ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Recurrent sepsis in secondary immunodeficiency induced by nasal steroid misuse

Sepse de repetição na imunodeficiência secundária por uso abusivo de corticoide nasal

Bruna Giavina-Bianchi[1], Adriana Pitchon[2], André Luiz Oliveira Feodrippe[2], Pedro Giavina-Bianchi[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 who presented with recurrent sepsis and was found to have secondary immunodeficiency induced by 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

Recomenda-se o uso de corticoides nasais como tratamento de primeira linha na rinite alérgica moderada a grave. Relatamos o caso clínico de um paciente com sepse de repetição no contexto de imunodeficiência secundária ao uso inapropriado de corticoide nasal, destacando-se os riscos associados ao uso abusivo de tais medicamentos.

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

Sepsis is a clinical syndrome defined as life-threatening organ dysfunction caused by a dysregulated or aberrant host response to infection[1]. When recurrent, it is usually attributable to anatomic lesions, functional disorders, or primary or secondary immunosuppression. Secondary immunodeficiencies are far more prevalent than primary immunodeficiencies and should be considered in the presence of underlying diseases such as diabetes mellitus, human immunodeficiency virus (HIV) infection, nephrotic syndrome, chronic renal failure, or administration of immunosuppressive drugs such as chemotherapeutic agents and corticosteroids[1].

We report the case of a 39-year-old male who was admitted to the Intensive Care Unit with a one-day history of progressive fever, malaise, cough, dyspnea, and hemodynamic instability. He has already experienced three prior hospitalizations: one for pneumonia at the age of seven, another for pulmonary thromboembolism of undetermined cause eight years ago, and a previous episode of sepsis secondary to pneumonia three years ago. Comorbidities included hypertension, hypercholesterolemia, depression, increased intraocular pressure, and a rib fracture not associated with any known trauma. The patient also reported a remote history of allergic rhinitis and asthma, which were in remission without any maintenance therapy. He had intermittently used a low-dose inhaled combination of corticosteroids and long-acting bronchodilator in the past but had not taken any medication for his asthma in the past five years. He likewise denied taking systemic corticosteroids for any reason 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.

Submitted: Nov 07 2024, accepted Nov 14 2024.
Arq Asma Alerg Imunol. 2024;8(3):269-

http://dx.doi.org/10.5935/2526-5393.20240041-en

Broad-spectrum antibiotics were started immediately upon admission. Due to progressive respiratory failure, the patient was placed on mechanical ventilation. Cardiocirculatory instability necessitated administration of vasopressors. The patient's condition continued to deteriorate; less than 24 hours after admission, extracorporeal membrane oxygenation (ECMO) was started. Multiple tests for COVID-19 were performed, all negative.

Blood cultures were positive for multisensitive *Streptococcus pneumoniae*. The patient improved on appropriate antibiotic therapy and systemic corticosteroids (methylprednisolone 0.75 mg/kg); ECMO was discontinued after 3 days, and he was extubated on the sixth hospital day. Thirteen days later, the patient had a recurrence of dyspnea. A saddle pulmonary embolism was promptly diagnosed and surgically removed. After 28 days of hospitalization, the patient was discharged to outpatient follow-up with an immunologist for etiological investigation of recurrent sepsis.

Laboratory results on the day of hospital admission were notable for an immunoglobulin G (IgG) of 601 mg/dL (reference value: 600-1500 mg/dL), which increased progressively throughout his hospital course. Other immunoglobulins were within normal range (Table 1). HIV serology was negative. The patient denied diabetes or any other cause of secondary immunodeficiency. There was no family history of consanguinity, adrenal insufficiency, recurrent infection, or inborn errors of immunity.

A review of the patient's medical records revealed that his serum cortisol and adrenocorticotropic hormone levels were below reference range 2 years earlier (Table 2). Regrettably, the patient was unaware of the purpose of these tests when performed, and no subsequent action was taken in response to their results. Osteoporosis was diagnosed through bone densitometry (lumbar spine T-score: -2.6 SD). Low serum levels of cortisol and aldosterone persisted (Table 2). When asked about exogenous use of corticosteroids, the patient finally reported self-administration of Decadron Nasal®, an over-the-counter fixed-dose combination of dexamethasone disodium phosphate 0.5mg/ml, neomycin sulfate 3.5mg/ml, and phenylephrine hydrochloride 5.0mg/ml for topical nasal administration. He had been using approximately 1ml per day, every day, for the past 21 years. The patient said he did not consider this product to be a "real medication"; he had originally borrowed it from his father to self-manage his rhinitis, and found it worked so well for his symptoms that he became dependent.

New measurements of immunoglobulin and its subclasses, lymphocyte immunophenotyping, complement system testing, and assessment of the response to pneumococcal vaccine were obtained and found to be unremarkable (Table 1). The patient had received the pneumococcal conjugate vaccine after his first two episodes of sepsis and before presenting to our facility; consequently, we were only able to measure post-vaccination antibody titers.

The patient was diagnosed with sepsis, secondary immunodeficiency due to nasal corticosteroid misuse, Cushing's syndrome, and adrenocortical insufficiency. He made good progress on daily replacement doses of hydrocortisone until complete recovery of adrenal gland function. Four years after his initial presentation, the patient is no longer dependent on continuous exogenous systemic steroid therapy and has not experienced any new manifestations of immunodeficiency or adrenal insufficiency. However, during infections and other stressful situations, he still receives stress doses of systemic corticosteroids.

Corticosteroids are essential hormones for life, as they regulate several physiological and developmental processes. The human endogenous glucocorticosteroid, cortisol, is synthesized in the adrenal cortex under the control of hypothalamic corticotropin-releasing hormone (CRH) and pituitary adrenocorticotropic hormone (ACTH), constituting the hypothalamic–pituitary–adrenal (HPA) axis. Through a negative feedback loop, cortisol inhibits CRH and ACTH release. Exogenous corticosteroids are likewise able to inhibit HPA axis function; if this stimulus is persistent, the reduction of endogenous ACTH secretion can lead to adrenocortical insufficiency and adrenal hypoplasia or atrophy[2,3].

Adrenocortical insufficiency (AI) may occur even with physiologic doses of exogenous corticosteroids but is more commonly observed with higher supraphysiologic dosages and long-term use. A higher risk of developing AI also has been linked with specific aspects of the treatment regimen, such as split daily doses and night-time administration, as well as with pharmacokinetic/pharmacodynamic properties of the involved corticosteroid and its route of administration. The risk of AI with intranasal corticosteroids should not be disregarded[3]. We hypothesize that the initial drop in blood pressure observed in our patient at the onset of hospitalization could be attributed not only to septic shock but also to adrenal insufficiency.

Table 1
Patient's immune parameters during and after hospitalization

Test	Day of admission	21st day of hospitalization	2 weeks after hospital discharge	18 months after hospital discharge	Reference values
Leukocytes (cells/mm^3)	16,310	8,260	8,290	5,940	4,000–11,000
Neutrophils (cells/mm^3;%)	11,920 (73.1%)	3,760 (45.5%)	3,460 (41.7%)	3,470 (58.4%)	2,500–7,500 (40–75%)
Lymphocytes (cells/mm^3;%)	1,660 (10.2%)	2,710 (32.8%)	3,440 (41.5%)	1,750 (29.5%)	1,500–3,500 (20–45%)
T CD4 cells (cells/mm^3;%)	–	–	1,577 (46.4%)	–	507–1,496 (31.0–56.0%)
T CD8 cells (cells/mm^3;%)	–	–	1,483 (43.6%)	–	303–1,008 (17.0–41.0%)
CD4/CD8	–	–	1.1	–	0.9–2.6
CD19 cells (cells/mm^3; %)	–	–	165 (12%)	–	140–950 (<5%)
Eosinophils (absolute; %)	470 (2.9%)	630 (7.6%)	430 (5.2%	260 (4.4%)	50–500 (8.0–18.0%)
IgG	601	1,084	1,107	729	600–1,500
IgG1	–	545	523	–	490–1,140
IgG2	–	316	321	–	150–640
IgG3	–	31	26	–	22–176
IgG4	– –	85 8–140	82		
Anti–pneumococcal antibodies: positive serotypes (µg/mL)	–	–	Positive serotypes: 6B (1.5); 9V (5.1); 14 (>20); 18C (4.6); 19F (12.6); 23F (4.5).	Positive serotypes: 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 (U/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

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

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

Subsequently, during his hospital stay, the patient received methylprednisolone as an adjunct to antibiotic therapy and ultimately recovered.

Besides induction of AI, the chronic use of supraphysiologic doses of corticosteroids is associated with several local and systemic adverse effects, which constitute the Cushing's syndrome and include cataract, glaucoma, gastric ulcers, striae and skin thinning, hirsutism, acne, growth restriction, osteoporosis, weakness, fatigue, myopathy, hypertension, hyperglycemia, obesity, and immunosuppression[2,3]. Our patient had high blood pressure, increased intraocular pressure, osteoporosis with a history of pathologic vertebral fracture, and thromboembolic episodes – all clinical manifestations commonly associated with Cushing's syndrome.

Corticosteroids have significant effects on the immune system, primarily due to their anti-inflammatory and immunosuppressive properties. They inhibit the production of pro-inflammatory substances, such as cytokines, chemokines, and prostaglandins, as well as several pathways of the innate and secondary immune responses, including the function of immune cells such as T cells and B cells, decreasing antibody production[2].

Nasal steroids (NS) are recommended as first-line therapy for patients with moderate-to-severe AR. The major advantage of NS administration is that high concentrations of the drug, with rapid onset of action, can be delivered directly into the target tissues, thus avoiding or minimizing systemic effects. These drugs have a favorable efficacy and safety profile[4]. However, our patient used a fixed-dose combination product which is not appropriate as maintenance therapy for allergic rhinitis, because it contains a vasoconstrictor, antibiotic, and dexamethasone, a high-potency, long-lasting corticosteroid with high systemic bioavailability. A recent case report described a 19-year-old male patient to whom dexamethasone nasal drops were prescribed because of nasal obstruction. The patient went on to use these drops for more than 5 years, with a daily dexamethasone dose of 0.7-1.0 mg. He eventually developed Cushing's syndrome with panhypopituitarism, growth retardation, osteoporosis, and hypertension[5].

The diagnosis of secondary immunodeficiency is classically established through the exclusion of other potential causes. In the current case, the likelihood of secondary immunodeficiency arising from nasal corticosteroid misuse is supported by the patient's clinical history, laboratory investigations, and the observed progression of the patient's condition.

Although nasal corticosteroids have been described as a cause of AI, they have not been associated with systemic immunosuppression or sepsis. To the best of our knowledge, this is the first case report of recurrent sepsis associated with nasal corticosteroids and should serve as a warning of the potential harms associated with misuse of these medications.

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