Acromegaly with No Evidence of Pituitary Adenoma or Ectopic Source

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Abstract
Acromegaly is caused by the uncontrolled hypersecretion of growth hormone (GH) and secondary increases of insulin-like growth factor–1. More than 95% of patients with acromegaly have a growth hormone-secreting pituitary adenoma. Ectopic GH or growth hormone releasing hormone (GHRH)-secreting tumors are rare cause of acromegaly. Pituitary adenomas that cause the hypersecretion of GH are nearly always visible on magnetic resonance imaging. Rarely, patients without an ectopic source may have normal pituitary imaging. In managing this rare circumstance, exploring pituitary or medical treatment with a somatostatin analog might be useful. We describe a patient with acromegaly with no pituitary adenoma and no evidence of ectopic source, who was treated with long-acting octreotide.

Keywords: Acromegaly; negative magnetic resonance imaging; somatostatin analog treatment

Özet

Anahtar kelimeler: Akromegali; negatif manyetik rezonans görüntüleme; somatostatin analog tedavisi

Introduction
Acromegaly is caused by the uncontrolled hypersecretion of growth hormone (GH) and secondary increases of insulin-like growth factor–1 (IGF–1) and has an incidence of 3–4 cases per million population per year (1). The clinical manifestations range from soft tissue swelling, acral enlargement, increase in the ring and/or shoe size, facial bone deformities, including jaw prognathism, to glucose intolerance or frank diabetes mellitus, hypertension, and cardiovascular disease (2). GH-secreting pituitary adenomas are the cause of acromegaly in over 95% of patients (3). Most of these tumors are large and easily identified on magnetic resonance imaging (MRI) of the sella. Very small microadenomas that are not visible on pituitary MRI are rare and could be identified on pituitary exploration (4). Ectopic GH- or growth hormone-releasing hormone (GHRH)-secreting tumors are a rare cause of acromegaly (5). Most frequently bronchial and pancreatic carcinoid tumors and less frequently pancreatic islet tumors, pheochromocytomas, medullary thyroid carcinomas, and small cell carcinomas of the lung are the sources of ectopic acromegaly because of GHRH secretion (6–10). We describe a patient with acromegaly with no pituitary adenoma and no evidence of ectopic source who was treated with long-acting octreotide.

Case Report
On March 2011, a 49-year-old woman was referred to our outpatient clinic with complaints of a headache, swelling of hands, and increase
Acromegaly is caused in over 95% of patients by a GH-secreting pituitary tumor. Pituitary enlargement with the absence of a detectable tumor is strongly suggestive of acromegaly secondary to ectopic GHRH secretion. Therefore, if the MRI is normal, abdominal and chest imaging should be performed to check for an ectopic focus of hormone secretion (11). Serum GHRH is the only specific marker for ectopic acromegaly, and if a clear pituitary adenoma is not seen on MRI, GHRH measurement should be performed if possible (12). Chromogranin A (CgA) level may be measured, but as CgA was thought as a prognostic tumor marker for patients with an established diagnosis to assess treatment response, it is not recommended as a diagnostic marker for neuroendocrine tumors such as carcinoids. We did not prefer to measure the CgA level (13,14). PET/CT scans with 68Ga-DOTANOC are highly sensitive and specific and increasingly used for detecting neuroendocrine tumors. Catheterization studies to demonstrate an arteriovenous gradient of either GH or GHRH in the tumor region are suggested if all these investigations fail (12). In this case, we could not measure GHRH and perform catheterization be-

Figure 1: (A) Acromegalic face and (B) acral enlargement.
cause of a technical failure. The ectopic source is mostly excluded with a 68Ga-DOTANOC PET scan and other imaging methods. Acromegaly secondary to a very small pituitary microadenoma not visualized on pituitary MRI is rare. Doppman et al. (15) described three patients with acromegaly who did not show any ectopic uptake and in whom MRI could not demonstrate pituitary adenomas. All three patients underwent pituitary exploration and the adenomas were identified at surgery (resected adenoma sizes: 6, 7, and 10 mm). Daud et al. (16) reported a patient with acromegaly who did not have imaging evidence of a pituitary adenoma with contrast-enhanced MRI. A 9-mm adenoma was later discovered at surgery and was successfully removed. Lonser et al. (17) reported a series of six patients with acromegaly in whom MRI failed to detect pituitary adenomas and who also lacked an ectopic source. However, on pituitary exploration, microadenomas were detected in all cases. Khandelwal et al. (4) reported a case of acromegaly in which imaging with conventional MRI, followed by a second, fine-cut MRI with special volumetric interpolated breath-hold examination sequences, failed to reveal a pituitary adenoma. However, on surgical exploration, a pituitary adenoma infiltrating the dura was identified and removed. An ectopic source of GH/GHRH was also ruled out. Pituitary exploration was one of the treatment options in our patient. However, in this condition, surgery should be followed by catheterization. Our patient was not desirous for surgery and because of the technical failure to measure GHRH, mild symptoms of the patient, and mildly elevated serum GH and IGF-1 levels, following up the patient with long-acting somatostatin analog therapy was decided. An effective treatment and suppression were provided.

In the medical treatment of acromegaly, somatostatin analogs are the first option. High numbers of somatostatin receptors are expressed on most tumor cells, especially growth hormone-secreting pituitary adenomas and most neuroendocrine tumors (18,19). Somatostatin analogs can slow the growth of these tumors by binding to specific cell surface receptors. The activation of somatostatin receptors induces apoptosis and cell cycle arrest primarily because of the regulation of mitogen-activated protein kinase and phosphotyrosine phosphatase activities. Moreover, somatostatin analogs indirectly reduce tumor growth by inhibiting tumor angiogenesis and growth factor secretion in somatostatin receptor-negative tumors (20). Cabergoline may be preferred as the first treatment of choice in the management of mild acromegaly. In a meta-analysis of 15 studies of cabergoline therapy in acromegaly, normal serum IGF-1 levels were achieved in 51 of 149 patients (34%) (21). In our patient, lanreotide 60 mg was used, but cabergoline might be preferred as an initial therapy.

Currently, there is no consensus for the treatment of patients with acromegaly and negative pituitary imaging (22). For several years, small ectopic carcinoid tumors could not be detected with available imaging methods. Therefore, because of the risks of unnecessary pituitary surgery, following up patients with somatostatin analog therapy may be an option for patients with mild disease.

### Authorship Contributions


### Conflict of Interest

No conflict of interest was declared by the authors.

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### References