We herein describe the case of a 47-year-old woman with pre-clinical Cushing’s syndrome caused by a left adrenal adenoma, which was diagnosed 6 years after trans-sphenoidal selective removal of a pituitary adenoma for acromegaly at age 35. The patient was started on bromocriptine and then somatostatin analogues after the surgery; however, since her serum insulin-like growth factor-1 (IGF-1) values remained above the age-adjusted normal range, the treatment for acromegaly was switched from somatostatin analogues to pegvisomant (10 mg daily), before a left laparoscopic adrenalectomy. After the subsequent adrenalectomy, the dose of pegvisomant could be reduced gradually to once every 4 days without any increase in the serum IGF-1 values. This is the first report describing the need for a different dose of pegvisomant for the treatment of acromegaly before and after adrenalectomy for pre-clinical Cushing’s syndrome.

Key words: acromegaly, pre-clinical Cushing’s syndrome, pegvisomant

Figure 1. Clinical course

postoperatively. However, her serum insulin-like growth factor-1 (IGF-1) values remained above the age-adjusted normal range. She was admitted to our hospital at age 45 for further evaluation of a left adrenal incidentaloma measuring 32 mm × 27 mm in size, first discovered 4 years previously by computed tomography (Fig. 2). She had no clinical endocrinological manifestations. An endocrine evaluation revealed a normal plasma cortisol level, although the circadian rhythm was disturbed (0900h, 9.5 μg/dL; 1700h, 6.3 μg/dL; 2100h, 7.1 μg/dL). Furthermore, neither 1 mg nor 8 mg of dexamethasone completely suppressed the overnight cortisol secretion (3.6 μg/dL, 3.8 μg/dL, respectively). Her urinary free cortisol level was 85.2 μg/day, and the serum level of adrenocorticotropic hormone (ACTH) was under 2 pg/mL. The patient’s plasma aldosterone concentration and plasma renin activity (71.3 pg/mL, 1.1 ng/mL/h, respectively) were within their respective normal ranges. Adrenal scintigraphy using I131-labeled adosterol revealed positive uptake in the left adrenal tumor, with no uptake in the right adrenal gland. These findings indicated that the production of cortisol by the adrenal tumor was not regulated by the hypothalamo-pituitary-adrenal axis.

Because the patient refused to undergo surgical removal of the adrenal tumor at the time, she was followed without intervention. Since her serum IGF-I values remained high (>627 ng/mL), the treatment for acromegaly was switched from octreotide acetate LAR to pegvisomant (10 mg once daily). At the two-month follow-up, her serum IGF-1 values had dropped to the age-adjusted normal range; however, severe swelling at the injection site developed. Therefore, administration of pegvisomant (10 mg/day) was decreased to once every other day. This was followed by another rise in the serum IGF-1 values (from 159 ng/mL to 284 ng/mL); therefore, the dose was increased again to the original dose. One year later, the patient underwent a left laparoscopic adrenalectomy. Because the swelling at the injection site persisted, the pegvisomant dose was again reduced to every other day. However, despite the decrease in the therapeutic dose, this time, there was no increase in the serum IGF-1 value for 4 months. It is worth mentioning that the parameters potentially affecting the serum IGF-1 levels, for example, the lipid metabolism, liver enzymes, and nutritional pa-
The coexistence of acromegaly and Cushing’s syndrome in the same individual is rare. Previously reported cases suffering from both of these endocrinopathies included patients with an ectopic ACTH- and GH-producing tumor (4, 5), pituitary tumors secreting both human GH and ACTH (6, 7), or pituitary tumors secreting GH and ACTH-independent adrenal hypersecretion (8-10). In the present report, we describe a rare case of pre-clinical Cushing’s syndrome caused by an adrenal adenoma discovered a few years after transsphenoidal selective removal of a pituitary adenoma for acromegaly. The association of acromegaly with preclinical Cushing’s syndrome is extremely rare. To the best of our knowledge, there have been only two reports of the coexistence of acromegaly with ACTH-independent preclinical Cushing’s syndrome (11, 12). In the first case, glucocorticoid replacement therapy could be withdrawn as early as 8 weeks after adrenalectomy. In the second case, insulin resistance was assessed by means of the euglycemic hyperinsulinemic clamp technique before and after treatment for each endocrinopathy (pituitary surgery and adrenalectomy). Our case report is the first to describe the difference in the dosing requirement of pegvisomant required for the treatment of acromegaly before and after adrenalectomy which was performed for pre-clinical Cushing’s syndrome. Coronal images of enhanced MRI obtained 3 years after the start of treatment with pegvisomant demonstrated no significant change in the residual tumor size in comparison with that before the start of treatment (Fig. 3).

A recent consensus statement suggests that pegvisomant monotherapy administered once daily normalizes the IGF-1 concentration in most patients with refractory acromegaly, and long-term experience indicates that pegvisomant therapy is effective, safe, and well-tolerated (3). However, alternate-day administration of pegvisomant monotherapy failed to maintain the serum IGF-1 values within the age-adjusted normal range (13). A recent study has demonstrated that the pegvisomant dose requirement can be decreased by the concomitant administration of a somatostatin analogue (14).

It has been shown that the administration of high-dose glucocorticoids to normal individuals suppresses the plasma GH levels, and conversely, the rise in plasma GH in response to several stimulating factors is suppressed in states of hypercortisolism (15, 16). However, the precise relationship between GH secretion and cortisol secretion, both in vivo and in vitro, remains under debate (17). Several studies have demonstrated that glucocorticoids can directly stimulate GH mRNA expression in GH-producing pituitary cell lines (18, 19), as well as inducing the mRNA expression levels of GH, GH-releasing hormone (GHRH)-receptor (GHRH-R), and the ghrelin receptor (GHS-R) in primary rat pituitary cell cultures (20). These results are also consistent with the findings of some studies that glucocorticoids enhance the mRNA expression of GH and GH release in cell cultures prepared from human somatotropinomas (21, 22). Other studies indicate that both hypothyroidism and adrenal insufficiency impair the GH-secretory response to GHRH in vivo, and that treatment with thyroid hormones and glucocorticoids enhances the expression of GH in response to GHRH (23).

Uchida et al (10) reported a similar case of Cushing’s syndrome associated with a GH-producing pituitary tumor, in which both GH secretion and the pituitary tumor growth clearly decreased after adrenalectomy. In vitro, dexamethasone was shown to increase GH secretion from the cultured GH-producing adenoma cells in a dose-dependent manner. It is therefore possible that in the present case, GH secretion from the residual pituitary tumor was glucocorticoid-dependent, as described above.

The role of insulin in regulating the expression of the growth hormone receptor (GHR) remains unclear, although there is strong evidence that insulin is essential for the GH-mediated stimulation of hepatic IGF-1 production (24, 25).
Diabetes mellitus is characterized by a state of GH resistance with low circulating IGF-1 levels, despite high serum GH levels and poor growth (26, 27). Insulin treatment normalizes the serum GH concentrations, increases the serum IGF-1 levels, and stimulates growth (28). However, despite the reduced serum levels of GH, the serum concentrations of IGF-1 in obese subjects have been reported to be normal or elevated (29). Although GH is considered to be a major stimulus for IGF-1 synthesis, other substances, such as insulin, are capable of stimulating IGF-1 production. Therefore, normal or elevated levels of IGF-1 in obese patients may be related to the hyperinsulinemia present in this condition (30, 31). In the present case, the 75 g oral glucose tolerance test performed 2 years after adrenalectomy (Fig. 1) revealed a significant reduction of the blood glucose and insulin levels in comparison with those before the operation. Therefore, this observation lent support to the other possible explanation, suggesting that improvement of insulin resistance participates in the decreased dosing requirement for pegvisomant after adrenalectomy.

The present case is the first to show a decrease in the necessary dose of pegvisomant, administered as monotherapy, for effective treatment of acromegaly after an adrenalectomy performed for preclinical Cushing’s syndrome. We have not yet been able to precisely determine why the pegvisomant dose requirement for the treatment of acromegaly decreased after the adrenalectomy was performed for preclinical Cushing’s syndrome. Therefore an accumulation of cases and studies in animal models would be enlightening.

The authors state that they have no Conflict of Interest (COI).

References

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