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Life-threatening *Pneumocystis jiroveci* pneumonia following treatment of severe Cushing's syndrome

J.K. Oosterhuis¹, G. van den Berg³, W.E. Monteban-Kooistra², J.J.M. Ligtenberg², J.E. Tulleken², J.H.J.M. Meertens², J.G. Zijlstra^{2*}

¹Department of Anaesthesiology, ²Intensive and Respiratory Care Unit, ³Division of Endocrinology/ Department of Internal Medicine, Groningen University Medical Center, University of Groningen, Groningen, the Netherlands, *corresponding author: tel.: +31 (0)50-361 61 61, fax: +31 (0)50-361 32 16, e-mail: j.g.zijlstra@int.umcg.nl

ABSTRACT

We describe two patients with a severe Cushing's syndrome due to ectopic production of ACTH. Both patients developed a life-threatening *Pneumocystis jiroveci* pneumonia (PCP) shortly after treatment of the hypercortisolism was started by means of inhibition of production of glucocorticoids and glucocorticoid receptor blockade. We presume that the restored immune response elicited the clinical symptoms of the opportunistic, previously subclinical *Pneumocystis jiroveci* infection. The immunocompromised state and the delicate glucocorticoid balance in patients with a severe Cushing's syndrome necessitate a specific diagnostic and therapeutic approach.

KEYWORDS

Cushing's syndrome, opportunistic infections, treatment

INTRODUCTION

Cushing's syndrome is a well-known but nevertheless rare syndrome with an incidence of 0.7 to 2.4 per million population per year and a prevalence of 39.1 cases per million, iatrogenic cases not included.^{1,2} Cushing's syndrome results from lengthy and inappropriate exposure to excessive concentrations of circulating free glucocorticoid. In most cases Cushing's syndrome is adrenocorticotropin hormone (ACTH) dependent, originating either from a pituitary ACTH-secreting tumour (Cushing's disease) or, less frequently, from nonpituitary tumours secreting ectopic ACTH. Of all

patients with endogenous Cushing's syndrome 9 to 18% have ectopic ACTH production.^{3,4} We describe two patients with opportunistic respiratory infections due to extremely high cortisol levels because of ectopic ACTH production. In both patients the symptoms developed shortly after the treatment of the hypercortisolism was started.

CASE REPORT 1

A 62-year-old woman presented with complaints of hypertension, hirsutism, oedema of the tongue, a moon face and visual disturbances. These complaints had already been present for three years but varied in intensity. She had lost 10 kg in weight over the last two months. Moreover, during the last weeks she also developed muscle weakness in the lower extremities. She was found to have hypokalaemia. She also had a new-onset diabetes mellitus. ACTH (296 ng/l, normal <46 ng/l), cortisol (1945 nmol/l, normal <800) and urine cortisol (51,414 nmol/24 h, normal <270 nmol/24 h) were markedly elevated. A pituitary adenoma was not seen with gadolinium-enhanced magnetic resonance imaging (MRI). She was referred to the Department of Endocrinology in our hospital under the suspicion of an ectopic ACTH-producing tumour. Inferior sinus petrosus sampling confirmed the already supposed absence of pituitary ACTH production. A computerised tomography (CT) scan of the abdomen and thorax revealed a solid mass of 1.5 cm in the left upper lobe of the lung. The pulmonary lesion showed an increased uptake on (18)F-DOPA-PET. This

made a pulmonary carcinoid very likely. Spironolactone and mifepristone (400 mg) were started as dual receptor blockade, in anticipation of pulmonary surgery.

A few days later she complained of dyspnoea. Bilateral infiltrates were seen on the chest X-ray. She was admitted to the intensive care unit because of severe hypoxia. A bronchial lavage was carried out but was negative for *Pneumocystis jiroveci* or other pathogens. Nevertheless, high-dose trimethoprim-sulphamethoxazole (3 x 1920 mg) was started because of the strong clinical suspicion of *Pneumocystis jiroveci* pneumonia (PCP). Dyspnoea, hypoxia and chest X-ray improved. She did not need ventilatory support and was transferred back to the ward. Few weeks later the patient underwent a left upper lobectomy. Histology indeed showed a carcinoid of the lung with evidence of ACTH production. Cortisone acetate substitution was necessary for six months following surgery. Afterwards endogenous cortisol production was sufficient, with normal suppression after repeated dexamethasone inhibition. She has been free of symptoms for one year now.

CASE REPORT 2

A 57-year-old woman was well until January 2006, when she noticed malaise. Hypertension was found in May 2006 for which she was referred to hospital. Cushing's syndrome was diagnosed. She was found to have multiple masses in the liver and a solid mass in the tail of the pancreas by CT scan. Percutaneous liver biopsy revealed an undifferentiated non-small-cell carcinoma with some neuroendocrine characteristics. Laboratory examinations revealed marked elevations of plasma ACTH (318 ng/l, normal <46 ng/l), cortisol (2371 nmol/l, normal <800) and urine cortisol (294.306 nmol/24 h, normal <270 nmol/24 h) and hypokalaemia. Her hypertension required medication. Insulin was started because of a diabetes mellitus de novo. She was referred to the Department of Endocrinology in our hospital in June 2006. A diagnosis of severe Cushing's syndrome was made, due to ectopic ACTH production, probably from a primary endocrine tumour of the pancreas with liver metastases. Palliative, but directly life-saving bilateral adrenalectomy was contemplated because of the extremely high cortisol level. Curative surgery was impossible but the usual slow growth of neuroendocrine tumours made this attempt worthwhile.

Symptomatic treatment was started with ketoconazole, shortly afterwards followed by additional dual receptor blockade with 400 mg mifepristone and spironolactone. Also trimethoprim-sulphamethoxazole prophylaxis (960 mg on alternate days) was started as *Pneumocystis jiroveci* pneumonia prophylaxis. Nevertheless, she became

dyspnoeic two days later and was transferred to the ICU. Physical examination on admission showed a typical Cushingoid appearance with moon face, alopecia, muscle weakness, striae and central obesity. She was tachypnoic (30 breaths/min) and had a peripheral oxygen saturation of 80% with a 100% O₂ non-rebreathing mask. She was haemodynamically stable. Chest X-ray revealed bilateral alveolo-interstitial opacities. Before further diagnostic procedures could be performed she had to be intubated and mechanically ventilated. A bronchial lavage was carried out, which revealed *Pneumocystis jiroveci*. Afterwards trimethoprim-sulphamethoxazole was given in a therapeutic dose (3 dd 1920 mg iv). Mifepristone was stopped and glucocorticosteroids (hydrocortisone 400 mg/24 h) were started because of hypotension. The pulmonary symptoms improved.

For better control of the cortisol levels she underwent the planned bilateral adrenalectomy five days later. Large tumours in the liver and pancreas were found during the laparotomy, as well as a peritonitis carcinomatosa. A biopsy from the peritoneum showed a neuroendocrine tumour. Adipositas and muscle weakness made weaning difficult but ultimately she could be extubated. She had a short but much valued time with her family before she died, probably due to tumour progression.

DISCUSSION

We describe two patients with Cushing's syndrome and very high cortisol levels due to an ectopic ACTH production. One patient had a proven PCP; the other patient was clinically very suspect for a PCP. Both patients responded well to specific PCP therapy. Opportunistic infections after external glucocorticoids are well known, but opportunistic infections in patients with endogenous cortisol overproduction are less common. However, as early as in 1952, infections and wound healing problems in 17 of 33 patients with Cushing's disease, all untreated for their Cushing's syndrome, were described.⁵ Graham described six patients with severe endogenous Cushing's syndrome and opportunistic infections.⁶ He showed that patients with Cushing's syndrome have the same spectrum of infections as patients treated with pharmacological doses of corticosteroids. The risk of an opportunistic infection in Cushing's syndrome is related to the cortisol level.^{6,7} An opportunistic infection is therefore less likely to occur in patients with pituitary Cushing's disease than it is in patients with higher levels of cortisol overproduction from adrenal tumours or due to ectopic ACTH secretion. But still there is an increased risk, also for pituitary gland related Cushing's disease.^{8,9} *Cryptococcus neoformans*, *Aspergillus fumigatus*, *Nocardia* spp and *Pneumocystis jiroveci* are the most frequently found pathogens.

Immunocompromised hosts other than HIV patients can have a low *Pneumocystis* load explaining the negative bronchoalveolar lavage in the first patient.^{10,11} Interestingly, in both patients the clinical symptoms occurred shortly after almost total blockade of cortisol activity by the use of mifepristone. This has been described previously. The reconstituted immune response might be responsible for this.⁸ Apparently there is a delicate balance between the immune system of the patient and the pathogen that can be disturbed by treatment. This is also illustrated by the treatment of severe PCP in HIV patients. In these patients PCP treatment is combined with glucocorticosteroids to avoid a life-threatening immune response.¹²

Mifepristone is used to induce medical abortion. It has also been suggested to potentiate infections in this setting. The mechanism behind this might be the innate immunity.¹³ This might be a complementary or alternative explanation for the sequence of events seen in our patients. The incidence of infection after mifepristone is, however, very low and it is a completely different population, so this is not very likely. Enzyme inhibitors as ketoconazole have a rapid onset of action but these drugs are not effective enough in severe Cushing's syndrome. Mifepristone is a highly potent antagonist of glucocorticoid and progesterone receptors, especially suited for use in severe Cushing's syndrome as temporary medical therapy. Indeed both patients became insulin independent after mifepristone therapy started. Titration of the mifepristone dose is difficult because the effect of mifepristone, as a receptor blocker, cannot be quantified by the cortisol level itself. Insulin dependence and blood pressure can both be measured for glucocorticoid activity. However, excess inhibition is less easily measurable and in case of doubt mifepristone should be stopped and cortisol be substituted. In addition, a mineralocorticoid receptor antagonist such as spironolactone is usually necessary to control hypokalaemia.¹⁴

Definitive therapy is surgical extirpation of the ACTH-producing tumour, if feasible. Bilateral adrenalectomy may be a useful palliative therapy in case of metastasised disease.^{15,16} In conclusion, high endogenous glucocorticoid levels are immunosuppressive. Glucocorticoid receptor blockade by mifepristone is a powerful temporary medical treatment, awaiting definitive surgical therapy. However, this might elicit clinical symptoms of a previous subclinical *Pneumocystis jirovecii* infection justifying at least prophylactic and maybe even therapeutic doses of trimethoprim-sulphamethoxazole. Titration of the optimal level of corticoid activity is a clinical challenge in these critically ill patients.

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