International Journal of Research in Medical Sciences
Singh A et al. Int J Res Med Sci. 2025 Feb;13(2):867-870
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20250271

Case Report

Definitive role of surgery in management of acromegaly due to ectopic growth hormone secretion: review of literature

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Received: 22 October 2024
Revised: 05 December 2024
Accepted: 27 December 2024

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ABSTRACT

Acromegaly, characterized by excessive growth hormone (GH) secretion, typically arises from pituitary adenomas. Ectopic GH production from non-pituitary tumors, such as carcinoid tumors, is exceedingly rare, <1%. The majority of the growth hormone-releasing hormone (GHRH) - secreting tumors are bronchial carcinoids. Other GHRH-secreting tumors in decreasing order of occurrence are pancreatic adenomas, gastro-intestinal tumors, thymic tumors, and tumors associated with the MEN-I syndrome. We present a case of a 43-year-old female who presented with features consistent with acromegaly and was found to have an ectopic source of GH from a mediastinal tumor. Diagnostic evaluation included biochemical testing, imaging studies, and histopathological confirmation. Surgical intervention led to complete resolution of clinical symptoms and normalization of GH levels. This case highlights the diagnostic challenges posed by ectopic GH secretion and emphasizes the critical role of surgery in achieving favorable outcomes in such rare presentations of acromegaly.

Keywords: Ectopic growth hormone, Ectopic acromegaly, Surgery for acromegaly

INTRODUCTION

Acromegaly results from persistent hypersecretion of growth hormone (GH). Excess GH stimulates hepatic secretion of insulin-like growth factor-1 (IGF-1), which causes most of the clinical manifestations of acromegaly. Ectopic GH production from non-pituitary tumors, such as carcinoid tumors, is exceedingly rare, <1%.[1] The majority of the growth hormone-releasing hormone (GHRH) - secreting tumors are bronchial carcinoids. Other GHRH-secreting tumors in decreasing order of occurrence are pancreatic adenomas, gastrointestinal tumors, thymic tumors, and tumors associated with the MEN-I syndrome.[2] The first well-documented association of an extrapituitary neuroendocrine tumor and acromegaly was published in 1959.[3] It was subsequently shown that extracts from such tumors had in vitro GH-releasing activity.[4] GHRH was characterized in 1982 following the isolation and sequencing of the peptide from two patients with GHRH-secreting pancreatic neuroendocrine tumors.[5,6] Herein, we present a case of a 43-year-old female diagnosed with acromegaly secondary to ectopic GH production from a mediastinal tumor. The clinical presentation, diagnostic challenges, and management of this rare condition, culminating in successful surgical resection and clinical resolution, are discussed in detail.

This case underscores the importance of considering unusual sources of GH secretion in patients with acromegaly, highlighting the critical role of surgery in effectively managing such cases with dramatic improvement post-surgery.

CASE REPORT

A 43-year-old premenopausal woman presented with a 1 year-long history of change in facial appearance like broadening of jaw and face, hyperpigmentation of skin, and swelling of hands and feet. She reported history of left sided chest pain on and off for 1 month with a normal electrocardiography (ECG) and 2D Echo investigations. She started snoring over last 2 months. Pain was dull aching in nature, no aggravating and relieving factors and no diurnal variation. There were no known drug allergies. She reported no history of smoking or alcohol consumption.

She developed hypertension and diabetes mellitus within last 1 year and was taking medications for same. She underwent surgery for intrathoracic mass through a thoracotomy 2 years ago, but no histopathology report was available for the resected mass.

On examination, she had a temperature of 37 °C, her blood pressure was 130/80 mm Hg, pulse was 80 beats per minute, respiratory rate 16 breaths per minute and oxygen saturation 100% on room air. There was no evidence of pallor, finger clubbing, cervical lymphadenopathy, or jaundice.

A thorough head-to-toe examination revealed notable supraorbital ridges, prognathism, macroglossia with thick lips, large ears, spade-like hands and feet. The systemic examination was normal.

Lab investigations revealed a normal complete blood count (CBC) and metabolic profile with an elevated IGF-1 (634 ng/ml), and GH (31.4 ng/ml). Serum adrenocorticotropic hormone (ACTH) - 34.1 pg/ml), cortisol (18.7 mcg/dl) and HbA1c (6.7) were within normal range (Table 1).

Magnetic resonance imaging (MRI) of the pituitary gland revealed normal neurohypophysis. Computed tomography (CT) scan of the chest revealed a large anterior mediastinal mass measuring 137×70×123 mm (Figure 1). A CT-guided biopsy of the anterior mediastinal mass confirmed the diagnosis of typical carcinoid based on histopathological examination and immunohistochemical (IHC) staining. On IHC, tumor cells expressed synaptophysin (diffuse, strong) and chromogranin (focal, weak). MIB-1 labelling index was 3%.

The patient underwent left anterolateral thoracotomy. The mass was found adherent to adjacent structures including the left lung, pulmonary trunk, and pericardium. Intraoperative findings revealed a well-defined mass lesion measuring approx 12×10 cm involving the anterior and superior mediastinum. Complete excision was achieved and an intercostals chest tube was placed for drainage (Figure 2). The patient's postoperative recovery was uneventful, and she was discharged 4 days after surgery.

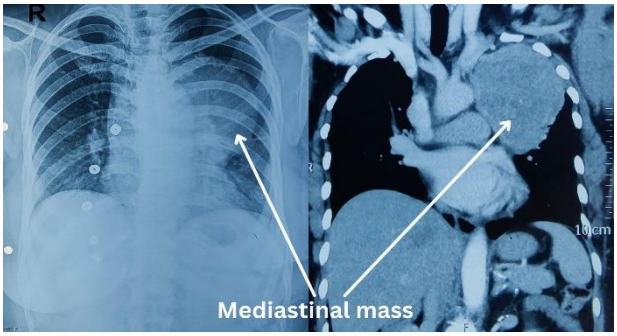

Figure 1: Mediastinal mass.

Final histopathology turned out to be atypical carcinoid with a mitosis of 5-6/10 hpf. No extracapsular extension was seen. There were areas of necrosis and lymphovascular invasion, but no perineural invasion.

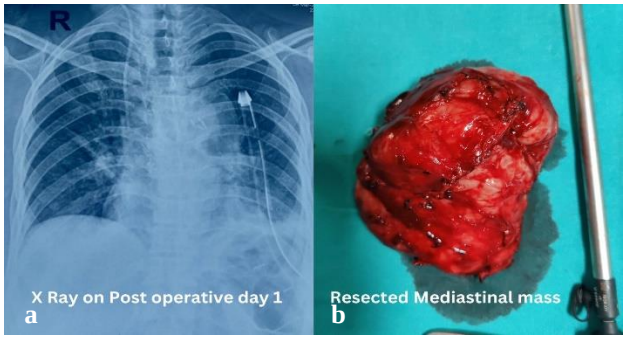

Figure 2: (a) X-ray post-operative day 1, and (b) resected mediastinal mass.

Table 1: Serum marker.

Serum marker	Preoperative	Post-operative (3 weeks after surgery)
IGF-1 (ng/ml)	634	226
GH (ng/ml)	31.4	6.2
ACTH (pg/ml)	34.1	26
HbA1c (%)	6.7	-

Figure 3: (a) Pre-operative photo, and (b) post-operative photo.

All features secondary to excessive growth hormone secretion were resolved within 30 days after surgery. Facial appearance became normal and can be very well appreciated in the image (Figure 3). IGF-1 (226 ng/ml) and GH (6.2 ng/ml) levels in serum done after 3 weeks of surgery were within normal limits (Table 1).

DISCUSSION

Ectopic GH secretion is an uncommon phenomenon, representing less than 1% of all acromegaly cases. Our patient's presentation was notable for typical acromegalic features, including prominent supraorbital ridges, prognathism, macroglossia, and spade-like hands and feet. Despite these characteristic signs, the systemic examination was unremarkable, emphasizing the importance of considering ectopic sources of GH in patients with normal pituitary imaging.

Differentiating between pituitary and ectopic acromegaly can impose significant diagnostic challenges. It cannot be differentiated based on clinical features and on biochemical analysis. IGF-1 and GH are elevated in both these conditions, with the latter failing to suppress following an OGTT. GHRH levels have been considered to be not only a reliable marker for the diagnosis of ectopic acromegaly (increased GHRH level are seen in ectopic acromegaly versus low levels in acromegaly of pituitary origin), but also an indicator of the disease activity following surgical treatment and a sensitive marker to detect disease recurrence.[7] Plasma GHRH estimation was not done in our patient as the assay was not available at our institute. However, a normal pituitary gland on magnetic resonance imaging, combined with laboratory evidence of GH hypersecretion, imaging finding of mediastinal mass with biopsy suggestive of neuroendocrine tumor and patient with clinical features of acromegaly constitute sufficient evidence for diagnosing an ectopic acromegaly caused by ectopic GH production.

The absence of a discrete pituitary adenoma is a strong indication to pursue further evaluation for ectopic GHRH syndrome.[2]

However, many published case series have shown that the pituitary is often abnormal on imaging. In one series, the pituitary was normal or homogenously enlarged in 58% of the cases but imaging was suggestive of a pituitary adenoma in 29%.[8] This has frequently led to mistaken pituitary surgery.

Once ectopic acromegaly is suspected, chest and abdominal imaging will frequently reveal the causative lesion or lesions. Octreotide scan, using radiolabeled somatostatin scintigraphy, can confirm the presence of neuroendocrine tumor leading to ectopic GH secretion.[9]

The treatment of acromegaly due to ectopic GHRH production has two major components: therapy directed at the underlying neuroendocrine tumor and/or therapy directed at the effects of excess IGF-1 production. Optimal treatment of ectopic acromegaly is complete surgical resection of the hormone secreting neuroendocrine tumor. In our patient, complete mediastinal mass excision through an anterolateral thoracotomy approach, with histological evidence of complete atypical carcinoid resection, brought about a dramatic and sustained decrease in GH and IGF-1 levels. It also brought about a dramatic decrease in total daily insulin requirement, resolution of facial features of acromegaly.

Historically, however, either by the time acromegaly is diagnosed, or recognized in a patient with known neuroendocrine tumors, the neuroendocrine tumor is frequently found to be metastatic and unresectable. In one series, 8 of 31 patients with ectopic acromegaly were found to have disseminated disease at diagnosis.8 In this situation, medical therapy with somatostatin analogues is the mainstay of treatment.

CONCLUSION

Our case highlights the importance of a high index of suspicion for ectopic hormone secretion in acromegaly patients with or without normal pituitary on scan. It also emphasizes the necessity for comprehensive imaging and biochemical evaluation to identify the underlying cause. Furthermore, it showcases that surgical resection is the mainstay treatment for ectopic acromegaly and the outcomes are dramatic following a complete resection. Metastatic and inoperable cases can be managed with somatostatin analogues.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Singh A, Sharma N, Shekhawat JS, Singh M, Sherawat RC, Chaturvedi A. Definitive role of surgery in management of acromegaly due to ectopic growth hormone secretion: review of literature. Int J Res Med Sci 2025;13:867-70.