

Case Series

Recognizing the Diverse Clinical Presentations of Acromegaly: Insight from a Case Series

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Abstract:

Purpose: Acromegaly is an endocrine disease due to growth hormone excess with slowly developing manifestations and diverse clinical presentations. There are chances that patients may present with common clinical problems and the underlying endocrine condition is overlooked and diagnosis is delayed. This case series will discuss the presentation, clinical features and investigations of four acromegaly cases to increase the clinical skills of physicians so that an early diagnosis is made and treatment is initiated early.

Methods: This is an observational study, where a series of four acromegaly cases, who presented to medicine inpatients or outpatients of Sylhet Women's Medical College, Bangladesh. They were analyzed through detailed clinical features and, investigation findings. MRI brain was used as the main tool for diagnosis. Serum levels of growth hormone, IGF-1, TSH, ACTH, and prolactin were assessed in all. Other anterior pituitary hormone assays were selectively done. Ocular examinations were performed on all patients.

Conclusion: Though a case series has lower value as medical evidence than systematic reviews and randomized clinical trials, it can help in generating future protocols of studies. This series emphasizes that a keen clinical eye of the physician can help in early diagnosis of acromegaly and thus an early MRI of brain based on clinical suspicion can ensure early treatment and prevent cardiovascular complications.

Key words: Acromegaly, Pituitary, Growth hormone, IGF-1, Macro-adenoma, Bitemporal hemianopia, Pituitary apoplexy

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Introduction:

Acromegaly is a clinical condition resulting from excessive growth hormone secretion, usually from a pituitary adenoma.

Its annual prevalence is 50-80 per 100,000 population across the globe¹ and, it has a diverse clinical presentation that might involve, almost all systems of the body. However, the facial and acral features are striking and a careful look often illuminates a diagnosis.^{2,3} Excepting the pituitary hyper-secretory condition before closure of epiphysis called gigantism, the median age of presentation of acromegaly is between 40 to 50 years.⁴ There is no significant gender preponderance but, the female patients were found to be older at diagnosis.⁵ Majority of the pituitary tumors which are benign and monoclonal in origin, are macro-adenomas at diagnosis.⁶ So early brain MRI with a focus on the pituitary fossa plays an important role in early diagnosis,⁷ which is very important because acromegaly progressively decreases quality of life and decreases life expectancy as well.⁴ These patients invariably have raised growth hormone levels and, its target, the serum IGF-1 levels. Other pituitary hormones i.e. prolactin, ACTH, TSH, FSH, and LH are also increased in the serum but at variable proportions.⁸ Headache, sweating, increasing the

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size of the body, joint pain, visual problems, hypertension, diabetes mellitus, heart failure, and respiratory failure are in most cases the presenting clinical conditions.^{1,2,3} The majority of these are common conditions in medical practice and thus, there are chances that the underlying growth hormone excess might escape consideration.^{9,10} This article presents the clinical details of four acromegaly patients, not presenting to an endocrinologist but to the internal medicine department with apparently 'common' medical issues. However, the external features in all of them were quite obvious for suspecting the underlying diagnosis of acromegaly. This article could be a valuable insight developer for an internist as well as an endocrinologist.

Methodology:

This is an observational study, where a series of four acromegaly cases, presenting to medicine inpatient or outpatient facilities of Sylhet Women's Medical College, Bangladesh, were analyzed through detailed clinical features and, investigation findings. The purpose was to observe the diversity and similarities in their presentations, clinical features, and biochemical and radiological parameters. Informed consent was taken from individual patients. The growth hormone and IGF-1 levels were measured at baseline without any glucose load by chemiluminescence EIA method at BIRDEM hospital. Serum ACTH, TSH, cortisol and prolactin levels were measured in all patients. Other hormone tests were done selectively. All patients were subjected to evaluation of the pituitary gland and sella turcica by MRI. And perimetry was performed in all.

The summary of cases

Case 1

A 29-year-old woman presented to medicine outpatient with poorly controlled hypertension for 3 years. She complained of occasional headaches and neck pain for the previous 3 months. She was a widowed homemaker with 3 kids. She had been on daily doses of bisoprolol 5mg, amlodipine 10mg and, olmesartan 40mg. On examination, her blood pressure was 180/100 mmHg and her GCS was 15. She had no focal

neurological features. She had coarse facies with thick lips, a protruded jaw, a broad nose and large hands (Figure 1). Her fundus was normal, but she had double arcuate visual field defect on perimetry (Figure 2). X-ray skull lateral view showed widened and deepened pituitary fossa but the heel-pad-thickness in the X-ray foot was normal (Figure 3). MRI of the brain revealed a lobulated mass measuring 2.3x2.0x2.0 cm in the sellar region with supra-sellar and parasellar extension (Figure 4). The lesion appeared iso-intense through T1WI, T2WI and, intermediate signal on FLAIR images. The post-contrast image showed moderate homogeneous enhancement of the lesion. Features suggested the diagnosis of pituitary macro-adenoma. She was a non-diabetic person but, her fasting blood glucose level was 9.1 mmol/L and HbA_{1c} was 6.1%. Serum growth hormone (60.8 ng/ml) and, serum IGF-1 (657ng/ml) levels were high. Serum Prolactin (33.9 ng/ml), ACTH (20 pmol/L) and Cortisol (678.69 nmol/l) were also high but serum TSH (0.96 mIU/ml), T3 (1.95 nmol/l), T4 (123.21 nmol/l), FSH (1.12IU/L) and, LH (1.07 IU/L) were within normal range. She was referred to BSSMU and there she underwent trans-sphenoidal pituitary adenectomy after 6 months of diagnosis.

Figure 1: a. coarse facies b. large hands c. prognathism

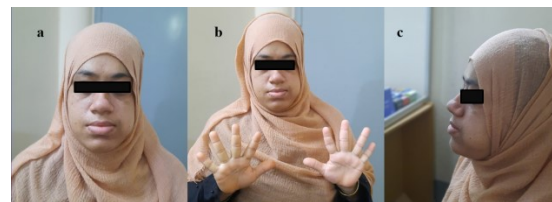


Figure 2: a. Fundal photograph and b. Perimetry

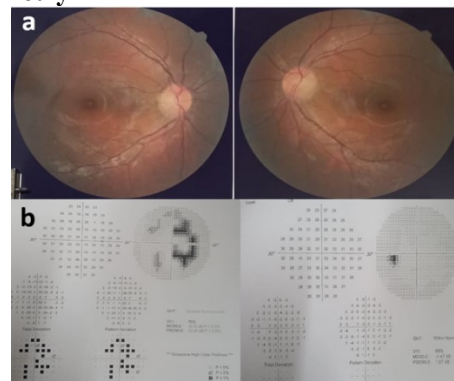


**Figure 3: a. X-ray foot: normal heel-pad-thickness
b. X-ray-skull lateral view: wide and deep pituitary fossa**

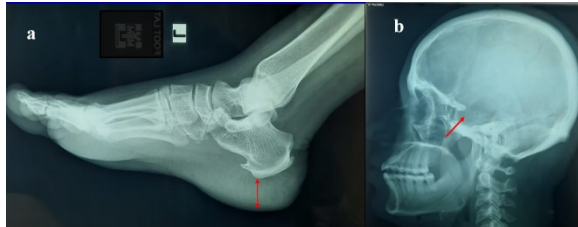
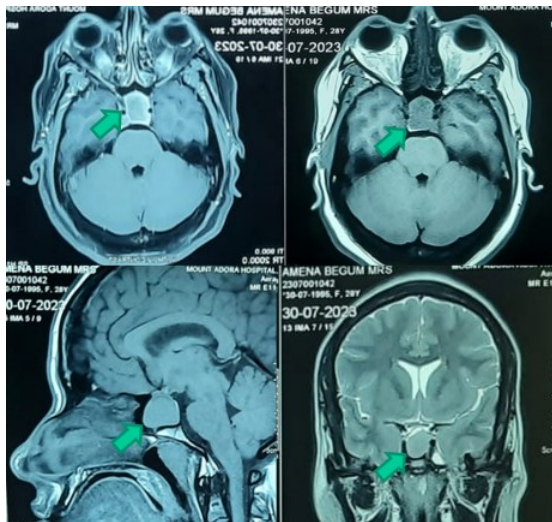


Figure 4: Sellar mass on MRI brain (arrow)



Case 2

A 55-year-old so far healthy lawyer with excessive sweating for 6 months and unexplained restlessness and insomnia for 1 month. But there was no intolerance to heat or weight loss. Rather, he gained 5 kilograms of body weight in the previous month. No anxiety, stressful life event or depression relatable to his symptoms, were found. His general physician treated him with multiple anxiolytics but, with no remarkable improvement. He had been a heavy smoker with an 18-pack-year history of smoking. But he never consumed alcohol or any other abusive substance. He was normotensive and non-diabetic. He experienced occasional dizzy spells but had no headache, focal weakness or, visual disturbance. He also did not have any fever, vomiting, cough, sputum, hemoptysis, breathlessness, chest pain, arthralgia, bowel disturbance and, urinary

problem. On examination, he looked robust with thick lips, broad nose, and thick greasy skin with deep furrows. He had a large tongue, prominent supra-orbital ridges, slightly protruded lower jaw, widely set teeth (Figure 5) and, large hands and feet (Figure 6). He had normal vitals and normal systemic examination features. His visual fields were normal and, fundoscopic findings were unremarkable. He was admitted in medicine inpatient for evaluation.

With a high degree of clinical suspicion for acromegaly, skeletal radiographic features were explored. X-ray of hands showed enlarged base of phalanx, whereas X-ray of feet revealed overgrowth of metatarsal and tarsal bones but, the heel-pad-thickness was within normal limit (Figure 7). X-ray skull showed a thickened vault and widened and deepened sella turcica (Figure 8a). MRI of brain revealed a sellar mass consistent with pituitary macro-adenoma with a 2.1x1.8x1.2cm dimension (Figure 8b). His serum growth hormone (11.7 ng/ml) and IGF-1(123.2 ng/ml) levels were raised but, serum prolactin (11.3 ng/ml), serum TSH (0.46uIU/ml), ACTH (15.2 pmol/L) and cortisol (204 nmol/L) levels were normal. He underwent transphenoidal removal of pituitary adenoma in a private specialized center within 2 months of diagnosis. The excised tumor was macroscopically a grayish firm pituitary tumor and the histopathology report was consistent with pituitary adenoma devoid of any evidence of malignancy.

Figure 5: a. Widely spaced teeth b. Large tongue c. Prognathism



Figure 6: a. Large hands and b. Large feet

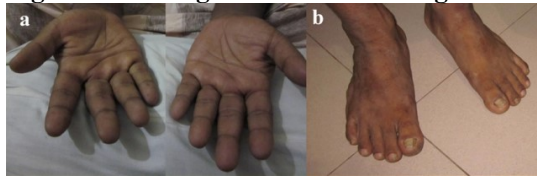


Figure 7: a. X-ray hands: enlarged base b. X-ray feet: over-grown tarsals and metatarsals

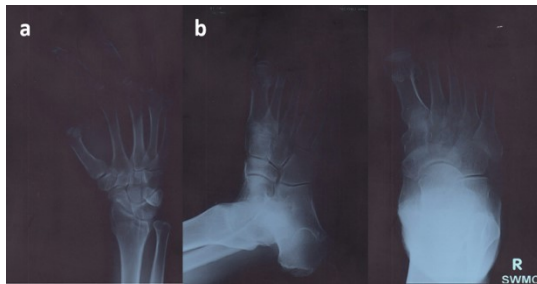
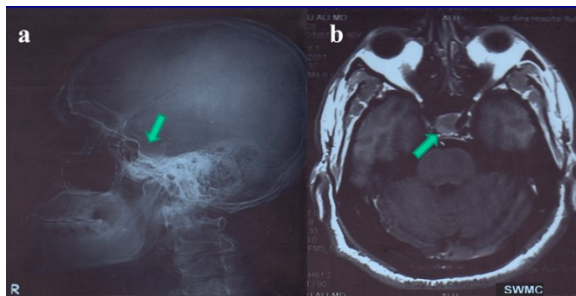


Figure 8: a Wide pituitary fossa b. Sellar mass (arrow)



Case 3

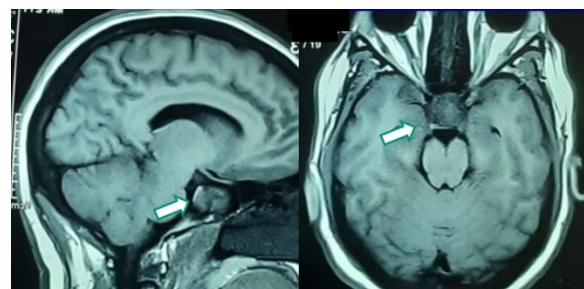
A 52-year-old man, who had been hypertensive and diabetic for 5 years, presented to the medicine inpatient with loss of consciousness for one hour preceded by vomiting and convulsion. He had been on daily doses of gliclazide 80mg and metformin 1000mg for diabetes and ramipril 5mg for hypertension. There was a history of inadequate meals before this event. Apart from his diabetes and hypertension, he had no other complaint of note except for a constant dull aching headache for the previous 5 years. He had been a smoker (10-pack-year), but non-alcoholic. He gave no family history of hypertension or diabetes. On examination, he had a large coarse face with prominent supraorbital ridges. His lips were thick, nose was broad and ears were large

(Figure 9a). He had prognathism (Figure 9b), spade-like hands (Figure 9c), macroglossia and, acanthosis nigricans. His thyroid gland was normal. His GCS was 6, blood pressure was raised (160/100 mmHg) but had normal body temperature (98.3°F) and, had no neck stiffness or any focal neurological findings. His random capillary blood glucose level was 2.5 mmol/l. His GCS score improved to 14 rapidly after glucose infusion. His fundus revealed bilateral retinal exudates and hemorrhage and confrontation test showed bi-temporal visual field loss. Due to the obvious clinical features of acromegaly in this patient, MRI of brain was done which revealed pituitary macroadenoma (Figure 10) with 2.2x1.9x1.6cm dimension with supra-sellar extension. His serum growth hormone, IGF-1, prolactin levels were 22.3 ng/ml, 99 ng/ml and 67ng/ml respectively. Other anterior pituitary hormones-serum TSH (1.2 mIU/ml), ACTH (16.1 nmol/L) were within normal ranges. His serum cortisol (233nmol/L) was also within normal range. He was referred to a higher neurosurgical facility but he refused any further evaluation and intervention for the time being. He was discharged with initial 2.5 mg dose of bromocriptin at bed time.

Figure 9: a Thick lips, broad nose, and prominent supra-orbital ridge b. Prognathism c. Spade-like hands



Figure 10: Pituitary macro-adenoma (arrow)



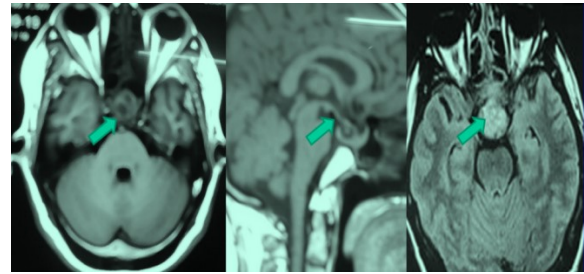
Case 4

A 60-year-old non-diabetic, normotensive woman came to medicine outpatient with complaints of sudden severe headache, vomiting and visual disturbance. She was a visitor in the city who arrived only a couple of days before. She gave no history of any health problems except for occasional tingling and numbness in both hands for the last 3 months. She neither took any hormonal medicine nor did she experience any head trauma. On examination, she was restless but had normal blood pressure (130/70 mmHg), and normal body temperature (97.5oF). She had mild neck stiffness, and had diplopia on the left lateral gaze, but had no visual field defect and, fundoscopic findings were normal. No other focal neurological signs were present, except for a bilateral Tinel's sign. Her random capillary blood glucose level was 9.3 mmol/L. She was admitted to medicine inpatient for further evaluation and management. She had coarse facial features with thick sweaty greasy skin, deep wrinkles and, a large jaw and hands (Figure 11). Her X-ray skull lateral view was normal, but an MRI brain revealed pituitary macro-adenoma (2.3x1.1x1.7 cm) with a few necrotic/infarcted areas in the T1WI, which was intensified on T2WI (Figure 12). She had elevated serum growth hormone (37ng/ml), IGF-1 (220 ng/ml) and, prolactin (140 ng/ml) levels. But her serum ACTH (11 pmol/L), TSH (0.75 mIU/ml), T3 (1.02 nmol/l), T4 (104.29 nmol/l) and, cortisol (144nmol/L) were normal. She was managed as a case of pituitary apoplexy with oral steroids. On alleviation of symptoms, she was promptly referred to a higher center for surgical intervention.

Figure 11: Coarse facies and spade-like hands



Figure 12: Pituitary macro-adenoma with areas of necrosis (arrows)



Results:

The four acromegaly patients, two males and two females, presented with quite diverse medical issues- case 1 presented with uncontrolled hypertension, case 2 had unexplained sweating, case 3 presented with hypoglycemic coma and case 4 had pituitary apoplexy. Headache was a common symptom among them. One of them had both hypertension and diabetes mellitus, one had hypertension and impaired fasting glucose and, the rest had none of these. The mean duration of symptom(s) was 25.5 months and, the mean age at presentation was 49 years but, only one patient was less than 50-year-old. All four cases had weight gain, coarse facial features, and big hands and feet. One of them had bitemporal hemianopia, one had double arcuate visual field defect and, the remaining patients had normal visual fields. One of the patients had features of carpal tunnel syndrome, one had acanthosis nigricans and, one had neck ache. None of the patients had heart failure. All the cases had pituitary macro-adenoma on MRI brain, the average size of adenoma was 2.23x1.7x1.63 cm. All of them had raised serum levels of growth hormone and IGF-1. However, among the other anterior pituitary hormones, prolactin was raised in 3 patients and ACTH was raised in one patient. The symptoms, signs, and investigation findings of the cases have been summarized in Tables 1, 2 and 3 respectively.

Table 1: Summary of symptoms of the series

Traits	Case 1	Case 2	Case 3	Case 4
Headache	+	-	+	+
Dizziness	-	+	-	-
Paresthesia	-	-	-	+
Weight gain	+	+	+	+
Visual disturbance	-	-	-	+
Sweating	-	+	-	-
Fatigue	+	-	-	-
Unconsciousness	-	-	+	-
Arthralgia	+	-	-	-
Hypertension	+	-	+	-
Diabetes	-	-	+	-
Smoking	-	+	+	-
Duration (months)	36	06	60	00

Table 2: Summary of physical findings of the series

Traits	Case 1	Case 2	Case 3	Case 4
Age at presentation (years)	29	55	52	60
Facial features	+	+	+	+
Spade hands	+	+	+	+
Large feet	-	+	+	+
Visual field defect	+	-	+	-
Other neurologic feature	-	-	-	Tinel's sign
Hepatomegaly	-	-	-	-
Heart failure at presentation	-	-	-	-
Acanthosis nigricans	-	-	+	-
Blood pressure (mmHg)	180/100	130/80	160/100	130/70
GCS at presentation	15	15	6	15

Table 3: Summary of investigations of the series

Traits	Case 1	Case 2	Case 3	Case 4
Random blood glucose at presentation (mmol/L)	8.0	6.0	2.5	9.3
X-ray hands tufting of terminal phalanges	+	-	-	+
X-ray hands enlarged carpal bones	+	-	-	+
X-ray foot- increased heel pad thickness	normal	normal	normal	normal
X-ray foot thick tarsals and metatarsals	+	-	-	-
X-ray skull showing wide pituitary fossa	+	+	-	-
MRI brain showing macro-adenoma (cm)	2.3X2.0X2.0	2.1X1.8X1.2	2.2x1.9x1.6	2.3x1.1x1.7
Serum GH (ng/ml)	60.8	11.7	22.3	37
Serum IGF-1 (ng/ml)	657	123.2	99	220
Serum TSH (mIU/ml)	0.96	0.46	1.2	0.75
Serum ACTH (pmol/L)	20	15.2	16.1	10
Serum Cortisol (nmol/L)	678.69	204	233	144
Serum Prolactin (ng/ml)	33.9	11.3	67	140

Discussion:

Pituitary adenomas are benign tumors of unknown etiology which can be secretory or non-secretory. It is the secretory adenoma that produces excessive anterior pituitary hormones.^{8,11} The excess growth hormone produced from it with or without over-secretion of other anterior pituitary hormones, leads to acromegaly.^{6,12} Both secretory and non-secretory varieties of adenoma may cause compression over surrounding structures, especially the optic chiasma due to its anatomical proximity to the gland. The diagnosis of acromegaly may be delayed up to many years due to the slow and delayed development of clinical features.¹³ Moreover, diabetes and hypertension and their related health problems are common among these patients which may obscure it from the attention of the healthcare professionals. This delay causes late surgical intervention and thus, can impart unfavorable effects on prognosis.¹⁴ As growth hormone is a somatotrope, the main feature of its excess is an enlargement of almost all body tissues causing an increase in the size of the body.⁸ A fully grown adult individual can experience an increase in garment or shoe size, and tightening of rings due to this condition. Prominent supra-orbital ridges, broad nasal

bridge, thick lips, large tongue, malocclusion of teeth and, prognathism are the common facial features that make diagnosis from facies easy sometimes.¹⁵ There is a popular saying that acromegaly patients conform more to each other than they resemble their relatives. The acral parts- the hands and feet are large regarding ethnicity and constitution of the patient.^{16,17} The mass effect of the pituitary adenoma produces visual disturbance in one-third to two-thirds of the patients. It is more so with the supra-sellar extension of the tumor. The classical ocular complication of acromegaly is bitemporal hemianopia type of visual field defect due to compression on the optic chiasma. Moreover, long-standing compression may lead to optic atrophy and blindness.^{18,19} In two of the reported cases of this article, there was visual field defect, one patient had the classical bitemporal type and the other had the double arcuate type of visual field loss.²⁰ One patient had diplopia on the left lateral gaze that might be due to compression of the oculomotor nerve. However, other cranial nerves that may be affected in acromegaly are trochlear, trigeminal and abducent due to tumor extension. Headache is common among patients mainly due to compression of the sellar diaphragm. Sweating is also a common symptom at presentation.^{13,15} Three of the four cases had headaches and one had sweating at presentation.

Both diabetes mellitus and hypertension are prevalent among acromegaly patients. In one RCT the prevalence of diabetes (52.5%) among acromegaly patients was significantly ($P < 0.001$) higher than the prevalence (14.3%) among the normal population.²¹ In another trial, the investigators found that 46% of acromegaly patients had high blood pressure in contrast to 25% of the controls ($P < 0.0001$).²² In the index article, the authors found two cases to be hypertensive, one diabetic, and one prediabetic. Both diabetes and hypertension were present in one of them.

Radiology plays an important role in the diagnosis of pituitary tumors. In the last quarter of the last century, observation of the radiological details of sella turcica was a useful means of diagnosing pituitary tumors.²³ Enlarged thickened skull bones, prominent frontal sinuses, enlarged mandible, and widened

pituitary fossa, its double floor and loss of clinoid processes are the few plain radiographic marks for diagnosis.²⁴ But owing to the low sensitivity of this test, MRI brain has taken its place as the investigation of choice now.^{7,10,15} All four of the reported cases in this study had macro-adenoma on MRI but only two of them had suggestive radiological features on skull radiograph.

Almost all acromegaly patients have raised growth hormone and IGF-1 levels. These assays, if done after loading a dose of glucose, yield more accuracy. The growth hormone secretion in our body occurs in a pulsatile manner, so it shows diurnal variations in test levels.⁴ On the other hand, the IGF-1 levels are subjected to minor variations which renders this test more reliable in clinical practice. Moreover, the degree of rise of IGF-1 level of an acromegaly patient at presentation correlates better with the failure to respond to surgery. Trans-sphenoidal pituitary adenoma resection is the treatment of choice.¹⁹ The medical treatment of acromegaly, though less efficacious than the surgical approach, focuses on reducing the growth hormone secretion from the pituitary.²⁵ Indirect inhibitors of growth hormones include the somatostatin analogs and dopamine agonists. The somatostatin analogs like octreotide and lanreotide produce better responses than the dopamine agonists like cabergoline and bromocriptine.^{4,19,26} A growth hormone receptor antagonist, pegvisomant, administered through injections, directly blocks the growth hormone receptors and thus blocks its effect. Medical therapies can reduce the serum IGF-1 level and alleviate the symptoms of growth hormone excess.²⁷ Three patients in the index report underwent surgical treatment and in one patient surgical treatment was held, due to financial causes and the patient's choice.

Pituitary apoplexy is one special entity of acromegaly cases with pituitary macro-adenoma where there is sudden enlargement of the gland usually due to hemorrhagic infarction. In some cases, necrosis occurs in the absence of any hemorrhage. These patients classically present with sudden severe headaches, and visual disturbance either in the form of a chiasmal type of field defect or ophthalmoplegia due to ocular cranial nerve palsy.²⁸ Sometimes there is

unconsciousness, Addisonian crisis and neck stiffness due to irritation of the subarachnoid area in apopleptic patients. One of the reported cases, with no previous feature or diagnosis of acromegaly, presented with features of apoplexy with non-hemorrhagic infarct in pituitary adenoma on MRI.²⁹ There is evidence, these patients improve in terms of elevated hormone levels and clinical features spontaneously after an apoplexy event.³⁰ The reported case with apoplexy was referred to a higher center but unfortunately, was lost to follow-up.

Mortality in acromegaly is largely due to the development of cardiovascular complications. In a cohort study on 1874 acromegaly patients, significantly higher rates of atrial fibrillation, heart failure and all-cause mortality were observed as compared to the general population.³¹ Early recognition and intervention can save these patients from premature deaths from cardiovascular complications.

Conclusion: Though a case series has lower value as medical evidence than systematic reviews and randomized clinical trials, it can help in generating future protocols of studies. This series emphasizes that a keen clinical eye of the physician can help in early diagnosis of acromegaly and thus an early MRI of brain based on clinical suspicion can ensure early treatment and prevent cardiovascular complications. None of the patients presented to an endocrinologist, but presented to an internist seeking medical assistance for an ordinary-looking medical problem. So, it is the responsibility of a good internist to look beyond the horizons of simplicity.

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