CASE REPORT

Mifepristone for ectopic ACTH secretion in metastatic endocrine carcinomas: report of two cases

Philippe A Cassier¹, Sawzan Abou-Amara-Olivieri², Pascal Artru³, Marie-George Lapalus⁴, Jean-Paul Riou² and Catherine Lombard-Bohas⁵

¹Unité de Jour d'Oncologie Médicale Multidisciplinaire and ²Service d'Endocrinologie, Hôpital Edouard Herriot, Lyon, 5 Place d'Arsonval, 69003, France, ³Service de Gastroenterologie, Clinique Saint Jean, 69008 Lyon, France, ⁴Service de Gastroentérologie, Fédération des Spécialités Digestives, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69003, Lyon, France and ⁵Service d'Oncologie, Fédération des Spécialités Digestives, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69003 Lyon, France

(Correspondence should be addressed to C Lombard-Bohas; Email: catherine.lombard@chu-lyon.fr)

Abstract

Ectopic adrenocorticotropin secretion (EAS) remains a therapeutic challenge whenever the tumor responsible for the syndrome is not amenable to curative resection. Two cases of EAS related to metastatic foregut-derived endocrine carcinomas led us to use mifepristone, an antagonist of both progesterone and glucocorticoids. Mifepristone clearly improved skin lesions and diabetes associated with hypercorticism. The beneficial effect lasted for about 10 months. In both cases, recurrent hypertension and hypokalemia eventually required adrenalectomy.

European Journal of Endocrinology 158 935–938

Introduction

Ectopic adrenocorticotropin syndrome (EAS) accounts for about 15% of the Cushing's syndrome (1). The responsible tumors or carcinomas most often belong to one of the following types: small cell lung carcinoma, bronchopulmonary or thymic carcinoid, medullary thyroid cancer, and gastrinoma (1, 2). Whereas the most bronchopulmonary and thymic carcinoids can be treated by radical resection, the syndrome related to gastrinomas usually reflects secondary secretory differentiation of metastases (3). No single therapy ubiquitously allows for long-term control of EAS in that context, whether surgical or radiological debulking, impairment of glucocorticoid synthesis, or reduction of ACTH secretion (1, 2). Mifepristone is an antagonist of both progesterone and glucocorticoids (4, 5). We report its use in two patients with ACTH-secreting metastases from foregut-derived neuroendocrine carcinomas.

Case 1

A 46-year-old lady was found to harbor a pancreatic gastrinoma with synchronous liver metastases in 1997. Following chemotherapy with three cycles of streptozocin plus doxorubicin and chemo-embolization of the liver metastases, the patient underwent splenopancreatectomy and right hepatectomy in 1998. Other liver metastases emerged 2 years later, leading to therapy with α -interferon and fluorouracil plus irinotecan, successively. The patient was kept under proton pump inhibitor

(omeprazole, 60 mg daily) because of hypergastrinemia (632 ng/l in October 1999, 2000 ng/l in May 2002). In May 2003, the tumor burden was stable, but the patient developed diabetes mellitus, facial swelling, muscle weakness, lower limb edema, and hypertension. Insulin therapy was initiated. Serum gastrin concentration was 6500 ng/l, and plasma chromogranin A level had increased to 8684 μ g/l (vs 6877 μ g/l in 2002 and 1950 μ g/l in 2001). Morning plasma cortisol was 700 nmol/l ($N < 550$) and plasma ACTH was 100 ng/l ($N < 24$). The lack of any abnormality at magnetic resonance imaging of the sella turcica, and a negative dexamethasone suppression test, were considered suggestive of ectopic ACTH secretion. A few hours after the first administration of aminoglutethimide the patient developed hypotension and acute respiratory distress syndrome and was transferred to the intensive care unit. The shock was later attributed to a combination of septicemia from *Klebsiella oxytoca* and colitis related to *Clostridium difficile*, and precluded any further attempt to use this drug. Rosiglitazone, a peroxisome proliferator-activated receptor (PPAR γ) ligand with potential inhibitory effects on ACTH secretion (6), was inefficient. Mifepristone (RU486), 400 mg daily, was obtained from Exelgyn Pharmaceuticals (Paris) on a special prescription authorized by the French Ministry of Health (Autorisation Temporaire d'Utilisation ATU). It resulted in a dramatic improvement of diabetes mellitus and of facial and truncal swelling within 3 months. At that time, blood pressure was 120/80 mmHg under 100 mg spironolactone daily. Hypokalemia was present before starting RU486

(3.1 mmol/l) and remained stable between 3 and 3.5 mmol/l during the following months in spite of oral supplementation with up to 3600 mg potassium chloride. Insulin therapy was substituted by oral glibenclamide in June 2005. Plasma cortisol and ACTH concentrations did not rise, as expected since this type of tumor is not usually responsive to the negative feedback of glucocorticoids. Diabetes mellitus, hypertension, and hypokalemia increased after 10 months of mifepristone therapy. Dose escalation to 600, 800, 1200, and eventually 1600 mg daily (Fig. 1) improved the glycemic control but failed to control hypertension, edema, and hypokalemia. From October to December 2005, serum potassium levels varied between 2.6 and 3.5 mmol/l in spite of heavy potassium intake (7200 mg KCl daily), and blood pressure was 180/100 mmHg under 200 mg spironolactone plus 40 mg nicardipine. Serum gastrin levels were massively elevated (60 274 and 101 250 ng/l in June and October 2005, without any similar trend of chromogranin A levels respectively 6110 and 7423 µg/l) (Fig. 2). Doses of the proton pump inhibitor esomeprazole were increased first to 120 mg and then to 240 mg daily. Attempts of chemotherapy were rapidly stopped because of severe infections. Throughout RU therapy, no side effect was noticed on liver, kidney, and thyroid function tests. Bilateral adrenalectomy in January 2006 resulted in the disappearance of edema, hypertension, and diabetes mellitus. Six cycles of gemcitabine plus oxaliplatin were tolerated and resulted in stable disease. In January 2007, the patient presented with jaundice because of biliary tract compression by the liver metastases. Attempts of biliary prosthesis failed, and the patient died from a septic shock in March 2007.

Case 2

A 25 mm tumor of the right lung lower lobe was removed in July 2002 in a 37-year-old female patient.

Although the pathological analysis showed a typical carcinoid without nodal involvement (T1N0), multiple liver metastases were detected in May 2003. Fine-needle aspiration showed carcinoid cells. Chemotherapy using fluorouracil, epirubicin, and dacarbazine was started 8 months later. Pain in the right hypochondrium resumed after three cycles, but the patient developed diarrhea and hypokalemia. Monthly Sandostatin LP 20 mg was initiated in April 2004. Four months later, the patient complained of asthenia, and presented a 7 kg weight gain, hypertension, hypertrichosis, and facial swelling. Ectopic ACTH secretion was suggested by elevated plasma ACTH and cortisol concentrations (114 ng/l, $N < 24$, and 998 nmol/l, $N < 312$ respectively), and by free urinary cortisol (1010 nmol per day, $N < 240$), whereas the magnetic resonance imaging of the sella turcica was normal. Serum potassium concentration was 1.9 mmol/l. Mifepristone, 400 mg daily, was started in February 2005 and improved facial swelling, muscular weakness, hypertrichosis, and skin hematomas within 3 months. Progression of liver metastases with increased plasma serotonin concentration (4.6 µmol/l, $N < 1.5$) led to hepatic artery embolization of the right lobe in July 2005. At that time, blood pressure was raised (160/100 mmHg), with hypokalemia (1.9 mmol/l) in spite of 3600 mg potassium chloride orally per day. The six subsequent months were marked with persisting hypertension, treated with perindopril, and hypokalemia. Massive oral potassium supplementation (6000 mg KCl per day) and spironolactone, 75 mg daily, failed to raise kalemia above 3.2 mmol/l (Fig. 3). In contrast, fasting blood glucose was permanently normal (hemoglobin A1c = 5.1% in September 2005). Embolization of the left hepatic artery in February 2006 was unsuccessful. Free urinary cortisol was 24772 nmol/day. Blood pressure remained elevated (160/100 mmHg) under perindopril plus spironolactone and bisoprolol, with serum

Figure 1 Plasma cortisol of patient 1 and corresponding doses of RU 486.

Figure 2 Plasma levels of ACTH, chromogranin A, and gastrin in patient 1.

potassium of 3.6 mmol/l under 9600 mg KCl per day. Serum creatinine and aminotransferase remained normal throughout RU486 therapy. One month after bilateral adrenalectomy in October 2006, blood pressure and serum potassium were back to normal.

Discussion

Cushing's syndrome is fairly frequent in the course of gastrinoma. It may reflect EAS in sporadic cases, predominantly through secondary secretory differentiation of liver metastases (3), or the coexistence of an ACTH-secreting pituitary adenoma in the context of multiple endocrine neoplasia type 1 (7). In case 1, the lack of any suggestive family history, and the absence of parathyroid hyperplasia and of other multiple endocrine neoplasia (MEN1)-related endocrine tumors after a

prolonged follow-up favored the hypothesis of a sporadic malignant gastrinoma with ACTH-secreting metastases.

In case 2, no sign suggestive of EAS was recorded at the time of resection of the primary bronchial carcinoid. The syndrome emerged after several months of metastatic progression in the liver, starting with chronic diarrhea that led to therapy with a long-acting somatostatin analog, without success.

EAS may be cured through resection of a bronchial or a thymic carcinoid in a substantial percentage of patients (1, 2). In contrast, the management of EAS induced by heavy metastatic diffusion of foregut-derived endocrine carcinomas remains extremely challenging. Somatostatin analogs have been reported to control the inappropriate ACTH secretion in anecdotal cases (8). Somatostatin analogs were used in case #2, but failed to prevent the emergence of the full syndrome. A number of alternate means have been used, including inhibition

Figure 3 Plasma cortisol concentrations and serum potassium levels in patient 2.

of the synthesis of glucocorticoids by aminoglutethimide, reduction of the metastatic load through surgical or radiological debulking, or inhibition of ACTH secretion by the dopaminergic agonist cabergoline (9).

Mifepristone antagonizes both progesterone and glucocorticoid receptors (4, 10) and was used to treat Cushing's syndrome as early as in 1985 (11). In the present patients, it induced a clear reduction of glucocorticoid-related symptoms such as diabetes, facial swelling, and muscle weakness for about 10 months. No side effects were recorded. Of interest is the fact that RU486 effects can only be monitored through clinical (skin abnormalities, muscle weakness, blood pressure) and indirect biological parameters (serum potassium), because the inappropriate secretion of ACTH and the resulting increase of plasma cortisol are not suppressed by the antagonist. No significant side effects were recorded in those two patients, even under the major doses used in case 1.

RU486 failed to control hypertension and hypokalemia in the long term. It is noteworthy that both patients had to be heavily treated for hypertension during RU486 therapy. This, together with persisting hypokalemia despite high doses of potassium supplementation, suggests that interaction of cortisol with the mineralocorticoid receptor may limit the therapeutic value of RU486 in ectopic ACTH syndrome.

In conclusion, mifepristone may be considered for the therapy of EAS in advanced endocrine carcinomas as a short-lived adjunct with the ability to control part of the hypercorticism. In spite of its limitations, it is well tolerated and may be valuable in the context of disabling metastatic diffusion with inappropriate ACTH secretion to temporarily control diabetes mellitus, muscle wasting, and the cutaneous hallmarks of the secretory syndrome. Hypertension and hypokalemia remain, however, to be controlled by other means.

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Received 28 February 2008

Accepted 14 March 2008