CASE REPORT

A Case of Juvenile Acromegaly that was Initially Diagnosed as Severe Congestive Heart Failure from Acromegaly-Induced Dilated Cardiomyopathy

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Abstract

Acromegaly is characterized by chronic hypersecretion of growth hormone (GH) and is associated with increased mortality rate because of the potential complications such as cardiovascular disease, respiratory disease, or malignancy, which are probably caused by the long-term exposure of tissues to excess GH, for at least 10 years, before diagnosis and treatment.

A 22-year-old man with a 2-month history of fatigue was admitted to our hospital because of chest discomfort, dyspnea, and pitting edema of the lower limbs experienced over a 1-month period. On admission, his height and body weight were 186 cm and 138.5 kg, respectively, with a BMI of 39.8 kg/m². He showed acromegalic features and elevated serum GH and IGF-1 levels, which were 11.5 ng/mL and 960 ng/mL, respectively. There was no GH suppression in the 75-g oral glucose tolerance test. Pituitary magnetic resonance imaging (MRI) revealed microadenoma. Chest X-ray revealed cardiomegaly, and echocardiogram showed dilated left ventricular (LV) cavity and diffuse hypokinesis with extremely decreased ejection fraction (EF). He was diagnosed as having acromegaly with congestive heart failure from diastolic cardiomyopathy.

After the successful transsphenoidal resection of the pituitary adenoma, the level of GH was normalized. However, the cardiac dysfunction did not show any improvement even after the administration of β-blockers, angiotensin-converting enzyme inhibitor (ACE-I), or diuretics. The patient was re-hospitalized, and he died of cardiac failure at the age of 25 years.

Patients with acromegaly have been reported to have about 30% higher mortality rate, and cardiovascular disease accounts for 60% of the deaths. We report a case of a patient with juvenile acromegaly who was diagnosed with severe cardiac failure at the time of diagnosis and failed to recover cardiac function even after the successful resection of the pituitary adenoma. Immediate diagnosis and treatment are required for better control of acromegalic cardiomyopathy.

Key words: acromegaly, acromegalic cardiomyopathy, dilated cardiomyopathy

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Introduction

Acromegaly is a disease characterized by chronic hypersecretion of growth hormone (GH) and is associated with an increased mortality rate (1, 2). Patients with acromegaly have been reported to have about 30% higher mortality rate, and cardiovascular diseases such as hypertension, left ventricular hypertrophy, or ischemic heart disease account for 60% of the deaths; respiratory disease for 25% deaths; and malignancy for 15% deaths; these conditions are probably caused by the long-term exposure of tissues to excess GH before diagnosis and treatment (3, 4). Normalization of GH secretion is associated with an improvement in the structural...
and functional cardiac abnormalities in patients with acromegaly; however, the long-term prognosis of patients with acromegaly remains unclear (5).

Case Report

A 22-year-old man with a 2-month history of general fatigue was admitted to our hospital because of chest discomfort, dyspnea, and pitting edema of the lower limbs experienced over a 1-month period. His condition was classified as New York Heart Association (NYHA) stage III-IV. He had a history of bronchial asthma, which was in good control without medication. There was no history of alcohol, smoking, or drug abuse. His mother and father had a history of bronchial asthma and diabetes mellitus, respectively.

Physical examination on admission showed that his height and body weight were 186 cm and 138.5 kg, respectively, with a body mass index (BMI) of 39.8 kg/m². Blood pressure was 130/80 mmHg, and heart rate was 102/min with sinus rhythm. He showed acromegalic features such as outstanding jaw and eyebrow area and enlargement of the nose, tongue, and lip. He also had large hands and feet, with a shoe size of 29 cm. Pulmonary auscultation revealed coarse crackles in the bilateral lower lobes, and cardiac auscultation was rhythmic, without murmur. The jugular vein was distended, and pitting edema was observed in the lower limbs. On the basis of his photographs from childhood, we determined that the changes in his appearance had begun to occur from at least 14 years of age.

Table 1 shows the laboratory findings on admission. The level of brain natriuretic peptide was elevated at 603 pg/mL. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 36 IU/L and 41 IU/L, respectively; the increase in levels of these enzymes might have been caused by fatty liver and congestive liver dysfunction. Although the plasma glucose concentration and glycosylated hemoglobin level were within the normal range, the homeostasis model assessment-insulin resistance index was elevated to 3.25, suggesting the presence of insulin resistance.

The level of serum GH was 11.5 ng/mL, and that of insulin like growth factor-1 (IGF-1) was 960 ng/mL. There was no suppression in GH in the 75-g oral glucose tolerance test (the minimum GH was 10.8 ng/mL). Instead of obtaining a positive reaction for GH in the luteinizing-hormone releasing hormone loading test, a paradoxical reaction was observed in the thyrotropin-releasing hormone loading test. GH level decreased to the lowest at 3-6 hours after the administration of octreotide (basal and minimum GH were 9.95 ng/mL and 0.42 ng/mL, respectively) and bromocriptine (basal and minimum GH were 10.7 ng/mL and 5.95 ng/mL, respectively).

Magnetic resonance imaging revealed microadenoma of the left pituitary gland (Fig. 1). X-ray of the feet revealed heel-pad thickness, and chest X-ray revealed an enlarged cardiac silhouette with a cardiothoracic ratio (CTR) of 68%. Electrocardiogram (ECG) obtained at rest showed normal sinus rhythm without arrhythmia. Transthoracic echocardiogram showed dilated left ventricular (LV) cavity (LV end-diastolic dimension, 92.6 mm; LV end-systolic dimension, 84.8 mm, interventricular septum diastolic 6.5 mm) with diffuse hypokinesis and an ejection fraction (EF) of 17.8%, which is extremely low (Fig. 2). The right ventricle and
atrium and left atrium were also dilated with mild mitral regurgitation (MR) and moderate tricuspid regurgitation (TR). Coronary angiography showed normal coronary arteries without stenosis. Left cineventriculography revealed an EF of 28.1% with diffuse left ventricular hypokinesis. Myocardial biopsy of the left ventricle was performed. Hematoxylin Eosin (H&E) staining of the biopsy specimen showed interstitial fibrosis, waxy degeneration, cardiomyocyte enlargement, and pleomorphism of nuclei (Fig. 3), which suggested hereditary dilated cardiomyopathy. Electromicroscopy revealed Z-disk preservation without mitochondrial degeneration or myofibrillar lysis. These results indicated that it was probably not a case of hereditary cardiomyopathy; therefore, we diagnosed the patient as having secondary dilated cardiomyopathy due to acromegaly.

Clinical course

The patient was diagnosed as having acromegaly with congestive heart failure secondary to acromegaly-induced dilated cardiomyopathy. At admission, his condition was classified as NYHA III-IV. Although his cardiac function improved after treatment, which included administration of diuretics; angiotensin-converting enzyme inhibitor; vasodilators; and β-blockers, he could not follow the strict water restriction regimen, which was essential for his status. There had been no major or minor attacks of bronchial asthma for more than five years without any medications, therefore we carefully administered β-blockers to the patient. After the administration of octreotide (200 μg/day) for the control of GH excess, the serum GH and IGF-1 concentration decreased from 11.5 ng/mL to 0.58 ng/mL and 960 ng/mL to 650 ng/mL, respectively. When transphenoidal resection of pituitary adenoma was performed successfully, the levels of GH and IGF-1 decreased to 0.22 ng/mL and 280 ng/mL, respectively. As the normal range of IGF-1 among males aged 20 to 29 years is from 85 to 369 ng/mL, we considered the operation to be successful. Accompanied with the normalization of GH and IGF-1 levels, the cardiac function also recovered with EF of 17.8% to 39.2%.

In addition to refusal to follow the water restriction regimen, he also was not compliant in following the drug or regular medical examination regimen. He was hospitalized again because of uncontrollable cardiac failure. One year after the operation, the level of GH had become re-elevated from 0.22 ng/mL to 4.02 ng/mL, while the level of IGF-1 remained 300 ng/mL. As we suppose this relatively low level of IGF-1 might have been the masked data by liver dysfunction from congestive hepatic failure or fatty liver, we
administered bromocriptine, which failed to suppress GH. He refused to take any further treatment for the control of GH excess. He died due to sudden cardiopulmonary arrest, 2 years and 3 months after the operation. Autopsy revealed hypertrophic changes in multiple organs, including the heart and liver. Diffuse eosinophilic pituitary adenoma containing GH positive cells was observed, therefore the final diagnosis was relapse of post transsphenoidal resection for acromegaly.

Discussion

Acromegaly is characterized by chronic growth hormone (GH) hypersecretion that leads to an increased mortality rate, with cardiovascular complications accounting for the highest number of patient deaths (1-3, 6). An excess of GH and IGF-1 causes a specific derangement of cardiomyocytes, leading to abnormalities in the structure and function of cardiac muscles, including specific cardiomyopathy. In the early phase of acromegaly, GH and IGF-1 hypersecretion induces a hyperkinetic syndrome, which is characterized by increased heart rate and systolic output. Untreated or unsuccessfully treated acromegaly persisting over many years may lead to the development of concentric biventricular hypertrophy, which is the most common feature of cardiac involvement in acromegaly, and diastolic dysfunction; these conditions might eventually progress to the final stage of diastolic congestive heart failure, frequently accompanied with valve dysfunction or rhythm disturbance (6, 7).

Dilated cardiomyopathy, although rare, is possibly associated with the long-term persistence of acromegaly (1). Patients with chronic dilated cardiomyopathy and LV systolic dysfunction have a poor diagnosis, similar to patients with chronic dilated cardiomyopathy of other causes. In less than 40-year-old patients with active acromegaly of 3-7 year duration, 54% were reported to have echocardiographic evidence of LV hypertrophy, and this figure rose to 72% in 41-60-year-old patients with the disease duration of 5-15 years (3, 8, 9). Colao et al conducted a cohort study and classified 25 acromegaly patients aged less than 40 years into 2 groups depending on the disease duration, i.e., less than or more than 5 years. They showed that the patients had an increase in LV mass and a decrease in LV performance, which was more evident in the patients with a longer disease duration (10). On the basis of these reports, we speculate that the present case, showing no clinical symptoms but only changes in the appearance for over 10 years, might have developed acromegaly at least 10 years previously, and cardiovascular complications would have developed gradually during that time. Moreover, the refusal of conforming to the water restriction or treatment regimen might have accelerated the progression of the disease.

Our histopathologic observations are in agreement with the morphologic features of dilated cardiomyopathy. Because the histopathologic features specific for idiopathic dilated cardiomyopathy cannot be identified easily, the differentiation of idiopathic dilated cardiomyopathy from heart disease of known causes becomes difficult (11). Nonetheless, our patient showed no signs of other basic diseases such as filtration of inflammatory cells leading to myocarditis or ischemic heart disease, but showed acromegaly alone. In addition, because the Z-disc structure was completely preserved without widening, dispersion, or irregularities, which are characteristic features of hereditary cardiomyopathy, we could rule out the possibility of hereditary dilated cardiomyopathy (12, 13). On the basis of these findings, we diagnosed the patient as having acromegaly with acromegaly-induced dilated cardiomyopathy; this condition is known to be associated with severe congestive heart failure.

Although the duration of acromegaly in our patient was suspected to be longer than 10 years, there is concern as to whether acromegaly was the only cause of severe chronic heart failure, especially considering the patient’s young age. The mechanisms involved in the progression of heart failure in acromegaly are not clearly known, except for the factors such as insulin-resistance, dislipemia, or alteration in the levels of clotting factors. GH and IGF-1 are also known to activate several signaling pathways that play a protective role against the development of heart failure (14). We assessed whether there were any other causes for the development of cardiomyopathy in the present case, including diabetes mellitus and hypertension, but we found that acromegaly and insulin resistance were the only causes. In addition, our patient was obese with a BMI of 39.8 kg/m², which might have also been one of the important factors for cardiac load. There are a few reports that suggest an association between obesity and congestive heart failure (15-18).

The treatment in the present case was based on 2 main principles: the control of GH and IGF-1 hypersecretion and the control of cardiac heart failure. The normalization of GH and IGF-1 levels in patients with acromegaly is essential to reverse or arrest cardiovascular disease development (22).
Transsphenoidal surgery remains the principal treatment option for GH-secreting tumors and is often used in combination with pharmacological treatments such as somatostatin analogues, GH-receptor antagonists, or dopamine agonists, which was the treatment modality used for our patient (23-25). We first controlled severe congestive heart failure so as to restore the patient’s cardiac function, allowing him to tolerate the resection of the pituitary adenoma. His cardiac function improved with the treatment, showing recovery of EF from 18% to 35%. The operation performed subsequently was successful, and with the administration of a GH-lowering drug, GH and IGF-1 levels returned to the normal range. Although a case report of severe congestive heart failure from acromegalic cardiomyopathy suggests that cardiac function could be recovered significantly and LV mass could be decreased with transsphenoidal surgery and administration of octreotide (26), other reports suggest that these beneficial effects appear earlier in young patients with short disease duration than in elderly patients (22). Some reports indicate that the treatment of acromegaly might improve cardiac function in the short term but has probably little or no effect on the long-term prognosis (5, 27). Considering the fact that our case initially responded to the treatment, there is a possibility that the patient’s cardiac function could have recovered considerably with better compliance and continuation of treatment.

**Conclusion**

We report a patient with juvenile acromegaly who developed congestive heart failure secondary to acromegaly-induced dilated cardiomyopathy. The contributing factors for the severe cardiac status might be not only acromegaly of 10-year duration but also other factors such as obesity or refusal to conform to the treatment and water restriction regimen. Early diagnosis and treatment with curative drugs are required for ensuring better outcome of acromegaly patients.

**References**


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