

Case Report

RELAPSE OF ASTHMA AFTER SURGICAL TREATMENT OF CUSHING'S SYNDROME

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ABSTRACT

Endogenous overproduction of glucocorticoids may mask the clinical course of some inflammatory/autoimmune disorders. In the present paper, we report a man with a history of asthma, which spontaneously remitted after 20 years of duration. Several years later, he was diagnosed with Cushing's syndrome of pituitary origin and underwent transsphenoidal microsurgery of an ACTH-producing pituitary adenoma. Shortly after tumour removal, he developed a severe asthmatic attack requiring hospitalisation and intensive treatment. We conclude that patients with Cushing's syndrome and coexisting inflammatory/autoimmune disorders should be closely supervised after normalisation of cortisol production for exacerbation of the associated disease and would eventually benefit from glucocorticoid treatment.

Key words: Cushing's syndrome, bronchial asthma, clinical picture, treatment

INTRODUCTION

It is commonly accepted that glucocorticoids produce multi-directional anti-inflammatory and immunosuppressive effects (1, 2). Glucocorticoids were found to suppress the production of many proinflammatory cytokines, lipocortin-1, prostaglandins and leukotrienes, down-regulate the expression of adhesion molecules on antigen-presenting cells, and, consequently, they inhibit both the cell-mediated and humoral immune responses (1, 2). Because of their potent therapeutic action against inflammation glucocorticoids constitute a cornerstone for the treatment of various clinical entities (3). However, excessive glucocorticoid release observed in Cushing's syndrome results in obesity, diabetes mellitus,

hypertension, muscle wasting, osteoporosis, depression, and cognitive deficits (4-6). Unless treated, the disease is associated with a four-fold increase of mortality rate compared to the normal population, and the 5-year cardiovascular mortality for untreated disease is up to 50% (4-6). Although all patients with Cushing's syndrome should be treated, preferably by surgery (4-6), a sudden reduction in plasma glucocorticoids may theoretically unmask coexisting occult inflammatory disorders.

We describe here the case of a man in whom the development of Cushing's syndrome resulted in the remission of bronchial asthma. Several years later, the patient developed a severe asthma attack after surgical removal of the pituitary tumor responsible for Cushing's syndrome.

CASE REPORT

In the reported patient bronchial asthma manifested for the first time 36 years ago at the age of 16. The patient was found to be allergic to dust and pollen. For the following 20 years, the attacks occurred 1-2 times a week and asthma symptoms were effectively controlled with inhaled short-acting β_2 agonists. At the age of 35, his condition improved and therefore no specific anti-asthmatic treatment was required. At the same time, he developed arterial hypertension which was initially well controlled with ramipril and amlodipine treatment. At the age of 39, he was admitted to hospital because of weight gain (a 31-kg increase in 2 years), fatigue, easy bruising and worsening of blood pressure control. Clinical examination revealed a central fat distribution with a prominent dorsal cervical fat pad (buffalo hump) and moon face, proximal myopathy, with marked purple striae on the abdomen, oedema of the lower extremities and increased blood pressure despite antihypertensive medication. On admission, biochemistry indicated metabolic alkalosis (pH – 7.49) and hypokalaemia (2.9 mmol/L). The 24-h urinary excretion of free cortisol was increased (620 and 570 $\mu\text{g}/24\text{h}$). Midnight plasma cortisol levels, late-night salivary cortisol

levels and plasma dehydroepiandrosterone sulfate were all elevated (15.2 µg/dL, 1.56 µg/dL and 710 µg/dL, respectively), while ACTH levels (48 pg/mL) were within the reference range (20-60 pg/mL). The patient showed an abnormal overnight 1 mg dexamethasone suppression test (cortisol – 18.2 µg/dL). The high-dose dexamethasone suppression test revealed a significant decrease (by 70%) of plasma cortisol. Bone density of lumbar vertebrae assessed by dual-energy X-ray absorptiometry revealed the presence of osteoporosis (Z-score – 2.6). A pituitary MRI revealed a 6-mm adenoma, while an abdominal MRI showed slight bilateral adrenal hyperplasia. Inferior petrosal sinus sampling was not performed. The patient was diagnosed with Cushing's syndrome of pituitary origin and, after pretreatment with ketoconazole, underwent transsphenoidal surgery, which is the first line treatment of this type of Cushing's syndrome (6). Urinary free cortisol taken on postoperative day 2 (18 µg/day) as well as a postoperative 1-mg overnight dexamethasone suppression test (0.92 µg/dL) were within normal limits (7). Because morning plasma ACTH and cortisol levels were within normal limits (29 pg/mL and 9.2 µg/dL, respectively), while the cortisol response to cosyntropin was adequate (22.4 µg/dL), no glucocorticoid was prescribed and several days later the patient was discharged from hospital. Two days after discharge, he developed asthmatic symptoms, such as dyspnoea, episodic wheezing and productive cough. The patient ignored these symptoms and did not contact his physician. Two weeks after discharge, he was again hospitalised due to a severe asthmatic attack. Chest examination showed moderate bilateral expiratory wheezing in all lung fields. Arterial blood gas analysis revealed 7.29 of pH, 69.2 mmHg of PaO₂ and 59.8 mmHg of PaCO₂. His condition improved only after the treatment with 100% oxygen, intravenous infusion of methylprednisolone, aminophylline and magnesium sulphate, and nebulised salbutamol and ipratropium bromide. Spirometry performed several days later showed reversible airflow limitation, while allergy tests provided the same results as in his teenage years. After discharge he was treated with an oral glucocorticoid (prednisone), and the doses were gradually decreased and two months later the treatment was discontinued. The control low-dose cosyntropin test again gave normal results (21.8 µg/dL). Since that time he has required chronic treatment with a long-acting β₂-mimetic (salmeterol), an inhaled glucocorticoid and ipratropium bromide. He only occasionally uses short-acting β₂-agonists. Normal 24-hour urinary free cortisol excretion (30-50 µg/day) and morning cortisol excretion were adequately suppressed by dexamethasone (0.2-0.9 µg/dL), assessed on a yearly basis, excluding a relapse of Cushing's syndrome.

DISCUSSION

Although in many patients bronchial asthma may spontaneously remit (8, 9), clinical improvement in our patient should be rather related to the excessive production of glucocorticoids, reducing bronchial hyperreactivity. Potent and multidirectional effects of glucocorticoids on inflammatory mediators (1, 2) may explain why the onset of arterial hypertension, increase in body weight and appearance of other typical symptoms of Cushing's syndrome were accompanied by the remission of the asthmatic symptoms.

To the best of our knowledge, our study is the first to demonstrate that surgical treatment of Cushing's syndrome may induce attacks of bronchial asthma, probably secondary to a marked decrease in cortisol production. A deterioration of bronchial asthma could have been prevented if the patient had received oral glucocorticoid therapy in the perioperative period. Interestingly, we have recently observed a young woman who developed ulcerative colitis after laparoscopic adrenalectomy due to ACTH-independent Cushing's syndrome (Krysiak et al., unpublished). This suggests that the course of many different inflammatory and autoimmune disorders may exacerbate after effective treatment of Cushing's syndrome, particularly in predisposed individuals. As illustrated in this case report, systemic glucocorticoids may be needed to prevent exacerbation of concomitant inflammatory diseases.

In conclusion, surgical removal of an ACTH-producing tumour may induce severe asthma attacks in asthmatic patients not receiving systemic exogenous glucocorticoids. In patients with associated autoimmune or allergic diseases, high suspicion of relapse of these disorders should lead to intensification of glucocorticoid treatment.

REFERENCES

1. Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. *J Steroid Biochem Mol Biol* 2010; 120: 76-85.
2. Belvisi MG. Regulation of inflammatory cell function by corticosteroids. *Proc Am Thorac Soc* 2004; 1: 207-214.
3. Buttgerit F, Burmester GR, Lipworth BJ. Optimised glucocorticoid therapy: the sharpening of an old spear. *Lancet* 2005; 365: 801-803.
4. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet* 2006; 367: 1605-1617.
5. Nieman LK, Ilias I. Evaluation and treatment of Cushing's syndrome. *Am J Med* 2005; 118: 1340-1346.
6. Bertagna X, Guignat L, Groussin L, Bertherat J. Cushing's disease. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 607-623.
7. Biller BM, Grossman AB, Stewart PM et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008; 93: 2454-2462.
8. Fanta CH. Asthma. *N Engl J Med* 2009; 360: 1002-1014.
9. Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe asthma in adults. *Lancet* 2006; 368: 780-793.

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