Improvement of Congestive Heart Failure after Octreotide and Transsphenoidal Surgery in a Patient with Acromegaly

Itaru Akaza, Kyoichiro Tsuchiya, Miho Akaza, Toru Sugiyama, Hajime Izumiyama, Masaru Doi, Takanobu Yoshimoto and Yukio Hirata

Abstract

A 59-year-old man was admitted because of congestive heart failure. He was suspected to have acromegaly, and magnetic resonance imaging revealed a pituitary macroadenoma. Endocrine examination revealed elevated plasma levels of growth hormone (GH) and insulin-like growth factor (IGF)-1, and an oral glucose tolerance test failed to suppress plasma GH levels, consistent with the diagnosis of GH-producing pituitary tumor. Treatment with octreotide, followed by transsphenoidal surgery resulted in normalization of plasma GH/IGF-1 levels, accompanied by the improvement of cardiac function. Thus, it is suggested that excess GH/IGF-1 axis is involved in the development of acromegaly-related cardiomyopathy in the present case.

Key words: acromegaly, GH, IGF-1, pituitary tumor, octreotide, cardiomyopathy

(Inter Med 48: 697-700, 2009)
(DOI: 10.2169/internalmedicine.48.1537)

Introduction

Acromegaly is a unique endocrine disease characterized by growth hormone (GH)-secreting pituitary tumors associated with an excessive production of insulin-like growth factor (IGF)-1 by the liver (1). Cardiovascular complications, such as hypertension, left ventricular (LV) hypertrophy, and cardiomyopathy, are the major causes of morbidity and mortality in acromegaly (2). Several clinical studies have suggested that suppression of GH/IGF-1 by administration of somatostatin analogues (3) and/or removal of the pituitary tumor by transsphenoidal surgery (TSS) (4) could improve cardiac dysfunction associated with acromegaly, whose exact mechanism(s) remains unknown.

We describe herein a patient who initially presented with severe congestive heart failure and was later found to have acromegaly. The patient showed a marked improvement in cardiac function after normalization of excess GH/IGF-1 by short-term treatment with octreotide, followed by removal of GH-producing pituitary tumor by TSS, suggesting the pathophysiological role of excess GH/IGF-1 in the development of acromegalic cardiomyopathy.

Case Report

A 59-year-old man with a 20-year history of hypertension was admitted because of nocturnal dyspnea in April 2005. He was 166 cm tall and weighted 71 kg (body mass index: 26). Blood pressure was 148/86 mmHg. Chest X-ray showed a marked cardiomegaly with pulmonary congestion (Fig. 1A). Electrocardiogram showed left ventricular (LV) hypertrophy with depression of the ST segment. Echocardiography showed markedly dilated LV dimension end-diastole (LVDd: 63 mm), and end-systole (LVDs: 54 mm), decreased ratio of peak early LV filling velocity to peak atrial filling velocity (E/A ratio: 0.53), the marker of diastolic function, reduced ejection fraction (EF: 28%), the marker of systolic function, and increased interventricular septal thickness (IVST: 13 mm), with moderate mitral regurgitation (Fig. 2). He also had an elevated plasma brain natriuretic peptide (BNP) level (657 pg/mL). These cardiac findings were consistent with the diagnosis of hypertensive heart failure. After conventional treatment for congestive heart failure (furosemide, dopamine, carvedilol, losartan, spironolactone), nocturnal dyspnea resolved, and his blood pres-
sure remained well controlled (114/64 mmHg). Cardiac function markedly improved with increased EF and decreased plasma BNP. Thereafter, he received antihypertensive drugs (losartan, carvedilol, amlodipine) at the same doses, while the dose of furosemide was reduced (20 mg), and spironolactone was withdrawn (Fig. 2). During hospitalization, he was suspected to have typical acromegalic face, and was referred to our hospital for endocrine evaluation.

On physical examination, he had typical acromegalic features, such as deep nasolabial furrows, macrognlossia, thick lip, and thickening of hands and feet (bilateral heel pad thickness: 26 mm). A grade II/IV diastolic murmur and slight leg edema were noted. Endocrine data showed elevated plasma levels of fasting plasma glucose (111 mg/dL) and hemoglobin A1c level (6.2%). Endocrine examination revealed increased basal plasma levels of GH (31.8 ng/mL) and IGF-1 (1,100 ng/mL). An oral glucose (75 g) tolerance test (OGTT) failed to suppress plasma GH levels (nadir value: 26.1 ng/mL). Plasma GH levels paradoxically increased after stimulation with TRH, but not with LH-RH. Plasma GH levels decreased from 27.5 to 10.7 ng/mL after oral administration of bromocriptine (2.5 mg), and from 29.3 to 1.91 ng/mL after subcutaneous injection of octreotide (100 μg), respectively. Secretion of other pituitary hormones was normal. Magnetic resonance imaging (MRI) of the head revealed the presence of a pituitary macroadenoma (10×10×15 mm) without enhancement by gadolinium.
Figure 3. Pituitary magnetic resonance imaging (MRI) and immunohistochemical examination. (A) Gadolinium-enhanced T2-weighted MRI showing a pituitary macroadenoma (10×10×15 mm) (arrows). (B) Immunostaining of GH (magnification ×400).

These data are compatible with the diagnosis of GH-producing pituitary macroadenoma.

Treatment with daily injection of 200 μg octreotide for six weeks decreased basal plasma levels of GH (6.41 ng/mL) and IGF-1 (326 ng/mL), along with concomitant improvement of cardiac performance by diminution of LV dilation and increases in both EF and E/A ratios by echocardiography (Fig. 2). TSS was performed in July 2005; immunohistochemical examination of the resected tumor specimens is consistent with GH-producing pituitary adenoma (Fig. 3B).

The postoperative course was uneventful without any evidence of residual tumor by pituitary MRI. Postoperatively, basal plasma levels of both GH (0.83 ng/mL) and IGF-1 (246 ng/mL) were normalized. OGTT showed a complete suppression of plasma GH (nadir value: 0.34 ng/mL) and normal glucose tolerance, and the paradoxical response of plasma GH to TRH disappeared. This is consistent with a biochemical cure of acromegaly. Three months after surgery, cardiac enlargement was reduced (Fig. 1B) and cardiac function further improved with decreased LV dilation and increased EF (Fig. 2).

Discussion

Several clinical studies have shown that patients with acromegaly have increased risk for cardiovascular morbidity and mortality, resulting from accumulation of multiple cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes (5, 6).

The present case of acromegaly who initially presented with congestive heart failure, had hypertension and IGT. In acromegaly, excess GH/IGF-1 has been reported to cause hypertension due to increased sodium and fluid retention as a result of the renal tubular reabsorption (7, 8). Furthermore, IGT and diabetes in acromegaly has an increased prevalence of systolic and diastolic dysfunction (9). Therefore, both hypertension and IGT could also be predisposing factors responsible for the development of cardiac hypertrophy and dysfunction. However, recent studies have shown that LV concentric hypertrophy and impaired systolic/diastolic function in acromegaly is independent of the coexisting hypertension and IGT, suggesting an acromegaly-specific cardiomyopathy (9, 10).

It has been shown that excess GH/IGF-1 induces cardiomyocyte hypertrophy (11-15). Rats implanted with GH-secreting tumors showed cardiac hypertrophy (11), and rats treated with GH showed increased proliferation and total number of cardiac myocytes in vivo (12). IGF-1 directly stimulates hypertrophic response in rat cardiomyocytes in vitro (13). Activation of IGF-receptors by excess systemic IGF-1 derived from the liver mediates several important effects on cardiomyocytes, such as an increase in myocyte size, anti-apoptosis, myocytes differentiation, and myogenesis (14, 15). GH receptor has been shown to be expressed in many tissues including the heart where GH directly acts (16). In fact, GH has been shown to increase IGF-1 production in the cardiomyocytes (17, 18), suggesting the role of local IGF-1 in the development of cardiomyocyte hypertrophy via an autocrine/paracrine mechanism. Taken together, both systemic and local GH/IGF-1 axis could be involved in the development of cardiac hypertrophy.

Somatostatin analogs have been reported to improve cardiovascular function and overall clinical performance in acromegalic patients with cardiovascular diseases. For example, acute suppression of GH secretion by 24-hr continuous infusion of octreotide in acromegalic patients improved cardiac function and maximal exercise capacity (19). Furthermore, chronic treatment with octreotide in acromegalic patients for 2 years improved cardiovascular function, including reduced LV hypertrophy and improved cardiac performance (20). Since improvement of LV hypertrophy and dia-
stolic dysfunction by octreotide depends on the biochemical control of GH and IGF-1 (21). octreotide could improve cardiac function via suppression of excess GH/IGF-1 secretion. Alternatively, somatostatin analogues may have a direct inhibitory effect on the heart, because cardiomyocytes express somatostatin receptors (type-1 and -2) (22). Thus, the short-term (6 weeks) treatment with octreotide in the present case could have partly contributed to the improvement in cardiac function, especially diastolic function as represented by increased E/A ratio.

TSS is the first line and the most effective therapy for reducing GH hypersecretion and tumor mass effect in acromegaly. In the present case, postoperative normal basal plasma GH and IGF-1 levels with complete suppression of plasma GH after OGTT (<1 ng/mL) are consistent with biochemical cure, and cardiac function further improved postoperatively, as represented by increased LVEF and decreased LV dimension. Normal IGF-1 levels and glucose-suppressed GH levels (<1 ng/mL) after successful TSS have been shown to reduce LV mass index after 6 months along with improvement of hypertension (4). Although the biochemical cure achieved in the present case implies a favorable cardiovascular prognosis, a long-term follow-up for the acromegaly-related cardiomyopathy is needed.

In summary, we report a case of acromegaly associated with congestive heart failure, in whom cardiac function improved after preoperative short-term treatment with octreotide, followed by surgical removal of the pituitary tumor. The possible involvement of excess GH/IGF-1 in the development of acromegaly-related cardiomyopathy is postulated.

**Acknowledgement**

This study was supported in part by Grants-in-Aid for the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare, Japan.

---

**References**