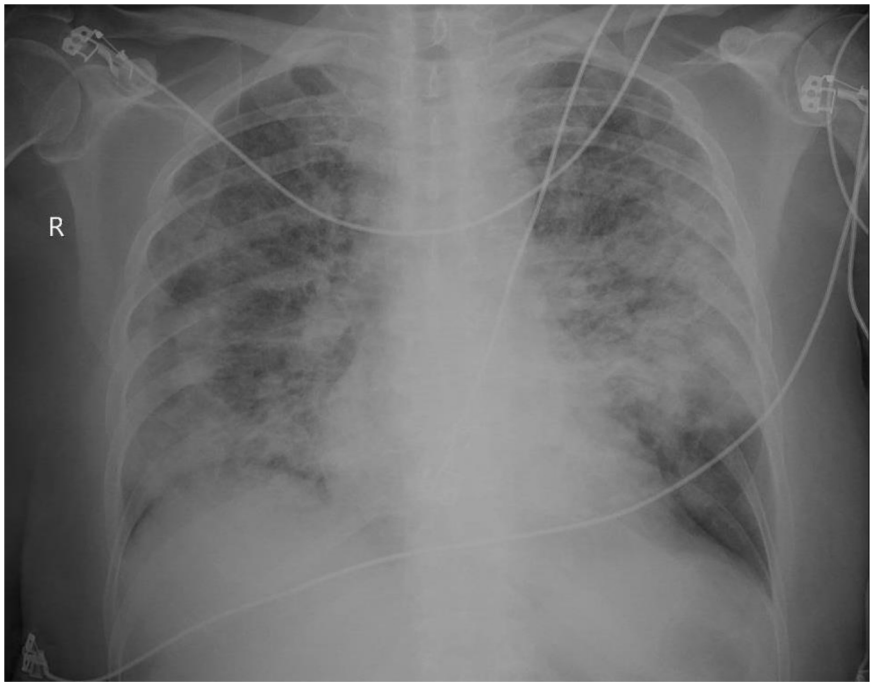

Figure 2 Chest radiography showing diffuse bilateral lung infiltrate.

frontal bone also involving a part of the ethmoid bone, which required further excision through an endoscopic approach. The patient then underwent adjuvant radiotherapy, receiving a total of 60 Gy 30 sessions. Follow-up imaging modalities showed no evidence of recurrence or metastasis.

After surgery, insulin, spironolactone and metyrapone were suspended. Due to endogenous cortisol production suppression, she initially remained on hydrocortisone replacement therapy at a maximum daily dose of 30 mg. The hypothalamic–pituitary–adrenal axis recovered after nearly 12 months, making it possible to suspend the steroid therapy. After a 3-year follow-up, she currently remains asymptomatic, with late-night salivary and 24 h urinary cortisol levels within normal ranges, and no imaging evidence of recurrence of the original lesion or of any other tumor locations.

Management and evidence

We consider our case particularly interesting for two reasons: the rarity of an ONB as a cause of the EAS (there are only 30 other cases reported worldwide) (Table 1)[8,11,12,14–38] and clinical progression with an opportunistic infection after starting corticosteroid-blocking therapy. To identify the 30 cases referenced we performed a literature review across PubMed, until August

Table 1 Case reports of olfactory neuroblastoma presenting with ectopic ACTH syndrome reported in the literature.

Study	Patient	Presentation	Treatment	Outcome
Reznik et al.[14]	Female, 48-years old	ONB diagnosed in 1980. ONB recurrence 2 years later. ONB recurrence with ectopic ACTH syndrome 5 years later – confusion, hypokalemia.	Surgery, chemotherapy Treatment of 1st recurrence: surgery, chemotherapy. Treatment of 2nd recurrence: aminoglutethimide.	Ectopic ACTH syndrome controlled with aminoglutethimide but died a few days after starting therapy. Only brain autopsy was performed.
Arnesen et al.[15]	Female, 36-years old	ONB with ectopic ACTH syndrome diagnosed in 1987 – moon face, central obesity, hyperglycemia, hypertension, proximal muscle weakness. ONB and ectopic ACTH syndrome recurrence 5 years later.	Nasal polypectomy. Treatment of recurrence: surgery, radiotherapy.	Ectopic ACTH syndrome controlled with surgery. No information on follow-up after recurrence.
Inagaki et al.[16]	Male, 33-years old	ONB diagnosed 6 years before ectopic ACTH syndrome. ONB recurrence with ectopic ACTH syndrome – dysgeusia, adynamia, stomatitis, generalized oedema, diarrhea, anxiety, irritability, insomnia.	Surgery. Treatment of recurrence: surgery, chemotherapy. Metyrapone.	Ectopic ACTH syndrome controlled with metyrapone. No recurrence at 24-month follow-up.
Yu et al.[17]	Male, 36-years old	ONB with ectopic ACTH syndrome – hypertension, hyperglycemia, lower limb oedema, proximal muscle weakness, confusion.	Radiotherapy. Metyrapone and etomidate.	Ectopic ACTH syndrome controlled after radiotherapy. No recurrence at 23-month follow-up.
Fish et al.[18]	Male, 45-years old	ONB with ectopic ACTH syndrome – weight loss, lower limb oedema, generalized weakness.	Ketoconazol.	Lost to follow-up.
Kanno et al.[19]	Female, 39-years old	Ectopic ACTH syndromediagnosed 1 year before ONB – generalized oedema and fatigue, Cushingoid appearance, hypertension. ONB recurrence with EAS 4 years later.	Surgery, radiotherapy, metyrapone. Treatment of recurrence: surgery, radiotherapy, metyrapone.	Ectopic ACTH syndrome controlled with metyrapone until surgery. No new recurrence at the 3-year follow-up.
Josephs et al.[20]	Male, 48-years old	ONB with ectopic ACTH syndrome – lower limb oedema, generalized weakness.	Surgery, radiotherapy. Ketoconazole.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 6-month follow-up.
Koo et al.[11]	Female, 66-years old	ONB diagnosed 2 years before ectopic ACTH syndrome. ONB progression with ectopic ACTH syndrome – fatigue, generalized oedema.	Treatment after progression: surgery, radiotherapy, ketoconazole.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 12-month follow-up.
	Female, 37-years old	ONB with ectopic ACTH syndrome – central obesity, proximal muscle weakness, hirsutism, hypertension.	Chemotherapy and radiotherapy. ketoconazol and octeotride.	CMV pneumonia after starting chemotherapy. *P. jirovecii* pneumonia after starting octreotide. Ectopic ACTH syndrome controlled after radiotherapy. No recurrence at the 2-year follow-up.

Table 1 (*Continued*)

Study	Patient	Presentation	Treatment	Outcome
Hodish et al.[21]	Male, 48-years old	ONB with ectopic ACTH syndrome – lower limb oedema, generalized muscle weakness.	Surgery, radiotherapy. Ketoconazole.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 9-month follow-up.
	Female, 30-years old	ONB with ectopic ACTH syndrome – weight gain, abdominal purple striae, acne, hypertension, fatigue, hirsutism, depression, insomnia.	Surgery.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 3-year follow-up.
Lin et al.[22]	Female, 64-years old	ONB with ectopic ACTH syndrome – generalized muscle weakness, confusion, hypertension, moon face, central obesity, easy bruising.	None.	Died (pneumonia) before starting therapy.
Mintzer et al.[23]	Male, 52-years old	ONB diagnosed in 1992. Multiple recurrences of ONB in 1996, 1998, 2002 and 2004. Recurrence of ONB with ectopic ACTH syndrome in 2007 – fatigue, confusion, proximal muscle weakness.	Surgery, radiotherapy. Treatment of recurrences: chemotherapy, radiotherapy. Treatment of last recurrence with ectopic ACTH syndrome: surgery, radiotherapy, ketoconazole and octreotide.	Multiple recurrences of ONB until 2007. Ectopic ACTH syndrome controlled after surgery. No recurrence at the 2-year follow-up.
Galioto et al.[24]	Male, 3-years old	ONB diagnosed when 10 months old. ONB recurrence with ectopic ACTH syndrome – moon face, central obesity, hirsutism, fatigue.	Surgery, chemotherapy. Treatment of recurrence: lymph nodes resection.	Ectopic ACTH syndrome controlled after lymph nodes resection. No recurrence at the 12-month follow-up.
Han et al.[25]	Male, 59-years old	ONB with ectopic ACTH syndrome – neck swelling, periorbital oedema, hypokalemia, hypertension, hyperglycemia.	Neoadjuvant chemotherapy, surgery. Ketoconazole and octreotide, followed by bilateral adrenalectomy.	Ectopic ACTH syndrome controlled after adrenalectomy and tumor resection. No recurrence at the 9-month follow-up.
Rodgers et al.[26]	Male, 51-years old	ONB diagnosed 5 years before ectopic ACTH syndrome. ONB recurrence with ectopic ACTH syndrome – asymptomatic hypokalemia.	Surgery, radiotherapy. Treatment of recurrence: surgery.	Ectopic ACTH syndrome controlled after second surgical act. No information at the follow-up.
Mayur et al.[27]	Male, 19-years old	ONB with ectopic ACTH syndrome – central obesity.	Neoadjuvant chemotherapy, surgery, radiotherapy.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 2.5-year follow-up.
Clotman et al.[28]	Female, 61-years old	ONB diagnosed 10 years before with metastasis. Ectopic ACTH syndrome 10 years later – fatigue, generalized weakness, hypokalemia.	Surgery and chemotherapy. Ketoconazole and metyrapone. Bilateral adrenalectomy.	Ectopic ACTH syndrome controlled after adrenalectomy; died after discharge from surgery. No autopsy.

Table 1 (*Continued*)

Study	Patient	Presentation	Treatment	Outcome
Matheny et al.[29]	Male, 52-years old	ONB with ectopic ACTH syndrome – hyperglycemia, weight loss, generalized weakness, severe hypokalemia.	Surgery, chemotherapy, radiotherapy. Ketoconazole.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 28-month follow-up.
Kadoya et al.[30]	Male, 50-years old	ONB diagnosed in 2011. ONB recurrence with ectopic ACTH syndrome in 2014–2015 – hyperglycemia, hypertension, hypokalemia.	Chemotherapy. Treatment of recurrence: chemotherapy, radiotherapy. Metyrapone.	Ectopic ACTH syndrome controlled with metyrapone at the 20-day follow-up.
Batacchi et al.[31]	Female, 62-years old	Ectopic ACTH syndrome 2 months after ONB – lethargy, lower limb oedema, proximal muscle weakness, central obesity.	Surgery, radiotherapy. Ketoconazole.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 2.5-year follow-up.
Kobayashi et al.[32]	Female, 52-years old	ONB diagnosed 10 years before. ONB recurrence with ectopic ACTH syndrome – fatigue, proximal muscle weakness, central obesity.	Surgery, radiotherapy. Treatment of recurrence: metyrapone and mitotane.	Ectopic ACTH syndrome controlled with metyrapone and mitotane. No information at the follow-up.
Yu et al.[33]	Male, 55-years old	ONB with ectopic ACTH syndrome – fatigue, generalized muscle weakness, central obesity, hypertension, confusion.	Surgery, radiotherapy. Metyrapone and ketoconazole.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 1-year follow-up.
Decaester et al.[8]	Female, 41-years old	ONB with ectopic ACTH syndrome – moon face, alopecia, hirsutism, proximal muscle weakness, amenorrhea, headache.	Surgery, radiotherapy.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 3-month follow-up.
Familiar et al.[34]	Male, 31-years old	ONB with ectopic ACTH syndrome – hypertension, central obesity, proximal muscle weakness.	Chemotherapy, radiotherapy. Ketoconazole followed by metyrapone.	Ectopic ACTH syndrome controlled after radiotherapy. Tumor stable at the 1-year follow-up.
Chung et al.[35]	Male, 46-years old	ONB with ectopic ACTH syndrome – ''cushingoid feature''.	Surgery, radiotherapy.	Ectopic ACTH syndrome controlled after surgery. No recurrence at the 1-year follow-up.
Abe et al.[12]	Female, 40-years old	ONB diagnosed 9 years before, with a local recurrence 3 years before ectopic ACTH syndrome. ONB recurrence with ectopic ACTH syndrome – central obesity, hypokalemia, hyperglycemia, generalized muscle weakness.	Surgery. Treatment of 1st recurrence: surgery, radiotherapy. Treatment of 2nd recurrence: lymph node resection, metyrapone.	Ectopic ACTH syndrome controlled after lymph node resection. No recurrence at the 6-month follow-up.
Ozhan et al.[36]	Male, 28-months old	ONB diagnosed 18 months before. ONB recurrence with ectopic ACTH syndrome – weight gain, moon face, acne.	Surgery Treatment of recurrence: surgery. Ketoconazole and fluconazole.	Ectopic ACTH syndrome controlled with keto-conazole/fluconazole. Residual tumor after surgery, with no growth at the 2-year follow-up.

Table 1 (*Continued*)

Study	Patient	Presentation	Treatment	Outcome
Alsarari et al.[37]	Male, 47-years old	ONB diagnosed 2016 with local recurrence in 2019. ONB recurrence with ectopic ACTH syndrome – lower limb weakness, moon face, buffalo hump, abdominal purple striae, central obesity, skin hyperpigmentation, hypokalemia.	Surgery and radiotherapy. Treatment of recurrence: surgery.	Ectopic ACTH syndrome controlled with surgery. No information at the follow-up.
Gnanathayalan et al.[38]	Female, 40-years old	ONB with ectopic ACTH syndrome – generalized oedema, hyperglycaemia, arterial hypertension, hypokalaemic alkalosis.	Surgery and radiotherapy.	Ectopic ACTH syndrome controlled with surgery. No recurrence at the 3-month follow-up.

ACTH: adrenocorticotropic hormone; ONB: olfactory neuroblastoma.

2024, using the keywords ''olfactory neuroblastoma'', ''esthesioneuroblastoma'', ''ectopic ACTH syndrome'' and ''Cushing's syndrome''.

The initial clinical presentation of our patient was mainly attributed to the complications of severe hypercortisolism (hypokalemia, hyperglyaemia, lower limb edema and atraumatic fractures). This was very suggestive of the ACTH syndrome, since it usually progresses with signs of mineralocorticoids excess and weight loss, developing over a short period.[9,23] In fact, although weight loss is not so consistent, hypertension, alkalosis with hypokalemia and peripheral oedema are present in almost all the other reported cases (Table 1). This clinical presentation made us hypothesize that a pituitary dependent Cushing's syndrome was less probable.[23]

ONB is a rare malignant neuroectodermal nasal tumor that comprises up to 3% of all tumors of nose and sinuses.[7,9] It seems to affect both genders equally and, although it can occur at any age, it demonstrates a bimodal peak of occurrence within the 2nd and 6th decades of life.[9,13] When looking at the previously reported patients with ONB presenting with the ACTH syndrome, approximately 43% (13/30) were women and the patients' median age was 46.5 years (Table 1). Only 3 patients were younger than 30 years.[24,27,36]

This tumor has a slow-growing course which makes it hard to diagnose in early stages and patients usually have a long history of symptoms.[7] It presents more commonly with unilateral nasal obstruction and epistaxis, but it can also progress with less frequent symptoms such as headache, rhinorrhoea, anosmia, or visual disturbances.[7] In our case, the anosmia and episodes of epistaxis within the past few months were probably already related to the tumor invading the upper nasal cavity. Since those episodes resolved quickly with local measures and were not associated with other symptoms, they never led to any further investigation.

Given the neuroendocrine differentiation of ONB, it can produce different types of peptides and hormones, leading to distinct paraneoplastic syndromes, such as syndrome of inappropriate antidiuretic hormone secretion, humoral hypercalcemia of malignancy, hypertension due to catecholamine or ACTH secretion.[9] However, as stressed before, ACTH-secreting olfactory neuroblastomas are an extremely rare cause of the ACTH syndrome.[9] Only about 1000 ONB cases have been reported worldwide,[10] only 30 presenting with ACTH secretion. In this regard, although 3% of cases of ONB reported in the literature presented with ACTH secretion, we estimate the real prevalence of this presentation is likely lower due to the expected underreporting of patients with ONB and no endocrinologic paraneoplastic features.

Of the 30 cases of ONB with ACTH secretion reported in the literature, 17 had ACTH secretion preceding and leading to the diagnosis of olfactory neuroblastoma, like the case we present here (Table 1). In some of these patients there were no symptoms or signs that could be attributed to any nasal or sinus disease. In the remaining 13 cases, patients presented with Cushing's syndrome years after the tumor was diagnosed, when it was left untreated or in the presence of tumor recurrence (Table 1).

Considering its extensive intracranial invasion, beyond the nasal cavity and paranasal sinuses, our patient's tumor can be categorized as stage C olfactory neuroblastoma according to the Kadish's clinical staging system, which predicts a 5-year survival <50%.[39] Recurrences develop in up to 30% of the cases, mainly in the 2 years following the initial management, regardless of the clinical staging.[7,13] In the reported cases of an ONB presenting with EAS there is a 15.6% recurrence rate, adjusted to follow-up. Three of the 30 patients died (1 before starting any therapy).[14,22,28] Thus, despite our patient favorable course after surgery and radiotherapy, and that she remains in remission ever since, a close follow-up to detect recurrences is warranted.

Areas of uncertainty

Although there is some doubt about the elevated infectious risk of these patients, not only due to hypercortisolism but also after starting steroid-blocking therapy, diagnosis of these complications is frequently delayed. Additionally, infectious chemoprophylaxis is not routinely instituted in these patients. Our case highlights these areas of discussion.

Once ACTH secretion is detected, steroid-blocking therapy is often initiated to control symptoms related to Cushing's syndrome. Metyrapone and ketoconazole have a quick onset of action and were the most frequently used inhibitors, either alone or in combination (Table 1). Metyrapone is a well-tolerated option and there are reports of its use for the long-term management of patients in which tumor surgery is not possible.[16,40] Aminoglutethimide, mitotane, octreotide, etomidate and fluconazole were other less frequently used options. In 10 of the reported cases, no steroid-blocking therapy was started before surgery or radiotherapy (Table 1). Conversely, in 2 cases, drug treatment was not enough to control the hypercortisolemia-associated symptoms and patients were submitted to bilateral adrenalectomy.[25,28]

Our patient started therapy with metyrapone and a week later she developed a serious *P. jirovecii* pneumonia. Although it is possible that this was a late infectious complication related to the severe prolonged hypercortisolism, there are many reports of opportunistic infections in patients with Cushing's syndrome after starting steroid-blocking therapy, regardless of the drug being used.[41–44] This phenomenon is probably explained by an immune reconstitution inflammatory syndrome as cortisol levels begin to normalize.[43,44] Despite the cause of the opportunistic infection, its clinical presentation can be insidious and its course severe, requiring a high suspicion index to avoid delays in its diagnosis and management.[43]

Of the 20 reported cases that started on optimal medical therapy to control their hypercortisolism, 1 opportunistic infection was reported,[11] which translates into a rate of infection in the literature of approximately 9.5%. Of note, however, that 1 patient, treated with aminoglutethimide, died a few days after starting this therapy.[14] Although it was admitted that the underlying ONB was the cause of death, only an autopsy of the brain was performed, so we cannot rule out the possibility of an overlooked infection.[14] Furthermore, there were 2 patients on steroid-blocking therapy for whom there is no information on their clinical progression afterwards.[18,32] Thus, we hypothesize that the rate of opportunistic infections in this group of patients may be higher.

None of the patients reviewed received any chemoprophylaxis. However, two were treated concomitantly with trimethoprim–sulfamethoxazole for infections diagnosed before starting steroid-blocking agents.[16,32] Another was also put on antibiotics (not specified by the authors) for a pulmonary empyema, when metyrapone was initiated.[19] This may also have influenced the true rate of opportunistic infections in this reported population. Nevertheless, knowing that opportunistic infections are a well described life-threatening complication in these patients, and the low prevalence of adverse reactions associated with chemoprophylaxis, this should probably be the routine approach in all patients.

Guidelines

Due to the rarity of ONB presenting with ACTH secretion, there are no specific and well-established guidelines that delineate the management of these conditions presenting simultaneously, but there are recommendations for the treatment of each of them separately.[2,13,45,46]

Regarding ONB management, surgery must be considered whenever it is feasible, and adjuvant radiotherapy is recommended in every case.[13,46] Adjuvant and neoadjuvant chemotherapy can be considered, depending on the initial tumor spread.[13,46] Of note, the latest guidelines have been specifically designed for the management of pediatric patients, yet recommendations for adults seem to follow the same general principles.[13,46]

Guidelines on the management of Cushing's syndrome rely mainly on controlling hypercortisolaemia and its underlying cause.[2,45] Furthermore, complications associated with high levels of cortisol, such as infections, diabetes mellitus and thromboembolic events, must also be actively addressed.[2,45] Steroid-blocking treatment is recommended when 24-h urinary cortisol is elevated more than 5-fold the normal range, and chemoprophylaxis with sulfamethoxazole–trimethoprim is suggested in all patients with signs of intense hypercortisolism.[2,45] In our case, metyrapone, surgery and radiotherapy allowed for adequate tumor control and ACTH suppression. Nonetheless, infectious chemoprophylaxis probably should have been started once the Cushing's syndrome was detected, alongside the other measures.

Lastly, these patients probably benefit from a mixed approach for their long-term management, combining the recommendations for ONB and Cushing's syndrome follow-up. Screening with repeated MRI and lab tests (24-h urinary cortisol, late-night salivary cortisol and dexamethasone suppression tests) should allow the identification of local tumor recurrences and early ACTH relapses.[45,46]

Conclusions and recommendations

EAS secretion is a cause of Cushing's syndrome and should be suspected in the presence of signs and symptoms of severe hypercortisolism, even without the typical Cushing's syndrome stigmata. Although ONB is a very rare cause of the ACTH syndrome, it should not be missed considering its poor outcome when left untreated. Hypercortisolism should be controlled until it is possible to treat the underlying tumor, bearing in mind that normalizing cortisol levels can precipitate opportunistic infections. Chemoprophylaxis for common agents, such as *P. jirovecii* should be considered as soon as diagnosis has been established.

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Conflicts of interest

None declared.

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