Case Report

Atypical Presentation in a Lady with Acromegaly : A Case Report

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Background : The blood IGF-1 level is a suitable marker for assessing the integrated secretion of GH and is advised for acromegaly diagnosis, monitoring and screening. Systemic diseases like Catabolic Disorders, Liver or KIdney Failure, Malnutrition and Diabetes Mellitus can lower IGF-1 levels and cause acromegaly screening to give false-negative results.

Case Report : A 49-year-old female presented with dysphagia, vomiting, abdominal distention with no associated pain but Grade 3 edema of both lower limbs, with frontal bossing, prominent jawline, and acral thickening. The abdomen was distended with fluid thrill otherwise unremarkable. Ascitic fluid showed predominantly mononuclear cells with an elevated protein (4.56 mg/dL) and normal ADA. Ascitic culture was negative with no evidence of malignant cells found. Lower levels of IGF-1, LH, FSH were observed with elevated TSH and Prolactin. Ultrasonography of the abdomen suggested Chronic Liver Parenchymal Disease with massive ascites. Doppler study of lower limbs showed DVT. Heel pad thickness of 30.7 mm and 26.4 mm on the left and right sides respectively. MRI of the Brain showed Pituitary Macroadrenoma (13 mm).

Discussion : IGF-I concentrations correlated with heel pad thickness, fasting blood sugar concentrations and response to an OGTT in patients with acromegaly. Low IGF-1 in the context of clinical acromegaly may also indicate a later stage of a disease process that was once linked to high IGF-1 and caused the clinical signs of acromegaly but has now “burned out”. Recent research has shown that acromegaly patients may have coagulation abnormalities causing hypercoagulable states and, therefore, increasing the risk of Thrombosis.

Conclusion : Renal or hepatic disease or impaired nutritional status should be viewed as confounding conditions and may cause alterations in IGF-I production and/or bioactivity, such that the IGF-I concentration may no longer accurately reflect disease activity.

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***Key words* : Acromegaly, IGF-1, VTE.**

Acromegaly is an endocrine disorder characterised by progressive facial and extremity deformities. It results from abnormally increased levels of serum Growth Hormone (GH) in adulthood and is most commonly caused by a pituitary adenoma. Many of the actions of Growth Hormone (GH) on somatic growth and tissue maintenance are mediated by insulin-like growth factor-1 (IGF-1), which is produced in response to GH by the liver. Biochemical confirmation of the diagnosis is substantiated by elevated IGF-1 levels and elevated blood GH levels that persist during Oral Glucose Tolerance Testing (OGTT). The blood IGF-1 level is a suitable marker for assessing the integrated secretion of GH and is advised for diagnosis, monitoring and screening of acromegaly. Systemic diseases like catabolic disorders, liver or kidney failure, malnutrition, and diabetes mellitus can lower IGF-1 levels and might give false-negative results while screening for acromegaly[1].

The prevalence of endocrine and liver problems is rising in the general population. The most common endocrine disorders are diabetes, thyroid and gonadal disorders. The most common liver disorders are chronic hepatitis and cirrhosis of the liver. In modern medicine, it is not unusual for illnesses that affect these two important systems to happen at the same time. The liver is an important organ for metabolism. It is also where proteins and different hormones are synthesised. In addition to the liver being a detoxifying site, systemic toxins build up when an individual develops chronic liver disease. Most proteins that bind to hormones, like Sex Hormone Binding Globulin (SHBG) and Thyroid Binding Globulin (TBG), are synthesised in the liver. Endocrinopathies are often linked to chronic liver conditions such as chronic hepatitis, primary biliary cirrhosis and autoimmune hepatitis. When the liver doesn’t function properly, there may be dysfunction of endocrine glands. This happens through direct toxic effects and indirect changes to the production of carrier protein[2].

Chronic Liver Disease (CLD) may lead to the

Editor's Comment :

- Serum IGF-1 may not be an accurate indicator of disease activity in patients with acromegaly, if the patient also presents with liver dysfunction concurrently.
- It may also indicate the later part of the disease process (previously linked with high IGF-1) suggesting “burnt-out acromegaly”.

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dysfunction of most endocrine organs, including the pituitary, thyroid and other glands. A few endocrine disorders linked to CLD may improve following liver transplantation. There are few reports from India on liver dysfunction in people with acromegaly.[2] Hence, we report a case of a patient with acromegaly who presented with low IGF-1 and Chronic Liver Disease.

Case Report

A 49-year-old female presented with difficulty in food intake, both solid and liquid, for the last 3 months with associated vomiting after every intake; abdominal distention for the last 2 months with no associated pain but with abdominal discomfort followed by reduced appetite and constipation. The patient also had swelling of both lower limbs, which was gradually progressive in onset and reduced urine output for the last 20 days, which improved after intake of medications during the hospital stay. The patient had a history of blurred vision for the past 10 years. The patient had no history of fever, cough, shortness of breath, jaundice, bleeding from the mouth or loose stools. The patient did not have any history of chronic illnesses like diabetes mellitus, hypertension, heart disease, thyroid disease, or tuberculosis. There was no history of a similar condition in any of her family members. The patient had no history of any trauma, headaches, convulsions, disturbed sleep or utterance of irrelevant words. The patient predominantly took a non-vegetarian diet. The patient had no history of intake of any herbal substance and no history of intake of alcohol. The patient is in post-menopausal status for last 8 years with history of normal menstrual cycles and no history of galactorrhoea. The patient had 2 sons.

Examinations — On examination, the patient had frontal bossing, a prominent jawline and acral thickening of both hands and feet (Figs 1&2), suggestive of acromegaly. The patient had normal hair and nails and had no ulcers in and around the mouth. The patient had no pallor, icterus, cyanosis, or clubbing but had Grade 3 edema. The patient had locomotor brachialis. There was no swelling in the neck, palpable lymph nodes and prominent neck veins. There were no signs of muscle wasting. There was no redness of the hands or skin discolorations or signs of petechial hemorrhage. The pulse was 84 beats/min, regular in rhythm, normal in volume and character, with no radio-radial and radio-femoral delay. All peripheral pulses were normal. Systolic and diastolic blood pressures were within normal limits. She had a normal respiratory rate with no signs of respiratory distress. On examining the abdomen, it was distended with no signs of umbilical herniation. The patient had no flapping tremors. There was no prominence in the abdominal veins. However, fluid thrill was present and there was no palpable liver or spleen. The routine eye examination was within normal limits. On testing for visual acuity, 6/36 in the right eye and 6/60 in the left eye and fundoscopy were also normal. Slit-lamp examination of the eye showed no signs of Kayser-Fleisher rings or any other abnormality. Perimetry was unremarkable for both eyes. Intra-ocular pressure was 12 mmHg of both eyes, measured using Goldmann Applanation Tonometer. Ocular Coherence Tomography was also within normal limits for both eyes, measured using Topcon 3D OCT-1 Maestro 2 system (Fig 3). The patient was although, advised refraction of -1.5 D for Right eye and -1.75 D for Left eye and +1.5 D for near vision for both eyes.

Routine blood investigations were done for the patient and are tabulated in Table 1. Routine urine examination yielded 4+ protein but otherwise was normal. Peripheral Blood Smear study was suggestive of microcytic hypochromic anaemia. Ascitic fluid analysis showed 185(87.2%) mononuclear cells and 27(12.8%) polymorphonuclear cells with an Ascitic Fluid Sugar of 20 mg/dL, a Protein of 4.56 mg/dL, and an Adenosine Deaminase of 16.77 U/L. Ascitic culture suggested no growth of organisms. There was no evidence of malignant cells in the ascitic fluid. HbsAg, anti-HCV and HIV turned out to be negative. Anti-Nuclear Antibodies (ANA), Anti-Smooth Muscle Antibodies (ASMA) and Anti- Liver-Kidney-microsomal Antibodies (Anti LKM) were negative. The hormonal assays were also done and are given in Table 2.

Ultrasonography of the abdomen suggested chronic liver parenchymal disease with massive ascites with a portal vein diameter of 14.7 mm. The patient also had a left renal complex cyst and a right renal simple cyst with hydronephrotic changes. Upper GI endoscopy suggested antral ulcer with multiple polypoid growths around the greater and lesser curvature of the stomach, leading to gastric outlet obstruction with no features of esophageal or gastric varies. A Doppler study of the bilateral lower limbs showed the patient to have Deep Vein Thrombosis. The D-Dimer of the patient was done following the Doppler study and came out to be 7.11 g/mL (N = 0–0.4 g/mL). An X-ray of both the feet showed elevated heel pad thickness

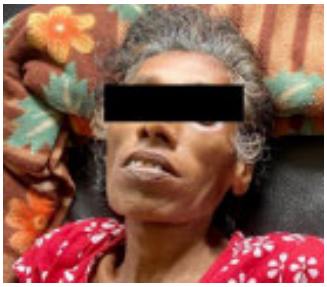
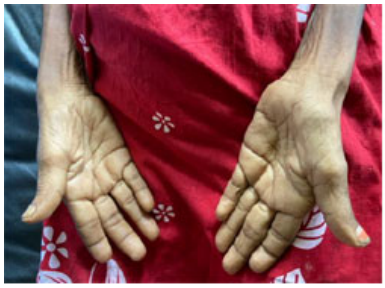


Fig 1



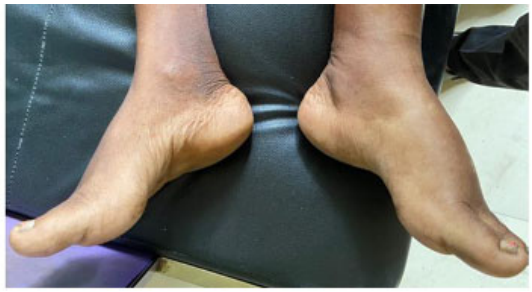


Fig 2

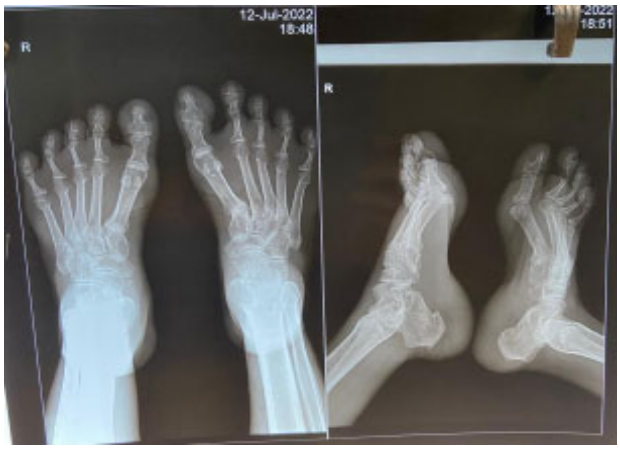


Fig 3

Table 1 — *Showing Blood Parameters*

Lab Parameters	Patient'S Value	Normal Value
Hemoglobin	9 g/dL	12-15 g/dL
Total count	6120/mm^3	4000-11000/mm^3
MCV	89.3 fL	80-100 fL
Platelet count	1.4*10^5/mm^3	1.5-4.5*10^5/mm^3
AST	48.40 U/L	14-36 U/L
ALT	26.20 U/L	<35 U/L
S Urea	34.91 mg/dL	15-36 mg/dL
S Creatinine	0.81 mg/dL	0.52-1.04 mg/dL
S Sodium	133 mmol/L	137-145 mmol/L
S Potassium	3.10 mmol/L	3.5-5.10 mmol/L
S Albumin	2.67 g/dL	3.5-5.0g/dL
Blood sugar(Random)	92 mg/dL	70-139 mg/dL
S Iron	30.40 g/dL	37-170 g/dL
Prothrombin time	25.2 sec	10.7-14.1 sec
INR	2.12	0.9-1.16

Table 2 — *Showing Hormone Assay*

Hormone Assay	Patient's Value	Normal	Method Used
IGF-1	29.5 ng/mL	94-252 ng/mL	Chemiluminescent Competitive Immunoassay
TSH	5.91 mIU/mL	0.465-4.680 mIU/L	Immunometric
fT4	0.86 ng/dL	0.78-2.19 ng/dL	Competitive Immunoassay
Prolactin	51.40 ng/mL	3.34-26.72 ng/mL	Immunometric
FSH	<0.66 mIU/mL	16.74-113.59 mIU/mL	Immunometric
LH	<0.216 mIU/mL	10.87-58.64 mIU/mL	Immunometric
Cortisol (8 am)	22.7 mcg/dL	4.82-19.50 mcg/dL	Electrochemiluminescent immunoassay
ACTH	20.8 pg/mL	≤46 pg/mL	Chemiluminescent Immunometric assay

of 30.7 mm and 26.4 mm on the left and right sides, respectively (Fig 4). Ultrasonography of the neck showed hypoechoic lesions with regular margins but with no echogenic foci and internal vascularity in both the thyroid lobes suggestive of TIRADS 2 lesion. A non-contrast CT scan of the brain revealed a hyperdense lesion around the pituitary fossa along with calcification of bilateral basal ganglia. A T1/T2 iso-intense lesion of size measuring approximately 13 mm was noted in the suprasellar region showing homogenous enhancement on post contrast MRI study; however, there were no blooming foci on the GRE/SWI sequence. The bilateral frontal sinus and jaw appear enlarged. The findings suggest pituitary macroadrenoma. (Figs 5,6,7,8) She was commenced on treatment with Bromocriptine 10 mg/day, as she was unwilling to undergo pituitary surgery and radiotherapy and because somatostatin analogues and pegvisomant were not routinely available at our hospital. She was also started on LMWH for Deep Vein Thrombosis. She was referred to a higher gastroenterology centre as she had gastric polyps causing Gastric Outlet Obstruction.

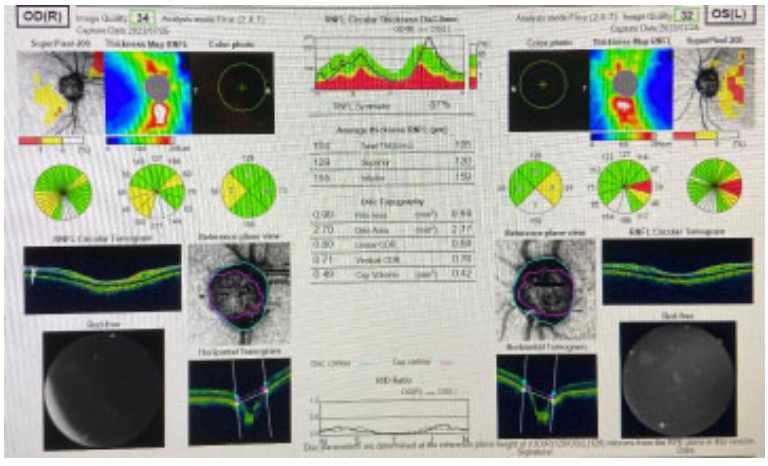


Fig 4

Discussion

It has long been known that serum IGF-I levels are correlated with disease activity in acromegaly. Clemmons, *et al* demonstrated that IGF-I concentrations correlated with heel pad thickness, fasting blood sugar concentrations, and response to an Oral Glucose Tolerance Test (OGTT) in patients with acromegaly. Also, the changes in IGF-I levels in 15 patients who were followed for a year after treatment matched the amount of clinical improvement[3,4].

Our case in point showed that acromegaly can cause hepatic and endocrine disorders. Acromegaly disrupts glucose and lipid metabolisms, increases free fatty acids, and causes hepatic and extra-hepatic insulin resistance and fat distribution alterations. Growth hormone promotes muscle and liver gluconeogenesis and glycogenolysis. It releases free fatty acids through lipolysis. High release of free fatty acids and insulin resistance are well established NAFLD risk factors. Conversely, enhanced lipolysis may prevent NAFLD in acromegaly patients.

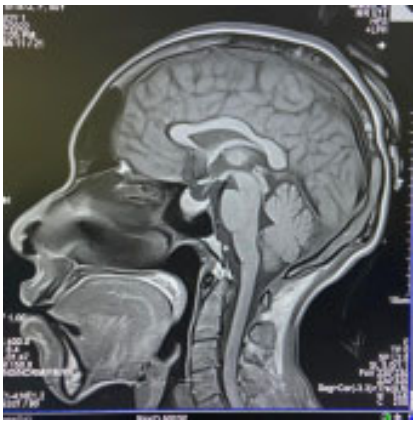


Fig 5

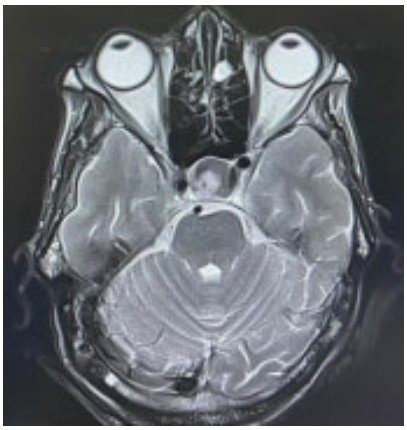


Fig 6

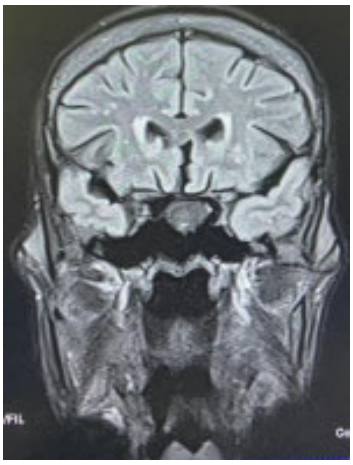


Fig 7

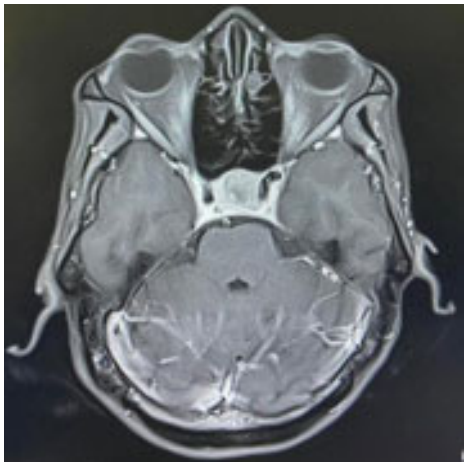


Fig 8

Henceforth, the complex metabolic actions of GH make debatable link between NAFLD and acromegaly[5].

Chronic Liver Disease frequently exhibit occult endocrine dysfunction, which correlates directly with the severity of liver dysfunction. Previous research indicates that 10-25% of cirrhotic patients had thyroid problems. [2] In people with acromegaly, goitre is predominately nodular, and the incidence of thyroid cancer is also elevated. Most likely, the cause of goitre in people with acromegaly is a high insulin-like growth factor-1 (IGF-1) that binds to its specific receptor on thyrocytes. In contrast, Thyroid Stimulating Hormone (TSH), another essential component related to goitre formation, is reduced or missing in certain patients with acromegaly. This is primarily due to secondary hypothyroidism, which is induced by adenoma compression, pituitary surgery, or irradiation[6].

Our patient showed dipstick proteinuria, which may be caused by Focal segmental Glomerulosclerosis (FSGS) in acromegaly patients. These patients may develop renal hypertrophy and enlarged kidneys than controls with significant rise in renal plasma flow and glomerular filtration. However, our patient did not undergo kidney biopsy for the confirmation of diagnosis. Clinical cases of glomerular lesions caused by high GH production are rare and have only been documented twice. Yoshida, *et al* described a 46-year-old acromegaly-FSGS in 1999. The administration of corticosteroids resulted in partial remission but after tapering of dosages, relapses were obseved. The subcutaneous administration of Octreotide acetate, and removal of pituitary adenoma via trans-sphenoidal surgery was done. After normalising creatinine clearance, steroids were gradually reduced to maintain remission. The case suggested that increased GH secretion might worsen renal glomerular disease. Another case by Takai, *et al* of a 53-year-old man with mild proteinuria for 6 years and acromegaly for 15 years showed renal biopsies having FSGS and enlargement of glomerular tufts. Trans-sphenoidal microsurgery of the adenoma did not eliminate proteinuria, despite normalised GH and IGF-1 levels. These two examples implied the development and progression of FSGS might be involved in patients with acromegaly. The intensity and duration of glomerulonephritis while undergoing treatment for acromegaly, may affect the outcome. There is strong evidence that GH and IGF-1 secretion may affect renal function and growth due to the expression of GH receptor, IGF-1 and IGF-1 binding proteins in different nephron segments, having unique anatomy and function[7].

Portal hypertension, which is generally asymptomatic until problems occur, was present in the patient. 80–90% of asymptomatic cirrhosis patients have high portal pressure, 40% of whom have oesophageal varices. Depending on portal hypertension severity, they may develop at 6-10% every year in persons without varices.[8]

Low IGF-1 in the context of clinical acromegaly may also indicate a later stage of a disease process that was once linked to high IGF-1 and caused the clinical signs of acromegaly but has now “burned out” (this is called “burnt-out acromegaly”). In addition, burnt-out acromegaly is frequently accompanied by additional hypopituitarism[1] symptoms, which were present in our patient. IGF-1 is mostly made in the liver and having CLD may cause IGF-1 levels to be low.

There are functional pituitary adenomas in which the cell type that makes them causes increased secretion of one or more anterior pituitary hormones. Nonfunctioning adenomas, on the other hand, do not secrete hormones but can potentially compress the anterior pituitary, resulting in hormonal deficiencies. Pituitary adenoma patients should be evaluated by a multidisciplinary team that includes endocrinology, ophthalmology and

Neurosurgery[9-11]. Low FSH and low LH with relatively preserved TSH and ACTH in this patient may be due to the compression effect of the macroadenoma causing low gonadotropins.

Recent research has shown that acromegaly patients have a wide variety of coagulation abnormalities in their serum. These abnormalities have the potential to lead to hypercoagulable states and, as a result, increase the risk of Thrombosis[12]. Few VTE instances in acromegalic patients have been reported since Coffey and Cummins described the first in 1912[13]. Al Dahmani, *et al* reported three VTE cases in uncontrolled acromegaly patients without risk factors in 2015[14]. Dal, *et al* examined Danish health registries of acromegaly patients to predict sequelae. The patients in this group experienced more VTE overall[15]. The link between serum IGF-1 and Thrombosis risk is uneven and unclear. In certain studies, higher IGF-1 levels were linked to early carotid artery atherosclerosis[16], whereas low levels were linked to increased intima-media thickness and atrial fibrillation[17,18]. Besides serum coagulation abnormalities, malignancy and obstructive sleep apnea can increase hypercoagulability risk in acromegaly. Studies also show that acromegaly increases the risk of colon, thyroid and kidney malignancies[12]. Our study's strength is its assessment of all hormonal axes in this patient; relatively few studies from our nation have been reported. We did not do a GH suppression test following the OGTT, we did not measure free Testosterone, TBG, or SHBG, and we did not perform colonoscopy to rule out polyps in the colon. The relationship between endocrine dysfunction and underlying Chronic Liver Disease could not be determined from our study.

Conclusion

Serum IGF-I concentration is a sensitive measure of integrated GH levels in patients with acromegaly that closely correlates with clinical and biochemical markers of disease activity. Renal or Hepatic Disease or impaired nutritional status should be viewed as confounding conditions. These conditions may cause alterations in IGF-I production and/or bioactivity, such that the IGF-I concentration may no longer accurately reflect disease activity. We describe a case of liver dysfunction in an elderly patient with acromegaly and low IGF-1 levels. In a patient with supportive clinical findings, a low IGF-1 test does not rule out acromegaly. It is imperative that a high index of suspicion be kept at all times in order to avoid losing out on this crucial diagnosis.

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