

Recurrent septicemia in secondary immunodeficiency induced by nasal steroid abuse

Sepse recorrente induzida por abuso de corticoide nasal em paciente com imunodeficiência secundária

Bruna Giavina-Bianchi¹, Adriana Pitchon², André Luiz Oliveira Feodrippe², Pedro Giavina-Bianchi^{1,2}

ABSTRACT

Nasal corticosteroids are recommended as first-line therapy for patients with moderate-to-severe allergic rhinitis. We report a case of a patient with secondary immunodeficiency who presented with recurrent septicemia induced by the inappropriate use of nasal corticosteroids, highlighting the risks associated with the misuse of this medication.

Keywords: Secondary immunodeficiency, nasal steroids, septicemia, Cushing's syndrome, corticosteroids.

RESUMO

Os corticosteroides nasais são recomendados como terapia de primeira linha para pacientes com rinite alérgica moderada a grave. Relatamos o caso de um paciente com imunodeficiência secundária que apresentou sepse recorrente induzida pelo uso inadequado de corticosteroides nasais, destacando os riscos associados ao uso incorreto desse medicamento.

Descritores: Imunodeficiência secundária, corticosteroides nasais, septicemia, síndrome de Cushing, corticosteroides.

Sepsis is a clinical syndrome defined as a life-threatening organ dysfunction caused by a dysregulated or aberrant host response to infection.¹ Recurrent episodes of sepsis are frequently associated with underlying anatomic abnormalities, functional disorders, and primary or secondary causes of immunosuppression. Secondary immunodeficiencies are substantially more common than primary immunodeficiencies and should be considered in the presence of underlying diseases, such as diabetes mellitus, HIV infection, nephrotic syndrome, and chronic renal failure, or in patients receiving immunosuppressive therapy, such as chemotherapeutic agents and corticosteroids.¹

We report the case of a 39-year-old man admitted to the intensive care unit with a 1-day history

of progressive fever, malaise, cough, dyspnea, and hemodynamic instability. His medical history included 3 prior hospitalizations: pneumonia at 7 years of age; pulmonary embolism of unclear etiology 8 years earlier; and an episode of sepsis associated with pneumonia 3 years earlier. Comorbidities included arterial hypertension, hypercholesterolemia, depression, ocular hypertension, and a rib fracture without antecedent trauma. He also reported a history of allergic rhinitis and asthma, both in remission without maintenance therapy. The patient had previously used low-dose inhaled corticosteroid/long-acting bronchodilator therapy intermittently but had been free of asthma medications for the past 5 years. No systemic corticosteroid use was reported during this period.

1. Faculdade Israelita de Ciências da Saúde Albert Einstein – São Paulo, SP, Brazil.

2. Clinical Immunology and Allergy Division, University of São Paulo School of Medicine – São Paulo, SP, Brazil.

On hospital admission, broad-spectrum antibiotic therapy was initiated. Due to respiratory failure, the patient required mechanical ventilation. Cardiocirculatory instability developed, necessitating vasoactive drug support to maintain blood pressure. The patient deteriorated rapidly, requiring extracorporeal membrane oxygenation (ECMO) within 24 hours of admission. Multiple COVID-19 tests were consistently negative.

Blood cultures were positive for multisensitive *Streptococcus pneumoniae*. The patient improved with antibiotics and systemic corticosteroid therapy (methylprednisolone, 0.75 mg/kg), ECMO was discontinued after 3 days, and extubation occurred on day 6 of hospitalization. Thirteen days later, the patient developed recurrent dyspnea. Imaging revealed a saddle pulmonary embolism, which was managed surgically with subsequent improvement. He was discharged after 28 days of hospitalization.

On the day of hospital admission, the patient's serum immunoglobulin G level was 601 mg/dL (reference range: 600-1500 mg/dL), with progressive increase during hospitalization. Other immunoglobulins were within the normal range (Table 1). HIV serology was negative. After discharge, he was referred to an immunologist for outpatient evaluation of recurrent sepsis.

The patient denied diabetes or any known causes of secondary immunodeficiency. There was no family history of consanguinity, adrenal insufficiency, recurrent infection, or inborn errors of immunity.

Review of the patient's medical records showed serum cortisol and adrenocorticotrophic hormone (ACTH) levels below the reference range 2 years earlier (Table 2). At that time, the patient was unaware of the rationale for the testing, and no further actions were taken based on the results. Bone densitometry confirmed osteoporosis (lumbar spine T-score of -2.6 SD). During follow-up, persistently low serum cortisol and aldosterone levels were documented (Table 2). When further asked about exogenous corticosteroid use, the patient disclosed long-term daily use of an over-the-counter topical nasal preparation available in Brazil under the brand name Decadron Nasal® (dexamethasone disodium phosphate 0.5 mg/mL, neomycin sulfate 3.5 mg/mL, phenylephrine hydrochloride 5.0 mg/mL). He had used approximately 1 mL daily for 21 years. The patient did not consider this formulation to be a medication. He stated that he began using the preparation, which was borrowed from his father, for rhinitis symptoms, found it highly

effective, and subsequently developed a long-standing dependence on its daily use.

Follow-up testing of immunoglobulins and their subclasses, lymphocyte immunophenotyping, complement system testing, and assessment of pneumococcal vaccine response yielded normal results (Table 1). As the conjugated pneumococcal vaccine had been administered after the 2 episodes of septicemia and before patient presentation at our service, only post-vaccination antibody titers could be assessed. Final diagnoses included septicemia, secondary immunodeficiency due to long-term intranasal corticosteroid use, Cushing's syndrome, and adrenocortical insufficiency (AI). The patient responded well to treatment with daily hydrocortisone replacement until recovery of adrenal gland function. At present, 4 years after the initial consultation, the patient has discontinued continuous exogenous systemic corticosteroid use and has remained free of new episodes of immunodeficiency or adrenal insufficiency. However, during infections or other stress-related conditions, he still requires supplemental doses of systemic corticosteroids.

Corticosteroids are essential hormones for life as they regulate physiological and developmental processes. Human endogenous glucocorticoid (cortisol) is synthesized in the adrenal cortex under the control of hypothalamic corticotropin-releasing hormone (CRH) and pituitary ACTH, constituting the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol, through a negative feedback loop, inhibits CRH and ACTH release. Likewise, exogenous corticosteroids suppress HPA axis activity, and persistent exposure can reduce endogenous ACTH, leading to AI and adrenal hypoplasia or atrophy.^{2,3}

AI may occur even with physiologic doses of exogenous corticosteroids, although the risk is higher with supraphysiologic doses and prolonged use. The increased risk of developing AI has also been associated with specific aspects of the treatment regimen, such as splitting daytime and nighttime doses, as well as with the pharmacokinetics/pharmacodynamics properties of the involved corticosteroid and its administration route. Even the intranasal route should not be disregarded.³ We hypothesize that the initial drop in blood pressure observed in our patient on hospital admission may be attributed not only to septic shock but also to AI. Subsequently, during hospital stay, the patient received methylprednisolone in combination with antibiotic therapy, leading to improvement.

Table 1

Patient's immunological assessment during and after hospitalization

Test	Day of hospital admission	Day 21 of hospitalization	2 weeks after discharge	18 months after discharge	Reference range
Leukocytes (cells/mm ³)	16,310	8260	8290	5940	4000–11,000
Neutrophils (cells/mm ³ ; %)	11,920 73.1%	3760 45.5%	3460 41.7%	3470 58.4%	2500–7500 (40%-75%)
Lymphocytes (cells/mm ³ ; %)	1660 10.2%	2710 32.8%	3440 41.5%	1750 29.5%	1500–3500 (20%-45%)
CD4 T cells (cells/mm ³ ; %)	–	–	1577 46.4%	–	507–1496 (31.0%-56.0%)
CD8 T cells (cells/mm ³ ; %)	–	–	1483 43.6%	–	303–1008 (17.0%-41.0%)
CD4/CD8	–	–	1.1	–	0.9-2.6
CD19 cells (cells/mm ³ ; %)	–	–	165 12.0%	–	140–950 (<5%)
Eosinophil (number; %)	470 2.9%	630 7.6%	430 5.2%	260 4.4%	50–500 (8.0%–18.0%)
IgG	601	1084	1107	729	600-1500
IgG1	–	545	523	–	490-1140
IgG2	–	316	321	–	150-640
IgG3	–	31	26	–	22-176
IgG4	–	85	82	–	8-140
Antipneumococcal antibodies: positive serotypes (values in µg/mL)	–	–	6B (1.5); 9V (5.1); 14 (>20); 18C (4.6); 19F (12.6); 23F (4.5)	1 (1.9); 3 (3.5); 4 (4.4); 14 (9.2); 19F (5.7); 23F (1.6); 19A (2.3); 9V (3.7)	≥1.3
IgA	210	310	271	230	50-400
IgM	81	79	85	102	50-300
Complement system testing (units/mL)	–	–	139	–	72-140
C3 (mg/dL)	–	–	171	–	90-190
C4 (mg/dL)	–	–	37.8	–	10-40
IgE (kU/L)	–	–	343	–	<100
Specific IgE-Der p (kU/L)	–	–	7.9	–	<0.35

Ig = immunoglobulin.

Table 2
Patient's cortisol and adrenocorticotrophic hormone levels over time

Test	2 years before hospital admission	2 weeks after discharge	4 months after discharge	18 months after discharge	Reference range
Cortisol (µg/dL)	<0.02	<0.5	0.6	13.0	6.7–22.6
Adrenocorticotrophic hormone (pg/mL)	5.5	6	26	60.0	7.2–63.3
Aldosterone (ng/dL)	6.3	–	–	11.8	<23.1

Besides the induction of AI, long-term use of supraphysiologic doses of corticosteroids is associated with several local and systemic adverse effects characteristic of Cushing's syndrome, including cataract, glaucoma, gastric ulcers, skin thinning and striae, hirsutism, acne, growth retardation, osteoporosis, weakness, fatigue, myopathy, hypertension, glucose elevation, obesity, and immunosuppression.^{2,3} Our patient presented with arterial hypertension, ocular hypertension, osteoporosis with vertebral fracture, and thromboembolic events, clinical manifestations consistent with Cushing's syndrome.

Corticosteroids exert significant immunomodulatory effects primarily due to their anti-inflammatory and immunosuppressive properties. They suppress the production of pro-inflammatory substances, such as cytokines, chemokines, and prostaglandins, and inhibit several pathways of innate and adaptive immune responses, including the function of immune cells such as T cells and B cells, decreasing antibody production.²

Intranasal corticosteroids are recommended as first-line therapy for moderate-to-severe allergic rhinitis. The major advantage of intranasal corticosteroid administration is that high concentrations of the drug, with rapid onset of action, can be delivered directly into the target organ, so that systemic effects are avoided or minimized. The drug has a good efficacy and safety profile.⁴

The preparation used by our patient was inappropriate for maintenance therapy in allergic rhinitis because it combined vasoconstrictors,

antibiotics, and dexamethasone, a high-potency long-lasting corticosteroid with high systemic bioavailability. A recent case report described a 19-year-old man, for whom dexamethasone nasal drops were prescribed for an episode of nasal obstruction, who developed Cushing's syndrome with panhypopituitarism, growth retardation, osteoporosis, and hypertension after more than 5 years of daily dexamethasone nasal drop use (0.7-1.0 mg/day).⁵

The diagnosis of secondary immunodeficiency is classically based on the exclusion of other potential causes. In the current case, the likelihood of secondary immunodeficiency arising from intranasal corticosteroid abuse is supported by the patient's medical history, laboratory investigations, and clinical evolution.

Although intranasal corticosteroids have been previously described as a cause of AI, they have not been associated with systemic immunosuppression or septicemia. To our knowledge, this is the first reported case of recurrent septicemia associated with intranasal corticosteroid use, underscoring the risks of abusive use of this medication.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
2. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. Nat Rev Immunol. 2017;17(4):233-47.

3. Gurnell M, Heaney LG, Price D, Menzies-Gow A. Long-term corticosteroid use, adrenal insufficiency, and the need for steroid-sparing treatment in adult severe asthma. *J Intern Med*. 2021;290(2):240-56.
4. Giavina-Bianchi P, Aun MV, Takejima P, Kalil J, Agondi RC. United airway disease: current perspectives. *J Asthma Allergy*. 2016 May 11;9:93-100.
5. Fuchs M, Wetzig H, Kertscher F, Täschner R, Keller E. Iatrogenic Cushing syndrome and mutatio tarda caused by dexamethasone containing nose drops. *HNO*. 1999;47(7):647-50.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Pedro Giavina-Bianchi
E-mail: pbianchi@usp.br