An Interesting Cause of Hyperhidrosis and Hyperphagia – Acromegaly

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ABSTRACT

Hypersecretion of growth hormone (GH) before the fusion of epiphysis results in gigantism, while acromegaly results after the epiphyseal fusion. The average life expectancy of an acromegalic patient is 10 years less than the average population and the overall standardized mortality ratio is 1.48. The diagnosis is usually delayed by 6.6-10.2 years because of its indolent course. Early diagnosis and treatment can add a decade to their lifetime. We present the case of a young male with features of acromegaly, diagnosed and treated in our hospital.

Keywords: Acromegaly, gigantism, pituitary macroadenoma, growth hormone, insulin-like growth factor, macroglossia

Acromegaly is a rare disease with an annual incidence of 3-4 cases/1 million due to hypersecretion of growth hormone (GH) from a pituitary tumor or an extrapituitary tumor like lymphoma or pancreatic islet cell tumor. Less commonly, it can be due to growth hormone-releasing hormone (GHRH) secreting tumors, usually carcinoids or small cell lung cancer. Pituitary adenomas are the most common cause of acromegaly. When the lesion is a pituitary GH - secreting somatotroph adenoma, acromegaly features are present. If the lesion is an acidophil stem cell adenoma secreting GH and prolactin, hyperprolactinemia features predominate and is frequently encountered in teenagers often causing gigantism.[1] If the culprit lesion is a mixed mammosomatotroph tumor, both the features are present. GH cell carcinomas are very rare and should be suspected when extracranial metastases are present. Carcinoids are the most common cause of acromegaly due to GHRH secreting tumors. Multiple endocrine neoplasia-1, familial acromegaly, Carney's syndrome and McCune-Albright syndrome are the familial syndromes causing acromegaly.

CASE REPORT

A 34-year-old male attended our Medical OPD with complaints of excessive sweating and increased appetite since 6 months. There was a history of excessive sleeping, easy fatigability, holocranial headache, increased frequency of micturition around 4 times in the night and breathlessness progressing from New York Heart Association (NYHA) Grade I to II. These symptoms started appearing one by one during the last 6 months. He noticed that his hands have become broad but attributed it to heavy work that he does. His shirt size had changed from 40 to 44 inches, footwear from 10 to 12 inches and brief from 90 to 100 cm. His wife complained that his voice had become hoarse since 5 months. There was no history of visual disturbance, vomiting, chest pain, leg swelling or change in personality. His sexual life was normal. He had a road traffic accident 3 years back. There was contusion of right hypothalamus with intraventricular hemorrhage for which drainage was done. Splenectomy was done for splenic injury and hemoperitoneum.

On general examination, he had coarse facies, high-arched palate, macroglossia, prognathism, spade like fingers and broad feet (Figs. 1 and 2). His vitals were blood pressure (BP) - 130/90 mmHg, pulse rate - 80/min, respiratory rate - 14/min. His systemic examination was normal. Eye examination was done by ophthalmologists. Both eyes had congested bulbar

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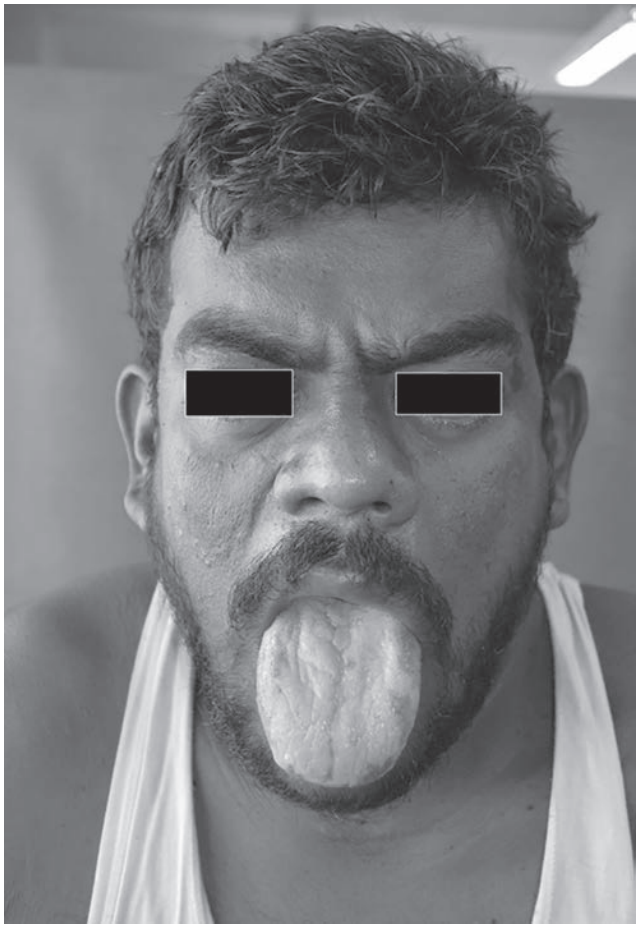

Figure 1. Acromegalic facies. Coarse skin, large fleshy nose, macroglossia and large mandible.

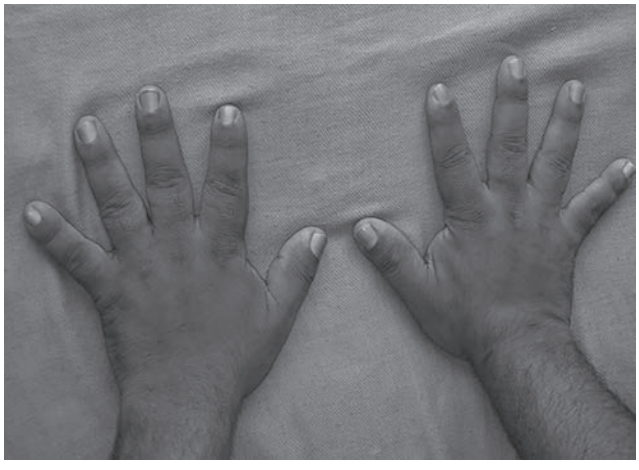

Figure 2. Paw hand. Massive hand with fat, cylindrical spatulate fingers with blunt tips.

conjunctiva, chemosis, proptosis, restricted abduction and adduction with normal fundus, color vision, field of vision. There was no diplopia on diplopia charting. Hematological investigations revealed dimorphic anemia (hemoglobin [Hb] - 6.8 g/dL) with thrombocytosis (8.17 lakh/mm^3). Renal and liver function tests were normal. Serum insulin-like growth factor 1 (IGF-1) level was elevated, 841 ng/mL (normal: 115-307). Serum prolactin was mildly elevated, 18.65 ng/mL (normal: 2.1-17.7). Computed tomography (CT) brain was normal. 1.5 Tesla magnetic resonance imaging (MRI) brain with contrast showed a well-defined oval-shaped mass of size 2 × 1.6 cm lesion in the sellar region (Fig. 3). It was isointense on T_1 and hypointense on T_2 images with heterogeneous enhancement post-contrast. The lesion did not extend to suprasellar region or involve optic chiasma. These features were suggestive of pituitary macroadenoma.

Screening of other organs was done since acromegaly affects almost all organs. Echocardiography showed concentric left ventricular hypertrophy with normal ejection fraction (60%). Ultrasound (USG) of the abdomen showed left Grade IV hydroureteronephrosis. CT abdomen showed left pelviureteric junction obstruction with gross hydroureteronephrosis (Fig. 4).

We suspected prior renal calculi. But his serum calcium (ionized - 4.2 mg/dL) and intact parathyroid hormone (37.97 pg/mL) were normal. USG of the neck showed diffuse nodular goiter confirmed by fine needle aspiration cytology. Thyroid function test was normal (free triiodothyronine [FT3] - 3.36 pg/mL, free thyroxine [FT4] - 1.20 ng/mL, thyroid-stimulating hormone

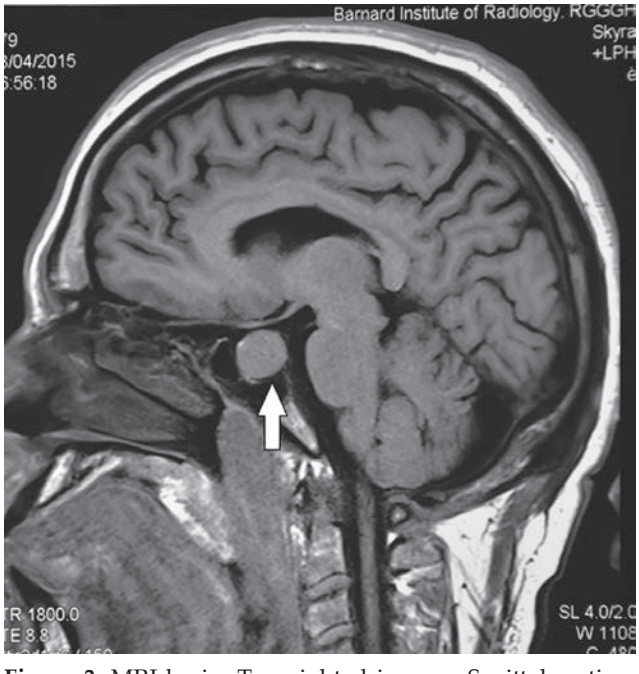

Figure 3. MRI brain. T_1-weighted image - Sagittal section. Well-defined isointense oval- shaped lesion of size 2 × 1.6 cm in the sellar region (*arrow*). Pituitary macroadenoma.

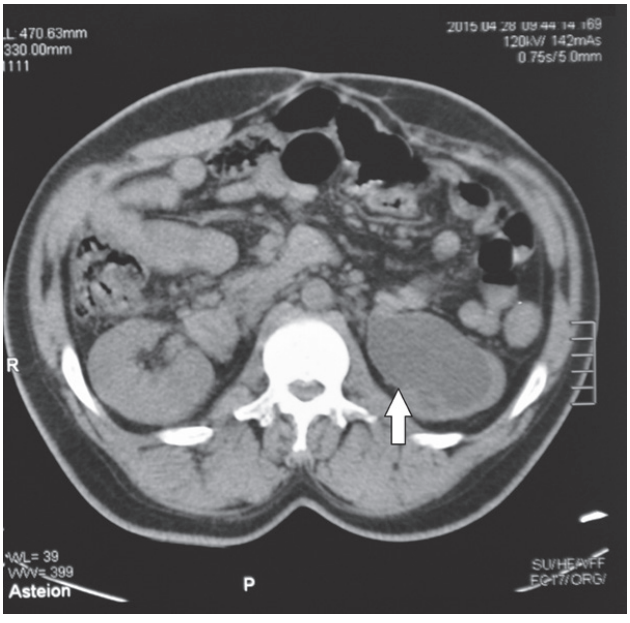

Figure 4. CT abdomen. Hydroureteronephrosis of the left kidney due to pelviureteric junction obstruction (*arrow*).

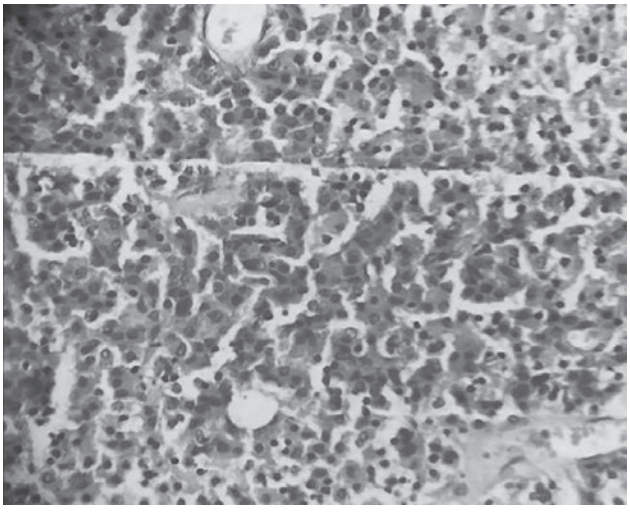

Figure 5. HPE 40X magnification. Fairly uniform round to oval cells with eosinophilic cytoplasm and centrally placed darkly staining nucleus arranged in cords, sheets and islands with focal areas of rosette formation. Tumor cells are separated by fibrovascular septae. Features of pituitary adenoma.

[TSH] - 1.16 μIU/mL). Multiple endocrine neoplasia was ruled out by the above investigations.

Tablet cabergoline 0.5 mg twice a week was started as per endocrine surgeon's advice. Two units of packed red blood cells (RBCs) were transfused. Team of endocrine and skull base surgeons resected the tumor by trans-nasal trans-sphenoidal endoscopic approach. Histopathological examination showed fairly uniform round to oval cells with eosinophilic cytoplasm and centrally placed darkly staining nucleus arranged in cords, sheets and islands. Focal areas of rosette formation and separation of tumor cells by fibrovascular septae was present (Fig. 5). These features confirmed the lesion as pituitary adenoma. Postoperatively, his IGF-1 and GH levels decreased. He was discharged and is on regular follow-up.

DISCUSSION

Growth hormone secretion is increased by GHRH, ghrelin, fasting whereas somatostatin and food intake suppresses its release. The effects of GH are mediated through GH receptors in the cartilages and liver. GH leads to IGF-1. IGF-1 levels are highest during late adulthood and in pregnancy. IGF-1 production is decreased in patients with hypothyroidism, hepatic disease, poorly controlled diabetes and in malnourished patients.[2] IGF-1 and GH act dependently and independently to cause the features of hypersomatotropism. Acromegalics have characteristic features like coarse facies, frontal bossing, large fleshy lips and nose, macroglossia, prognathism, increased gap between lower incisors, spade like fingers.

At the time of diagnosis around 60% of the patients have hypertension, arrhythmia and valvular heart diseases, which causes concentric ventricular hypertrophy and diastolic heart failure.[2] Our patient had concentric hypertrophy but didn't progress to heart failure at the time of diagnosis. Heart failure is reversible with octreotide treatment while hypertension, and valvular regurgitation are not.[2] Resting ECG can show ST-segment depression, T-wave abnormalities, conduction defects and arrhythmias in 50% of patients. Colon cancer risk is twice as common than in the general population hence screening by colonoscopy once in 3-5 years is advised.[3] Our patient was not co-operative for the procedure; however, stool occult blood was negative. Obstructive sleep apnea, snoring and narcolepsy due to soft tissue deposition around the larynx, macroglossia and nasal polyps are present in more than 50% patients.[4] Central sleep apnea associated with high GH and IGF-1 levels is also common. Voice changes are also common due to the fixation of vocal cords, laryngeal stenosis, tracheal calcification and cricoarytenoid joint arthropathy. Our patient had a deep voice, snoring and macroglossia.

Musculoskeletal manifestations are the most common features in acromegaly. Up to 70% patients have arthropathy in the form of joint swelling, hypermobility and cartilage thickening. Knee, elbow, shoulder, ankle hip and lumbosacral joints are commonly affected.

Kyphoscoliosis is common; our patient had kyphosis. Carpal tunnel syndrome is seen in half of patients due to median nerve enlargement and its entrapment in the wrist. Osteophytes are commonly seen in the anterior aspects of vertebrae and in the phalangeal tufts mainly the distal phalanges giving an appearance of spade like fingers on X-ray. Hyperhidrosis and malodorous oily skin is present in 70% of patients and is an early sign. Our patient sought medical attention for this, which helped us diagnose the pituitary lesion.

Increased glycosaminoglycan deposition and collagen production causes the typical coarse facies with skin wrinkles, nasolabial folds, fleshy nose, macroglossia, increased heel pad thickness. Heel pad thickness is measured in X-ray of the foot in a lateral view. The distance is measured between the lower most point of the calcaneum and the lower most point of the heel pad soft tissue shadow. If the measurement is >23 mm in males and >21 mm in females, the heel pad thickness is said to be increased. Phenytoin therapy, obesity and myxedema can also cause heel pad thickening. Exophthalmos if present is frequently masked by frontal bossing. Skin tags if more than 3 in number in patients above 50 years of age is a marker of colonic adenomatous polyps not related to the GH and IGF-1 levels.

Impaired glucose tolerance and diabetes mellitus is very common because of the anti-insulin effects of GH. This is reversed after surgery or somatostatin analog therapy. Our patient was euglycemic. Around 30% of patients have co-existing hyperprolactinemia; our patient had mildly elevated prolactin. Hypogonadism is present in 50% of patients which is often reversible. Thyroid dysfunction is quite common and may present with Grave's disease, nodular or diffuse goiter, toxic or nontoxic goiter. Our patient had diffuse goiter with normal thyroid function test. Screening for multiple endocrine neoplasia type 1 (MEN1) syndrome was done but parathyroid hormone was within normal levels. Age, level of GH before and after treatment, IGF-1 levels, size of the tumor, degree of invasion and duration of symptoms before the diagnosis is made are important determinants of co-existing illnesses.[2]

Some important mortality determinants are high IGF-1 levels, GH level >2.5 μg/L, older age, cardiac disease, hypertension, inadequately replaced adrenocorticotropic hormone (ACTH)-dependent adrenal insufficiency and history of pituitary radiation.[5] Younger age, shorter duration of the disease, GH levels <2.5 μg/L, absence of hypertension independently predict longer survival.[6]

The single best test to diagnose acromegaly is age- and sex-matched serum IGF-1 level. It is elevated in all patients with acromegaly distinguishing it from normal individuals.[7] Our patient had a very high level of IGF-1. GH is secreted in a phasic manner in normal individuals with the lowest levels during the day often <2 μg/L, while in the night it can be as high as 30 μg/L.[8] GH level is also influenced by sleep and food intake with a very short half-life (20 min). Hence, serum IGF-1 levels are preferred over GH levels.

However, in patients with equivocal IGF-1 levels, measurement of GH levels is additive. Oral glucose tolerance test (OGTT) is the most specific dynamic test. It is also the gold standard test to determine control of GH secretion post surgery. OGTT is done by measurement of GH levels over 2 hours of ingestion of 75 g of glucose. GH levels ≥0.4 μg/L in OGTT is diagnostic of acromegaly. GH <1 μg/L signifies disease control.

MRI brain with contrast is the radiological investigation of choice. Information on size of the tumor along with compression and invasion of adjacent structures can be obtained. Even a tumour of 2 mm can be identified but it doesn't differentiate functioning and nonfunctioning tumors. Macroadenoma (>1 cm) is seen in 75% patients. Other endocrine glands should be imaged as a part of routine work-up. ACROSCORE is a clinical tool developed for general practitioners and nonendocrinology specialists for easier identification of acromegaly. It classifies the patient into low-, medium- or high-risk of suspicion of acromegaly.

Surgical resection is the first management option for all acromegalics.[9] The transphenoidal approach normalises IGF-1 and GH in >80% microadenomas and <50% macroadenomas. Recurrence or persistence of tumor is 6% in this approach. Conventional radiotherapy and stereotactic radiosurgery causes hypopituitarism in >50%, while normalizing IGF-1 and GH in only 30%. The somatostatin analogs (octreotide, lanreotide) shrinks the tumor by 50% by normalizing IGF-1 and GH in 70% of patients.

The GH receptor antagonist pegvisomant normalizes IGF-1 in >90% patients.[2] Currently, this drug is preferred when other treatment modalities have failed, levels of IGF-1 (>900 ng/mL) are very high or whose glucose tolerance is worsened by somatostatin analogs.[9] The dopamine agonist cabergoline is less commonly used nowadays because <15% normalization of IGF-1 and GH.

REFERENCES

1. Maheshwari HG, Prezant TR, Herman-Bonert V, Shahinian H, Kovacs K, Melmed S. Long-acting peptidomimergic control of gigantism caused by pituitary acidophilic stem cell adenoma. J Clin Endocrinol Metab. 2000;85(9):3409-16.
2. Melmed S. Medical progress: Acromegaly. N Engl J Med. 2006;355(24):2558-73.
3. Renehan AG, Shalet SM. Acromegaly and colorectal cancer: risk assessment should be based on population-based studies. J Clin Endocrinol Metab. 2002;87(4):1909; author reply 1909.
4. Rosenow F, Reuter S, Deuss U, Szelies B, Hilgers RD, Winkelmann W, et al. Sleep apnoea in treated acromegaly: relative frequency and predisposing factors. Clin Endocrinol (Oxf). 1996;45(5):563-9.
5. Ayuk J, Clayton RN, Holder G, Sheppard MC, Stewart PM, Bates AS. Growth hormone and pituitary radiotherapy, but not serum insulin-like growth factor-1 concentrations, predict excess mortality in patients with acromegaly. J Clin Endocrinol Metab. 2004;89(4):1613-7.
6. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab. 2004;89(2):667-74.
7. Stoffel-Wagner B, Springer W, Bidlingmaier F, Klingmüller D. A comparison of different methods for diagnosing acromegaly. Clin Endocrinol (Oxf). 1997;46(5):531-7.
8. Peacey SR, Toogood AA, Veldhuis JD, Thorner MO, Shalet SM. The relationship between 24-hour growth hormone secretion and insulin-like growth factor 1 in patients with successfully treated acromegaly: impact of surgery or radiotherapy. J Clin Endocrinol Metab. 2001;86(1):259-66.
9. Cook DM, Ezzat S, Katznelson L, Kleinberg DL, Laws ER Jr, Nippoldt TB, et al; AACE Acromegaly Guidelines Task Force. AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract. 2004;10(3):213-25.

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