

# Diagnosis and Management of Acromegaly: Giant Invasive Adenoma

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## ABSTRACT

*Acromegaly is a rare disorder caused by excessive growth hormone. Majority of acromegaly are due to pituitary adenoma. It is estimated that 5% of pituitary adenoma become invasive and may grow to gigantic sizes (>4 cm in diameter). We would like to describe a man with giant invasive adenoma.*

*We describe the case of 52-year-old man with acromegaly. The patient was presented to medical care because of hemichorea. He also had visual field defect, uncontrolled diabetes, and dyslipidemia. Hormonal profile showed increment of GH 2-hour after a standard 75-g oral glucose load and of high IGF-1 level with low level of FSH and LH. The next was performed by pituitary imaging. Magnetic resonance imaging showed a macroadenoma with diameter 2.3x3.5x6.6 cm<sup>3</sup> that fills the sella tursica, and enlarges into suprasella, genu of corpus collosum, and invades third ventricle.*

*This report describes a rare case of acromegalic patient with giant invasive adenoma. This could be a demonstrative case and lesson for diagnosis and manage acromegalic patient.*

**Key words:** *acromegaly, giant, pituitary, adenoma, hemichorea.*

## INTRODUCTION

Acromegaly is a rare disorder with an estimated incidence of 3 to 4 cases per million people and prevalence 33 case per million population. Acromegaly develops when somatotrophs (cells in the anterior pituitary gland that produce growth hormone) proliferate and oversecrete the hormone. The constellation of clinical pictures of acromegaly results from hypersecretion of growth hormone (GH) and insulin-like growth factor (IGF-1). Almost 98% of cases, the cause of the GH hypersecretion is a pituitary adenoma. Other causes rarely found are ectopic GHRH production by lung or pancreatic tumor.<sup>1-4</sup>

The term acromegaly derived from the Greek *akron* (extremity) and *megale* (great), that describe part of clinical features found in acromegaly patient. Clinical findings found are due to local growth of the tumor and hypersecretion of GH. Local growth of the tumor will invade adjacent structure that would manifest like headache, visual field defect, and cranial nerve palsies. Less common symptoms depend on the extent and direction of tumor growth like cognitive abnormalities, generalized seizure, or hemiparesis.<sup>2</sup>

Hypersecretion of GH has wide manifestations since it affects many organs. Some of GH action mediated from IGF-1, produced in the liver. We could find enlargement of the hands, feet, and bones of the face. The patient could also complain of carpal tunnel syndrome, arthritis and athralgias, hypertension, glucose intolerance, hyperhidrosis, oily skin, and diabetes mellitus.<sup>2,3,5</sup>

The morbidity and mortality associated with acromegaly are due to both the metabolic consequences of GH hypersecretion and mass effects from the tumor.

The mortality rate of patients with acromegaly is 2 to 4 times higher than healthy subject. Appropriate treatment would lead to normalize serum IGF-1 and GH level would reduce the morbidity and mortality rate.<sup>6</sup>

In foreign literature, it is written that about 40% of acromegaly cases are initially diagnosed by an internist. Meanwhile, the rest are diagnosed when patients are seen by ophthalmologists for visual disturbances, by dental surgeons for bite disorders, by gynecologists for menstrual dysfunction and infertility, by rheumatologists for osteoarthritis, or by sleep-disorder specialists for obstructive sleep apnea.<sup>4</sup> So, it is important for internists to recognize the acromegalic patients and to treat them appropriately in order to reduce mortality and morbidity rate in those patients.

This case report will describe acromegalic patient with giant invasive adenoma presenting with movement disorders and diabetes mellitus. This case report will discuss about clinical feature, diagnosis, and treatment aspect.

#### CASE ILLUSTRATION

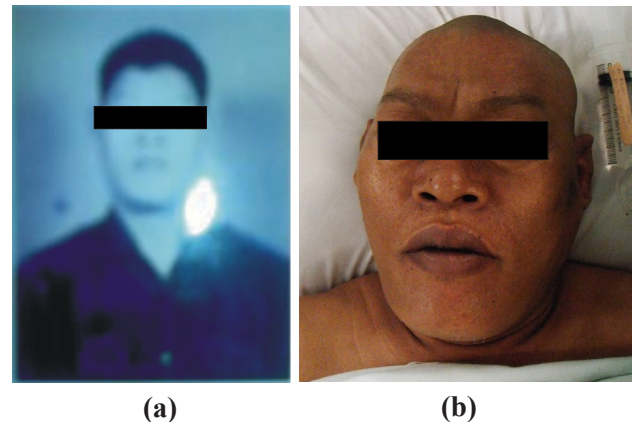
A 52-year-old man was admitted to the hospital with abnormal movement of his left upper extremities since one day before admission. The patient couldn't afford his left arm to move. During abnormal movement episodes the patient was conscious. There was not hemiparesis or seizure. There wasn't prior history of head trauma. One year before the patient also had same complains. At that time the patient was diagnosed pituitary macroadenoma and was planned to go through surgical treatment, but the patient refused.

Two years before, he had been diagnosed diabetes mellitus and had been prescribed metformin and insulin for glucose control, but it was not regularly used. He also had felt weakness, increased appetite and thirst, hyperhidrosis, impotency, visual field defect, oily skin, and teeth loss. During night her wife also heard him snoring. Sometimes the patient had headache that felt like cramp. The abdomen started distended.

The symptoms was firstly noted at about nine years ago when the patient reported increasing of shoe size. He also felt that the face and voice began to change.

The patient appeared weak. He was 174 centimetres tall and weighted 85 kilograms, with body mass index 28,07 kg/m<sup>2</sup>. On initial examination, his blood pressure was 120/80 mmHg, heart rate was 88 bpm and respiratory rate was 24/minutes. His temperature was 36,4°C. The skin was oily and sweaty. Physical

examination showed an acromegalic appearance. Facial changes observed include large lips and nose, wide nasal bridge, protruding jaw and frontal skull bossing (**Figure 1**). Other marked abnormalities that found in physical examination were enlargement of hands, foot, and abdominal distension (**Figure 2**).



**Figure 1.** The facial change (a) old picture before the acromegaly sign appeared (b). after the patient suffered acromegaly, discovered wide nasal bridge, large lips and nose, frontal skull bossing, and protruding jaw.



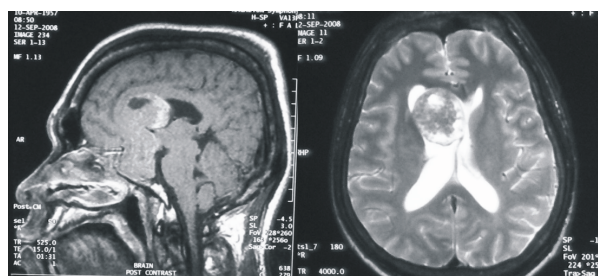
**Figure 2.** The enlargement of foot, compare with healthy subject.

Laboratory studies revealed a blood glucose level of 575 mg/dL with positive ketone and normal blood gas analysis. Hormonal profile showed increment of growth hormone level 2-hour after a standard 75-g oral glucose load (glucose-tolerance test) and of IGF-1 level with low level of FSH and LH (**Table 1**). Other marked abnormalities were high cholesterol and triglyceride level, 299 mg/dl and 660 mg/dl consecutively.

**Table 1. Hormonal profile**

Hormone	Level	Normal range
Prolactin	7,83 ng/ml	4,04-15,2
Growth Hormone	>200 ng/ml	<1
IGF-1	589 ng/ml	90-360
Cortisol	11,9 ug/dl	5-25
FSH	0,63 mIU/ml	1,5-12,4
LH	0,21 mIU/ml	1,7-8,6
TSHs	0,851 uIU/ml	0,27-4,20
fT4	1,01 ng/dl	0,93-1,70

Electrocardiography and chest x-ray examination revealed normal result. Magnetic resonance imaging (MRI) scan showed a macroadenoma of pituitary gland with diameter 2.3x3.5x6.6 cm3 that fills the sella tursica, and enlarges into suprasella, genu of corpus collosum, and invades third ventricle. The lesion was enhanced with contrast administration (**Figure 3**).



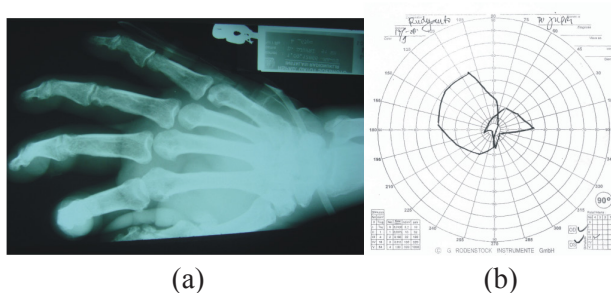
**Figure 3.** Macroadenoma of pituitary gland with diameter 2.3x3.5x6.6 cm3 that filled sella tursica, enlarge into suprasella, genu of corpus collosum, and invade third ventricle.

Based on medical history, clinical manifestasion, and initial workup, patient was assessed as: movement disorder, diabetic ketotic, acromegaly, obese, and dyslipidemia. For further evaluation we planned to consult departement of neurosurgery, neurology, ophtalmology, pulmonology dentistry, dermatology, and cardiology consultation. Manus x-ray, abdominal ultrasound, echocardiography, and colonoscopy were planned.

The patient was treated with intravenous insulin to control blood glucose level, bromocriptine twice daily with incremental dose, metformin 500 mg twice daily, gemfibrozil 300 mg twice daily. Surgical removal of the tumor with transcranial approach was planned.

At the beginning of treatment, the abnormal movement was diminished. During hospitalization the patient experienced seizure. Blood glucose level hardly controlled with intravenous and subcutaneous insulin injection. The patient got intravenous insulin up to 20 unit/hour with subcutaneous injection 30 unit three times daily. Blood glucose level was varying between 69 mg/dl until 638 mg/dl. Blood ketone examination showed negative result.

Additional imaging studies revealed some abnormalities. Manus x-ray showed cortex thickening and abdominal ultrasound found severe fatty liver with simple left renal cyst. Further evaluation along with colleagues from other departments found peripheral sensoric and motoric neuropathy, dermatitis akneiformis, diabetic retinopathy, gingivitis, and bitemporal hemianopia (**Figure 4**). Echocardiography and colonoscopy were not performed.



**Figure 4.** (a) Manus x-ray showed cortex thickening. (b) Ophtalmological examination reveal visual field defect.

**DISCUSSION**

The diagnosis of acromegaly is based on clinical, radiological, and biochemical findings. Classic clinical findings in acromegaly patient stated in the literature are found in this case. The patient complained of weakness, increased appetite and thirst, hyperhidrosis, sleep disturbance, oily and sweaty skin, and teeth loss. At physical examination the patient had facial changes including large lips and nose, wide nasal bridge, protruding jaw, and frontal skull bossing. Examination of the extremities found enlargement of hands and foot. The patient nutritional status is obese. According to study of 500 patients with acromegaly, nearly three-quarters of patients were overweight and 12% severely overweight.<sup>1,2,4,6,7</sup>

Actually, this patient has already felt the symptoms since 9 years ago, when he noted increment in shoe size. The insidious clinical manifestation was typically found in acromegaly, and caused a delay in diagnosis, approximately 10 years from first symptom onset.<sup>1</sup> The age at diagnosis at this patient was 51 years old, this finding is older than the mean age of western literature, which is 40 to 45 years.<sup>7,8</sup> Acromegaly occurs with equal frequency in men and women.

Mostly, chief complain that leads to the diagnosis was acral changes (24%), follows by headaches (20%).<sup>9</sup> Movement disorder suffered by the patient is uncommon clinical feature of acromegaly patient. Bhatoe et al reported that one from seven patients with brain tumor that presents with movement disorder



was pituitary macroadenoma.<sup>10</sup> Meanwhile, Erer et al reported first case of acromegaly presenting with hemichorea and hemiballismus.<sup>11</sup>

This patient was admitted to the hospital with ketotic hyperglycemia. Hyperglycemia is often reported to manifest as hemiballismus and hemichorea in elderly patient with diabetes mellitus. The basic pathophysiology of this finding is that the reduction of regional blood flow in basal ganglia caused by hyperglycaemia leads the metabolism into an anaerobic pathway which damages GABA-inhibitory neurons in the striatum. This condition will disinhibit the external segment of the globus pallidus (GPe) and subthalamic nucleus that will further result in hyperkinetic abnormal movements expressed as hemichorea. The manifestation of this condition is hyperintense image in MRI. In this patient, we didn't find hyperintense image. A possible explanation is the time when MRI was conducted, the patient had already in asymptomatic condition. The hyperintense image in MRI resulted from hyperglycemic hemichorea is stated as reversible.<sup>11</sup>

Mass effect of brain tumor that produces direct or indirect pressure to other brain structure hypothesized to be the possible cause of movement disorder. The extension into middle cranial fossa can result in hemiparesis, partial-complex seizures, and visual field deficit.<sup>2</sup> During hospitalization this patient also suffered partial-complex seizures.

The biochemical finding in this patient showed increased in GH and IGF-1 level. The GH examination should be performed 2 hour after glucose tolerance test. The GH concentration should be 2 ng/ml (radioimmunoassay) or < 1 ng/ml (immunoradiometric or chemiluminescent assay) in a non acromegalic person. Measurement of a random GH concentration is usually has no diagnostic value because it fluctuates so much spontaneously. Practical way to confirm the diagnosis is by measuring the serum IGF-1 concentration, which is relatively stable and so can be measured at any time.<sup>6,12</sup>

The occurrence of hypopituitarism in pituitary macroadenoma is common. Tumor induced increased in intrasellar pressure that compromises the blood flow into normal pituitary tumor and resulting in ischemia and infarction. Increased intrasellar pressure also impairs the delivery of hypothalamic releasing and hypothalamic inhibiting factors and resulting in "stalk syndrome".<sup>2</sup> In this case, we found that the level of gonadotropin (FSH and LH) were decreased. This condition results in impaired gonadal synthesis and secretion of sex steroid hormone. In this case we find

the patient had the diminished libido and impotency.<sup>2</sup>

Growth hormone induced swelling of the soft tissue is the result of increased deposition of glycosaminoglycan in the dermis. Soft tissue swelling also induced by sodium and water retention by the kidneys. The GH excess also disproportionate enlargement of distal skeleton. Overgrowth of the skull and facial bones produces several characteristic features of acromegaly like frontal bossing. In the skin there will be overreactivity of the eccrine and apocrine sweat glands and the sebaceous glands that result in oily and sweaty skin. Symmetric peripheral sensory and motor neuropathy is common and may be enhanced by uncontrolled diabetes mellitus. Thickening of the vocal cords and expansion of the paranasal sinuses results in the deepening of the voice with enhanced resonance.<sup>2,13,14</sup>

Impaired glucose tolerance and over diabetes mellitus are seen in 36 and 30% of acromegalic patients, respectively. Those abnormalities occur as a result of direct antiinsulin effects of GH that increases hepatic glucose production and decrease glucose use by peripheral tissue.<sup>1,2</sup> Blood glucose control in this patient was hardly achieved. This condition was caused by high appetite and also counterregulatory was action of GH against insulin. Hypertriglyceridemia was caused by abnormalities in hepatic triglyceride lipase and lipoprotein lipase.<sup>2</sup> In this case we found high level of triglyceride and cholesterol level.

The colonoscopy examination was planned to evaluate the colon polyps. Benign colon polyps (adenomatous and hyperplastic) have been reported in 45% of 678 acromegalic patients. The echocardiography is planned to evaluate cardiac function and structure. The most common cardiovascular manifestation of acromegaly is biventricular cardiac hypertrophy.<sup>1</sup> In this case both colonoscopy and echocardiography were not performed due to facilities limitations.

The next step after measuring the GH and IGF level, is performing an MRI to look for a somatotroph adenoma, as the cause of the excessive GH. If MRI demonstrates a clearly delineated pituitary lesion, that lesion can be assumed to be the cause. Pituitary MRI with the administration of contrast material is the most sensitive imaging study. More than 70% of somatotroph tumors are macroadenomas (tumor diameter >10 mm) when the diagnosis is established. In this case the patient had giant invasive macroadenoma with diameter 2.3x3.5x6.6 cm<sup>3</sup> that enlarges into suprasella, genu of corpus collosum, and invade third ventricle. Suprasellar extension is observed in 71–88% of cases with acromegaly and optic chiasm is compressed or

deviated in 70–73% cases.<sup>4,15</sup> It is estimated that about 5% of pituitary adenoma become invasive and may grow to gigantic sizes (>4 cm in diameter). The invasive feature in this case is extensive suprasellar extension reaching third ventricle.<sup>16</sup>

Mortality in acromegalic patients compared with general population is higher twofold up to fourfold higher. Dekkers et al, in their metaanalysis found that the standardized mortality ratio (SMR) 1.72 (95% CI 1.62–1.83), which means a 72% increase in mortality in acromegaly population compared to general population.<sup>17</sup> Deaths are attributable to cardiovascular, respiratory, and malignant disease. Treatment that normalizes serum IGF-I levels abolishes this risk. Similarly, normalization of GH secretion with reduction of circulating GH levels to less than 2,5 ng/mL leads to mortality rates comparable to those of the normal population. These data stress the importance of early diagnosis and appropriate treatment.<sup>6,18</sup>

The goals of treatment in acromegaly are to reduce or to control tumor growth, to inhibit GH hypersecretion, and to normalize IGF-I levels. The three approaches of therapy are surgery, medical

management, and radiotherapy (**Table 2**). Complete surgical removal of GH-secreting tumors results in hormonal control of acromegaly and improvement of soft tissue changes. In this case the patient had giant invasive macroadenoma, so the complete surgical removal was unlikely achieved. Approximately 40–60% of macroadenomas are unlikely to be controlled with surgery alone. Treatment of giant invasive macroadenoma with conventional ways results in high recurrence rates. Options for this case are primary medical therapy or primary surgical debulking followed by medical therapy for hormonal control and/or radiation therapy for rest of the tumor.<sup>3,16,19</sup> The choice for surgical primary debulking therapy in this patient is based on seizure activity caused by tumor mass related effect.<sup>21</sup> In this case, the transcranial approach is preferred to transphenoid since the patient had tumor with significant suprasellar extension.<sup>20</sup>

In this case, there are several less favorable predictors of surgical outcome. Factors related to tumor itself include the secretory activity, tumor size, invasiveness. The pre operative GH level has inversely related to post operative remission. This patient had

**Table 2. Treatment summary for acromegaly<sup>4</sup>**

Variable	Surgery	Radiotherapy	Somatostatin receptor ligand	Growth Hormone Receptor Antagonist	Dopamine Agonist
<b>Type of therapy or dose of drug</b>	Transphenoid surgery	Conventional or radiosurgery	Ocreotide (50-400 ug every 8 hr); ocreotide LAR; (10-40 mg deep sc every 4 week); lanreotide (30 mg im every 10-14 days); lanreotide gel (60-120 mg deep sc every 4 weeks)	Pegvisomane (10-40 mg sc daily)	Cabergoline (1-4 mg orally weekly)
<b>Biochemical control</b>					
<b>Growth hormone &lt;2,5 ug/l</b>	Macroadenomas <50%;microadenomas >80%	Approximately 35% in 10 years	Approximately 70%	Level increased	<15%
<b>Normalization of IGF-1</b>	Macroadenomas <50%; microadenomas >80%	<30%	Approximately 70%	>90%	<15%
<b>Onset of response</b>	Rapid	Slow (years)	Rapid	rapid	Slow (weeks)
<b>Compliance of patient</b>	One-time consent	Good	Must be sustained	Must be sustained	Good
<b>Tumor mass</b>	Debulked or resected	Ablated	Growth contrained or tumor shrunk about 50%	unknown	Unchanged
<b>Disadvantage</b>					
<b>Cost</b>	One time charge	One time charge	Ongoing	Ongoing	Ongoing
<b>Hypopituitarism</b>	Approximately 10%	>50%	None	Very low IGF-1 level if overtreated	None
<b>Other</b>	Tumor persistence or recurrence, 6%; diabetes insipidus, 3%; local complications, 5%	Local nerve damage, second brain tumor, visual and CNS disorder, approximately 2% cerebrovascular risk	Gallstones 20%; nausea, diarrhea	Elevated liver enzymes	Nausea, approximately 30% sinusitis; high dose required

<sup>4</sup>The goals of acromegaly management include the control of tumor growth and the secretion of growth hormone and IGF-1, the relief of any central compressive effects, the preservation or restoration of pituitary trophic hormone function, the treatment of coexisting illnesses, the prevention of death, and the prevention of biochemical recurrence. Percentages denote the proportion of patients who have the results after treatment. LAR denotes long acting release

suprasellar extension and invasiveness into third ventricle.<sup>20</sup>

There are particular perioperative issues related to acromegaly patient. Since acromegaly is a complex and multisystem disease, a variety of medical condition coexist in this patient. Diabetes mellitus adds element of risk to operative procedure. The enlargement of jaw and tongue can complicate perioperative airway management. In this case, the anesthesiologist had already recognized the risk of difficulties in airway management.<sup>20</sup>

Preoperative endocrine assessment and management in this case are conducted by performing thorough endocrine evaluation before operative procedure. Special attention is given into pituitary adrenal and thyroidal axis. This patient had normal TSH and free thyroxine level. Meanwhile, the cortisol level in this patient is within normal range, but not in high or high normal level (>20 ug/dl). In this condition the measurement of basal and stimulated serum cortisol is necessary, unfortunately the two tests couldn't be conducted. Ideally, the glucocorticoid replacement therapy was hydrocortisone as given before, during, and after the procedure<sup>21</sup>

The medical therapy of acromegaly consists of three classes of drugs: dopamine agonists, somatostatin receptor ligands, and GH receptor antagonist. From those three classes, the only available and affordable option in this patient is dopamine agonist. The efficacy of dopamine agonist in acromegaly patients is 10-15%.<sup>3</sup>

Radiotherapy has rarely become first line treatment. In this case, radiotherapy could be used to control residual after surgical therapy. The main limitation to the use of radiation therapy in acromegaly is safety, especially when other safer treatment modalities exist. Hypopituitarism is observed in more than 50% of patients receiving radiation therapy. Other limitation of radiotherapy is delay effectiveness. The conventional fractionated radiation therapy may take 10 to 20 years to be fully effective.<sup>3,1</sup>

## CONCLUSION

This report describes a rare case of acromegalic patient with giant invasive adenoma. This patient come to medical attention with unusual main complain, the hemichorea. Until now, in the literature, there is only one case report that reports the same condition found in this patient.

This patient had classical acromegalic appearance, that has been proven biochemically and radiologically. The patient also had uncontrolled diabetes mellitus.

Blood glucose control in this patient requires high dose of insulin.

This case is a beneficial for medical profession, especially internist to manage patient with acromegaly. As had been stated earlier, in the western population, 40% diagnosis of acromegaly was made by internist. The metabolic consequence that related to acromegaly also needs internist attention.

Data concerning prevalence, incidence, clinical profile, and treatment effectiveness in Indonesian population are unavailable. Hopefully, this case report became additional data for acromegaly patient in Indonesia.

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