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Histopathological Improvement of Acromegalic Cardiomyopathy by Intermittent Subcutaneous Infusion of Octreotide#

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Abstract. We studied functional and histopathological changes in acromegalic cardiomyopathy following intermittent subcutaneous infusion of octreotide. A 68-year-old female patient with acromegaly associated with congestive heart failure due to dilated cardiomyopathy was initially treated with cardioactive medication for three months, but it was not effective in correcting echocardiographic abnormalities. Further treatment with intermittent subcutaneous infusion of octreotide (20 μg/2 h) for 12 months not only reduced circulating GH and insulin-like growth factor-I (IGF-I) levels but also considerably improved histopathological changes in the myocardial specimen biopsied. These findings provide the first evidence of the favorable effect of octreotide on histopathological changes in acromegalic cardiomyopathy.

Key words: Acromegaly, Cardiomyopathy, GH, Octreotide, Myocardial biopsy, Electron microscopy
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CARDIOVASCULAR mortality and morbidity are increased in acromegalic patients [1–3]. Congesive heart failure occasionally develops in acromegalic cardiomyopathy, which is accompanied by such histopathological abnormalities as myocardial hypertrophy and interstitial fibrosis [2]. Some cases of acromegalic cardiomyopathy are resistant to conventional cardioactive medication [4, 5]. It has been demonstrated that octreotide was effective for acromegalic cardiomyopathy [6–8], but there have been conflicting reports indicating that acromegalic congestive heart failure could be worsened by octreotide through a negative inotopic action of somatostatin [9–11].

In the present study we report the case of a female with active acromegaly complicated with congestive heart failure due to dilated cardiomyopathy, which was successfully treated with octreotide in combination with intensive cardioactive medication. Furthermore, cardiac muscle biopsy revealed the first evidence for beneficial effect of octreotide treatment on histopathological changes in acromegalic cardiomyopathy.

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Case Report

A 68-year-old women was referred to an intensive care unit of cardiology for severe pulmonary edema and congestive heart failure. She had been suffering from exertional dyspnea for last five months. Physical examination showed that body temperature was 35.8 °C and pulse rate was

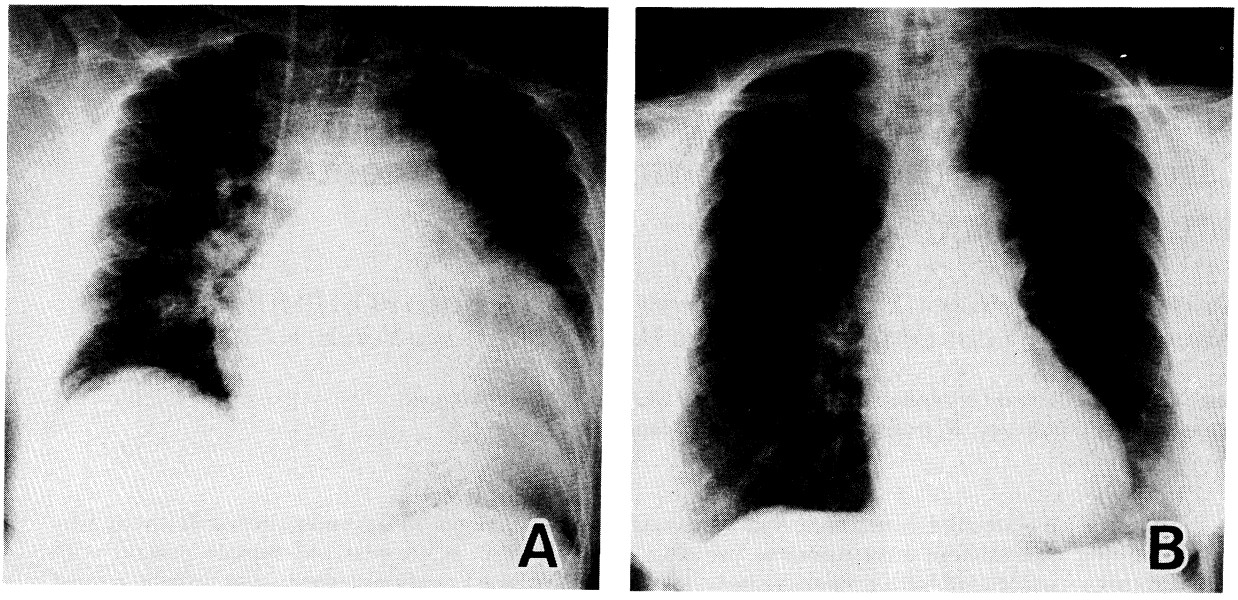

Fig. 1. Chest rentgenogram before (A) and after (B) octreotide treatment. Massive cardiomegaly and pulmonary edema were noted before treatment. A remarkable reduction in heart size was found after octreotide treatment.

84/min, irregular. Respiratory rate was 20/min and blood pressure was 154/86 mmHg. Breath sounds were diminished and inspiratory crackles were audible at lung bases. The third heart sound and systolic murmur (Levine 2/6) were audible at the apex. There was no peripheral edema. Her lips and tongue were thick, and hands and feet were enlarged, which had been noticed by the family for over ten years.

Marked cardiomegaly and pulmonary edema were noted on chest X-ray (Fig. 1A). ECG showed left ventricular hypertrophy, pathological QS wave and poor R wave progression. Echocardiography revealed diffusely hypokinetic heart (left ventricular fractional shortening: 11%), dilated left ventricle and increased left ventricular mass as shown in Table 1. Coronary angiography did not demonstrate any abnormality.

Intensive medical therapy was immediately started with digitalis, furosemide, angiotensin converting enzyme inhibitors and anti-arrhythmic agents. Congestive heart failure was improved three months after the start of the cardioactive medication, but echocardiographic parameters were not remarkably changed (Table 1). Cardiac muscle biopsy of the left ventricular endomyocardium demonstrated severe myocardial degeneration with infiltration of inflammatory cells into the intercellelar space (Fig. 2A). Furthermore, electron microscopic examination of the specimen revealed huge and bizarre-shaped nuclei, various mitochondrial alterations and lysis of myofilaments of myocardial cells (Fig. 3A).

Table 1. Echocardiographic parameters before and during octreotide treatment

	Months after octreotide				
	−3	0	1	3	12
E.D.D. (mm)	75	65	59	56	56
E.S.D. (mm)	67	54	47	43	30
F.S.(%)	11	11	20	23	38
E.F.(%)	29	29	49	55	76
I.V.S.T. (mm)	10	11	10	11	10
L.V.P.W.T. (mm)	9	11	11	12	12
L.V.M. (g)	425	386	293	303	212

E.D.D., End-diastolic dimension; E.S.D., End-systolic dimension; F.S., Fractional shortening; E.F., Ejection fraction; I.V.S.T., Interventricular septum thickness; L.V.P.W.T., Left ventricular posterior wall thickness; L.V.M., Left ventricular mass.

Under a clinical diagnosis of acromegaly, the patient was then referred to an endocrinologist. Laboratory examination revealed that plasma GH (33.1 ± 1.3 ng/m*l*), urinary GH (483.7 ng/day) and plasma insulin-like growth factor-I (IGF-I) (410 ±

20 ng/ml) levels were markedly increased, whereas other pituitary hormones were within the normal range. MRI revealed a pituitary macroadenoma, for which surgery was not yet indicated.

In order to treat the hypersecretion of GH as the possible basic disease in cardiomyopathy, octreotide treatment was started along with cardioactive medication. Octreotide was continually given as intermittent subcutaneous injection in a dose of 20 μg every 2 h by means of a portable infusion pump (Nipro 3TI) as described previously [16]. During the treatment with octreotide, mean plasma GH, urinary GH and plasma IGF-I levels were effectively lowered from 33.1 ± 1.3 ng/ml to 2.0 ± 0.2 ng/ml, 483.7 ng/day to 38.0 ng/day and 410 ± 20 ng/ml to 140 ± 18 ng/ml, respectively.

After the treatment with octreotide for one year, cardiac size was normalized on chest X-ray (Fig. 1B) and ECG findings were within the normal limit. Echocardiography parameters were gradually improved during the treatment as shown in Table 1. Fractional shortening had remarkably improved from 11% to 38% one year after the start of octreotide treatment. As shown in Fig. 2B, myocardial biopsy revealed that myocardial fibers were almost normaly reconstituted without hypertrophy, although fibrous tissue remained unchanged. Electron micrography showed that neither abnormal nuclei nor lysis of myofilaments was any longer observed in the myocardial cells after octreotide treatment for one year (Fig. 3B). Finally, cardioactive medication was successfully tapered off without any clinical deterioration.

Discussion

Cardiomegaly is commonly found in acromegaly. In the early stage of the disease, increased

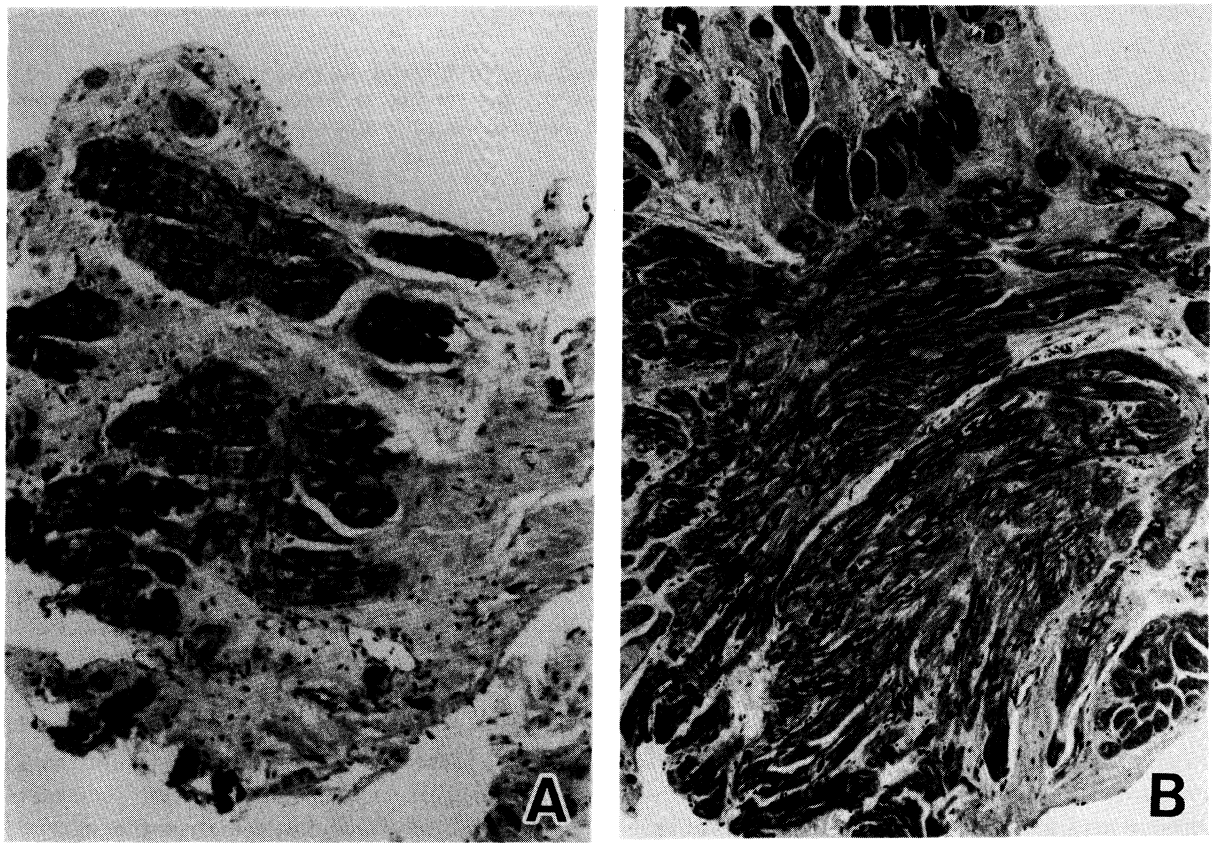

Fig. 2. Hematoxylin-Eosin staining of cadiac biopsy specimens before (A) and after (B) octreotide treatment (× 100). Severe hypertrophy, degeneration of myocytes and extensive fibrous tissue were noted before treatment. Myocardial fibers were reconstituted without hypertrophy after octreotide treatment.

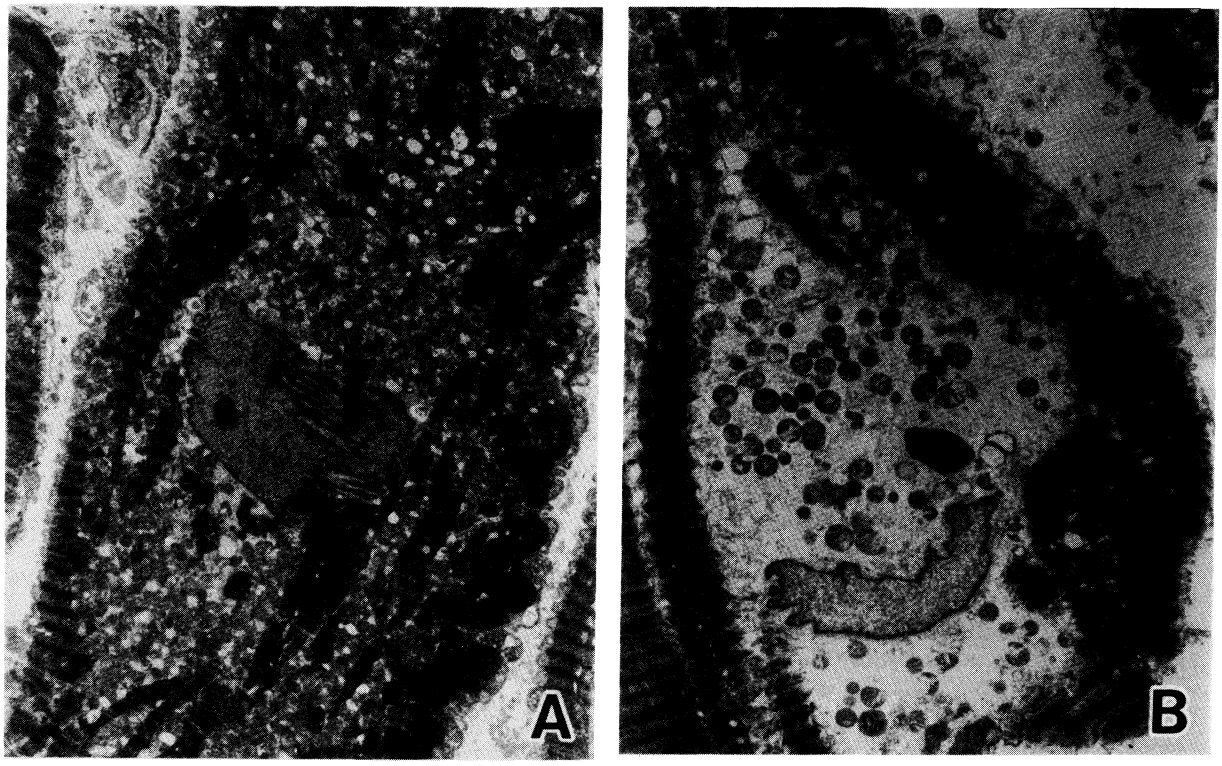

Fig. 3. Electron microscopic view of cardiac biopsy specimen before (A) (× 2000) and after (B) octreotide treatment (× 3000). Huge and bizarre-shaped nuclei and mitochondrial changes in myocardial cells, and lysis of myofilaments were present before treatment. Myofilaments were normally reconstructed after octreotide treatment.

ventricular contractility with high cardiac output is observed [2]. At least two different mechanisms, an increased circulating plasma volume and a direct myocardial effect of GH or IGF-I, have been implicated in the pathogenesis of acromegalic cardiomyopathy. However, Severe congestive heart failure associated with ventricular dilatation and low cardiac output occasionally develops in acromegalic patients, especially those with long duration of the disease [1]. There is no difference in histological findings between acromegalic cardiomyopathy and idiopathic dilated cardiomyopathy [5]. Idiopathic dilated cardiomyopathy was characterized by fibrosis and interstitial infiltration of inflammatory cells. Myocyte changes included various degrees of hypertrophy and atrophy, myofiber disorganization and myocytolysis [14]. In electron microscopy, abnormal arrangements of myofibril, myofibrillary lysis, changes in mitochondria and nuclear changes were seen [15].

Accumulating evidence indicates that octreotide treatment results in suppressed circulating GH and IGF-I levels, shrinkage of pituitary adenoma and improved hemodynamics in acromegalic patients [17]. There have been several reports, however, suggesting deterioration of congestive heart failure by octreotide [9, 11]. This adverse effect could be attributed to a negative inotropic action of somatostatin possibly through a reduction in the transmembrane calcium current, as seen in animal studies [12, 13]. In order to prevent the negative inotropic effect of somatostatin, it was suggested that octreotide treatment should be started after the heart failure has been stabilized especially in acromegalic patients associated with coronary artery diseases or a very low left ventricular ejection fraction [10].

In the present case, an intensive treatment with digitalis, furosemide, angiotensin converting enzyme inhibitors, and anti-arrhythmic agents for three months elicited some clinical improvements. Left ventricular end-diastolic diameter (LVEDD) slightly decreased but the ejection fraction

remained unchanged. After the treatment with octreotide for one year, LVEDD further decreased and the ejection fraction increased to 76%. Cardioactive medication was successfully tapered off without any clinical deterioration. This favorable clinical course after octreotide treatment might be due to an appropriate initial medical therapy for congestive heart failure for three months and the absence of coronary artery disease in the present case.

Interestingly, we found not only functional but histopathological improvement in cardiomyopathy in the present case. After octreotide treatment, nuclear and mitochondrial alterations and lysis of myofilaments were not longer observed. Myocardial hypertrophy and disarray were also improved, but interstitial fibrosis remained unchanged. These findings suggest that morphological abnormalities in acromegalic cardiomyopathy except fibrosis are reversible in the present case. Legrand *et al.* [8] reported that myocardial degeneration was improved in an acromegalic patient associated with severe dilated cardiomyopathy following treatment with transsphenoidal surgery in combination with octreotide. In their case, however, no evident clinical improvement was noted until surgical ablation of the pituitary adenoma following octreotide treatment for three months. The present study, therefore, the first line of evidence indicating that octreotide by itself histopathologically improved acromegalic cardiomyopathy. The role of direct and indirect actions of octreotide in the amelioration of cardiac histology remains unclear. Since both cardiac dysfunction and GH hypersecretion resolved during octreotide therapy, it remains to be further elucidated whether the amelioration of cardiac histology is explained by the direct action of octreotide or the indirect action of the drug through the improved GH-IGF-I axis. It is hypothesized, however, that the indirect action could account for the beneficial effect because successful surgery also reversed histological abnormalities in the reported case [7].

On the other hand, it is on the same lines as the report of Legrand *et al.* [8] that the interstitial fibrosis was irreversible in our acromegalic patient. These findings correspond to clinical findings showing that acromegalic cardiomyopathy the end stage is resistent to cardioactive medication [4, 5] since irreversible myocytosis would be followed by fibrosis the advanced stage.

In summary, a female patient with acromegaly associated with congestive heart failure due to dilated cardiomyopathy was effectively treated with octreotide following intensive cardioactive medication. Myocardial biopsy revealed that histopathological abnormalities except fibrosis were reversibly corrected by the octreotide treatment. Octreotide treatment is therefore useful for acromegalic cardiomyopathy at the stage without coexisting coronary artery disease.

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