Cardiovascular disorders are the leading cause of morbidity and mortality in patients with acromegaly. Acromegalic cardiomyopathy is a distinct entity characterized by specific structural changes like myocyte hypertrophy and interstitial fibrosis of both ventricles and functional changes like diastolic dysfunction followed by systolic dysfunction and finally leading to congestive cardiac failure. Complex ventricular arrhythmia and death follows overt congestive heart failure (CHF), and it is one of the poor prognostic sign of acromegaly. Though prevalence of biventricular hypertrophy present in 90% of autopsied older and 20% of younger patients with acromegaly, presence of overt CHF is less common. The estimated frequency of overt CHF ranges from 1% to 4% in the literature. The literature on prevalence of overt CHF and their outcomes is sparse and none from India till date and hence, this study was planned.

Study design
This is a retrospective analysis of hospital records of consecutive patients with acromegaly between 1996 and 2007 from the acromegaly registry of Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
Patient selection
Records of the patients with the diagnosis of acromegaly and presence of overt heart failure were retrieved from the departmental acromegaly registry. Acromegaly was diagnosed based on elevated IGF-1 compared to age and sex-matched normative data and/or failure to suppress growth hormone (GH) following 75 gm anhydrous glucose load in a patient with signs and symptoms suggestive of acromegaly. These patients were treated as per the standard management of acromegaly including transnasal sphenoid surgery followed by medical and/or radiotherapy for persistent or recurred disease. As per the departmental protocol and pre-operative assessment, all the patients with active acromegaly were subjected for ECG and echocardiography to rule out cardiomyopathy in accordance with standard guidelines. Patients diagnosed to have cardiomyopathy were followed up at regular interval at endocrine and cardiology clinics of the institute, and therapy for cardiomyopathy was decided by the cardiologist. The diagnosis of overt congestive heart failure (CHF) was based on clinical signs as described by Framingham heart study group and the New York Heart Association (NYHA) classification and echocardiography showing a left ventricular ejection fraction (LVEF) of ≤ 45%.

Cardiology assessment
Detailed history, hormonal and radiological investigations and cardiovascular procedures, treatment modalities, and outcomes were recorded separately and analyzed. M-mode, two-dimensional and pulsed doppler echocardiography were done by commercial ultrasound system using 2.5 – MHz transducer in three to five consecutive cardiac cycles. Left ventricular end diastolic diameter end systolic diameter, interventricular septal thickness, left ventricular posterior wall thickness, and left ventricular ejection fraction (LVEF) were recorded. Decision for cardiac catheterization and coronary angiography with left ventricular angiography were taken by the opinion of the cardiologist, and their data were analyzed by them (RBV and KSR).

RESULTS
A total of 150 patients were diagnosed to have acromegaly during the period of 11 years. Of these, 20 had evidences for left ventricular hypertrophy and/or left ventricular diastolic dysfunction (13.3%), 1 had LV systolic dysfunction due to previous coronary artery disease, and 6 patients had evidence of overt congestive heart failure (4%). Out of 6 patients, in 4 patients, congestive heart failure (CHF) was presenting manifestation of acromegaly and 2 developed CHF during the course of the illness. There were 5 males and 1 female with the mean age of 41 ± 17.3 years (range 24-50 years). The lag time before the diagnosis of acromegaly was 7.8 ± 0.8 years. Mean GH level following oral glucose load was 41 ± 17.5 ng/dl (range 12-64 ng/dl). Three patients were hypothyroid, and 2 were hypocortisolic at the time of diagnosis and were on replacement therapy. MRI showed macroadenoma (size > 1 cm) with evidence of apoplexy in 1 case (case 3), and 1 developed apoplexy during hospital admission (case 4). In 1 patient, pituitary was not separately visualized due to fibrous dysplasia involving sphenoid sinus (case 5). Baseline hormonal and radiological profile is shown in Table 1. Four patients had CHF at the time of presentation and 2 developed it during course of illness (case- 2 and 6). Four patients had NYHA class IV dyspnea while 2 had class III, left ventricular ejection fraction was 30 or less with echocardiographical features suggestive of global biventricular hypokinesia in all patients. None of them had electrocardiographical or historical evidence of myocardial infarction. Two patients had history of hypertension and controlled with medications, and 1 had diabetes who was on high dose of insulin (120 units/day) to control his blood glucose. Data on coronary angiography was available in 3 cases, which showed dilated left ventricles with normal coronary arteries in all these cases [Figure 1] and confirmed by autopsy in 1 patient. Out of these 6 patients, the patient with fibrous dysplasia lost to follow up, 1 patient died before planned surgery, and 2 underwent transsphenoidal surgery for removal of pituitary macroadenoma. One patient, already underwent transfrontal surgery for pituitary macroadenoma 6 year back, had recurrence of disease and was presented to

| Case No. | Age/gender | GH  | Treatment | MRI     | NYHA | LVEF | Coronary angiography | HT/DM | Outcome |
|----------|------------|-----|-----------|---------|------|------|----------------------|-------|---------|
| 1        | 42/M       | 40  | TSS       | Macro   | 4    | 20   | DCM + NC             | +/-   | Death (CA) |
| 2        | 38/M       | 51  | TFS/ SA/ TSS | Macro   | 3    | 25   | DCM + NC             | +/-   | Death     |
| 3        | 39/M       | 12  | TSS       | Macro+Apoplexy | 4  | 25   | DCM + NC             | +/-   | Alive     |
| 4        | 35/F       | 37  | -         | Macro+Apoplexy | 4  | 22   | NA                   | +/-   | Death (CA) |
| 5        | 50/M       | 42  | -         | Not visible (fibrous dysplasia) | 3 | 30   | NA                   | +/-   | Lost follow-up |
| 6        | 24/M       | 64  | TSS       | Macro   | 4    | 26   | NA                   | +/-   | Death (CA) |

M: Male, F: Female, GH: Nadir growth hormone after 75 gm oral glucose, LVEF: Left ventricular ejection fraction, HT: Hypertension, DM: Diabetes, TSS: Transphenoidal surgery, TFA: Transfrontal surgery, SA: Somatostatin analogue, Macro: Macroadenoma, DCM: Dilated cardiomyopathy, NC: Normal coronary arteries, NA: Not available, CA: Cardiac arrhythmia
CHF after 6 years, he was given somatostatin analogues in interim period and after stabilization of general condition, he underwent transphenoideal surgery (case 2). Another patient underwent TSS 1 year back before he presented with CHF, and he died before investigation and management was contemplated. Of 5 cases available for outcome analysis, only 1 patient is alive (case 3). He was young with short duration of acromegaly and treated timely and did not have other risk factors like hypertension and diabetes, furthermore, his GH levels were lowest compared to other 5 patients after 75 gm oral glucose load. After trans-sphenoidal surgery, GH normalized, and at 3 month, left ventricular ejection fraction improved to 35% from 25% at baseline and furthermore, there was normalization of cardiac size on serial chest X-ray [Figure 2]. Three patients died of ventricular arrhythmias and 1 due to sepsis and CSF over drainage from lumber drain. One patient died of apoplexy followed by ventricular arrhythmia, and autopsy was performed in this case (case 4). Autopsy confirmed normal coronaries, severe concentric biventricular hypertrophy, myofibrillar necrosis, and interstitial fibrosis [Figure 3].

**DISCUSSION**

We report 6 cases of overt congestive heart failure out of 150 cases of acromegaly (4%). Mortality due to cardiac arrhythmias is very high in these cases. Only 2 patients had hypertension, and 1 had diabetes.

Cardiovascular disorders are the leading cause of mortality in acromegaly. Most common cardiovascular manifestation is biventricular hypertrophy independent of hypertension. Clinical symptoms and signs of heart failure were found in about 10% of newly diagnosed acromegaly, and they were characterized by normal systolic function implying high output failure. However, the overt CHF were reported as less than 1% in one study, while another recent study estimated its prevalence as 4%. Our study finds prevalence of overt CHF as 4%, which is in consonance with later study.

Diabetes mellitus and systemic hypertension are independent risk for morbidity and mortality, and they aggravate the heart failure. However, in present study, only 1 had diabetes and 2 had hypertension suggesting elevated GH is most important factor for overt CHF. Serum GH and IGF 1 levels are independent predictors of mortality in acromegaly. GH and IGF-1 have been shown to cause hypertrophy of rat cultured cardiomyocyte. Normalization of GH and IGF levels either with medical or surgical management have been shown to reverse the cardiac manifestation effectively and reduce morbidity and mortality. All our patients had active disease, and growth hormone level was very high. Somatostatin analogues normalize GH and IGF-1 levels in 60-70% of cases and with short treatment of 1-3 months have been shown to reduce LV posterior and interventricular wall thickness, and more significant effect is achieved with long-term treatment. The main obstacle in using these analogues in India is high cost. We used somatostatin analogue in one patient to normalize GH and stabilization of CHF before surgery.

Biopsy and autopsy studies indicate that interstitial fibrosis is the main histological features that gradually impair architecture and function. Other histological features are increased extra cellular collagen deposition, myofibrillar derangement, and areas of lymphocytic infiltration gradually impairing whole architecture. Generally, coronary arteries remain uninvolved as is evident by normal epicardial coronaries in all our 3 patients who underwent angiography and 1 patient at autopsy. Echocardiography shows initial cardiac chamber enlargement followed by diastolic dysfunction and at the end, global hypokinesia with component of systolic dysfunction. The cardiac function can be restored to normal with control of the disease. In all studies, diastolic dysfunction improved,
but ejection fraction and exercise performance remained variable.\[15\]

The prevalence of cardiac arrhythmias in acromegaly was reported between 3.7\% in one study and\[6\] 48\% in another.\[16\] In our study, 50\% of patients died of refractory ventricular arrhythmias. The increased frequency is thought to be due to the abnormal remodeling of the ventricular wall.

This is the first study from India to examine prevalence of CHF in large number of acromegaly patients with complete work up including angiography data and autopsy finding in one. These are the strength of the study. However, retrospective nature and lack of comparative group are the limitations.

In conclusion, prevalence of overt CHF is 4\% in present series. Overt CHF is associated with high mortality and hence, this complication should be recognized at earliest and medical management to normalized cardiac function should be given utmost priority.

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