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Chapter

Thyroid Cancer and Acromegaly

Carla Souza Pereira Sobral, Marcelo Magalhães and Manuel dos Santos Faria

Abstract

Acromegaly results from oversecretion of growth hormone and subsequent insulin growth factor-I. Some studies have described an association between acromegaly and increased risk of some cancers, including thyroid cancer, the most common endocrine malignancy. It is well known that follicular thyroid cells express IGF-I receptor and that GH and IGF-I have both proliferative and anti-apoptotic effects and their hypersecretion may theoretically induce tumor development and stimulate its growth, despite the fact that research data is conflicting and population-based data on thyroid cancer and acromegaly is rare. Some molecular alterations, including point mutations in *BRAF* and *RAS* genes and *RET/PTC* gene rearrangements, have been associated with oncogenesis of PTC. However, the implications of these genetic markers in the development of PTC in patients with acromegaly are not yet well known. In this chapter, we discuss epidemiology, pathogenesis, molecular biology aspects, and how to screen and to manage acromegalic patients with nodular thyroid disease and thyroid cancer.

Keywords: acromegaly and thyroid cancer, IGF-I and cancer, thyroid and acromegaly, GH and cancer, molecular markers and thyroid cancer

1. Introduction

Acromegaly is a rare disease that results from the oversecretion of growth hormone (GH) and subsequent insulin growth factor I (IGF-I) [1]. It is associated with important complications that may reduce life expectancy of these patients [2, 3].

Most acromegalic patients die from cardiovascular, cerebrovascular, or respiratory diseases [3, 4]. Nevertheless, in the past two decades, some studies have also described an association between acromegaly and an increased risk of some cancers such as colorectal and thyroid cancer (TC), which is the most common endocrine malignancy, among others [5].

Part of the difficulty in determining the true incidence of cancer in this population is due to the relative rarity of acromegaly [6]. On the other hand, with improvement in surgical and radiotherapeutic procedures as well as advances in medical treatment, an increase of the survival rate of patients with acromegaly has been shown. As a result, patients may have a longer exposure to high GH levels [7].

As the prevalence of thyroid cancer has been shown to increase among patients with acromegaly, this should draw attention for clinicians to investigate thyroid disease, particularly thyroid cancer.

2. Epidemiology

The association between acromegaly and TC is supported by preclinical data showing that GH-IGF system plays an important role in cancer development and progression [6]. However, clinical studies that addressed the association between acromegaly and cancer produced controversial results, partly due to the different methodological approaches used (case-control and population-based designs) [8].

A comprehensive meta-analysis showed an increased risk of both nodular thyroid disease (NTD) (OR = 6.9, RR = 2.1) and TC (OR = 7.5, RR = 7.2) in acromegaly. It showed a prevalence slightly below 60% of NTD and of around 4% of TC [8]. Within this context, a consistent Brazilian multicentric study with 124 acromegalic patients in a case-control design showed a higher prevalence of 7.2% for TC and 0.7% in the control group [9].

These findings may result from the fact of improving diagnostic and treatment of acromegaly extending the life duration which increases the prevalence of both benign and malignant neoplasms [3–11].

On the other hand, the co-occurrence of autoimmune thyroid diseases and acromegaly is not common. So far only a handful of cases of Graves-Basedow disease in acromegalic patients have been reported, while Hashimoto's disease occurs more frequently (4.6%) [12, 13].

3. Molecular pathogenesis of TC in acromegalic patients

3.1 Molecular basis of acromegaly

The pituitary gland integrates hormonal signs that control several homeostatic processes such as metabolism, growth, and reproduction. Cell clusters localized in the anterior pituitary, somatotrophs, secrete GH responsible for cellular proliferation through membrane-bound growth hormone receptor (GHR) present in various organs and systems [14]. The interaction between GH and GHR results in activation of intracellular protein Janus kinase 2 (JAK2). As shown in **Figure 1**, once phosphorylated JAK2 activates the signal transducers and activators of transcription (STAT) protein that is translocated to the nucleus and initiates transcription of genes in response to GH [15], the STAT is able to bind to IGF-I promoter regulating the transcription of this gene [16]. Thus, the presence of GH can induce the synthesis of IGF-I that occurs mainly in the liver and is composed of 70 amino acids and has mitotic and anti-apoptotic effects [1].

In the vast majority of cases, the excess of GH in acromegaly is originated from proliferating somatotrophs (somatotropinoma). The pituitary adenomas are of monoclonal origin, indicating that the tumor rises from a single cell that acquires proliferative advantage [17]. The primary defect that leads to development of somatotropinoma may result from genetic and epigenetic alterations inducing the activation of oncogenes or inactivation of tumor suppressor genes [1]. Mutations in the alpha subunit of transmembrane G protein is observed in 40% of GH-secreting tumors [1]. This abnormality may cause constitutive activation of cyclin AMP (cAMP) and consequent hypersecretion of GH. Loss of expression of proapoptotic molecules such as GADD45γ (growth arrest and DNA damage-inducible 45γ protein) and overexpression of oncoproteins, including PTTG (pituitary tumor-transforming gene), are phenomena also observed in pituitary adenomas [17, 18].

Most cases of acromegaly occur sporadically; however, approximately 5% of cases may be related to inherited diseases such as multiple endocrine neoplasia type 1 (MEN1), Carney complex (CNC), and familial isolated pituitary adenoma

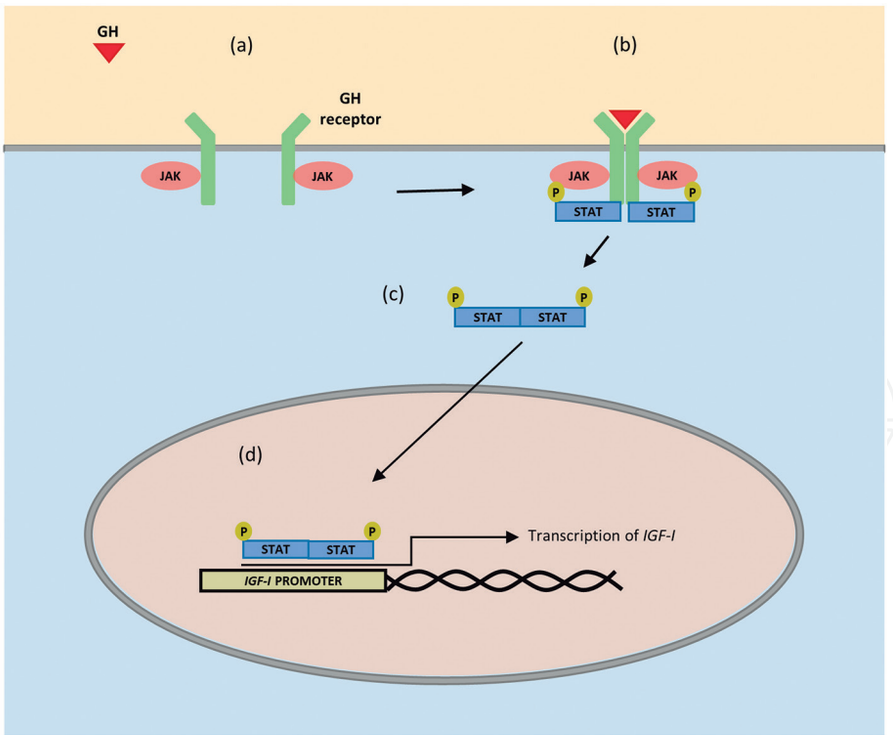

Figure 1.
Activation of JAK/STAT pathway mediated by GH (growth hormone). (a) JAK/STAT pathway components are inactive. (b) GH leads to dimerization of its receptor promoting phosphorylation of JAK and consequent activation of STAT proteins. (c) Once activated, STAT forms dimers that are translocated to the cell nucleus. (d) The STAT dimers in the nucleus are capable of binding to IGF-I promoter, initiating the transcription of this gene.

(FIPA) [17]. Germline mutations in aryl hydrocarbon receptor-interacting protein (*AIP*) gene seem to be the most frequent genetic alteration detected in sporadic and familial acromegaly patients [19]. The MEN1 and CNC are caused mainly by defects in genes *MEN1* (menin) and *PRKAR1A* (regulatory subunit type 1 alpha), respectively [17].

3.2 Cross talk between acromegaly and thyroid cancer

The serum GH excess may promote proliferation and suppress apoptosis in many tissues [15]. Thus, it is suggested that acromegaly is responsible for the increased risk for development of many malignancies. PTC is the most common thyroid cancer observed in acromegaly [7, 9]. This type of pituitary tumor can also be associated with benign thyroid conditions such as diffuse and nodular goiters [9].

The mechanism of thyroid carcinogenesis in acromegaly is attributed to an autocrine/paracrine loop for GH/IGF-I in tumor tissue [8]. As the thyroid follicular cells also produce IGF-I and express genes encoding IGF-IR, the long-term exposure of thyrocyte to high GH/IGF-I levels may work synergically with this loop in promoting goiter development and malignant transformation [20].

3.3 Molecular mechanisms and potential biomarkers of thyroid carcinogenesis in acromegaly

As shown in **Figure 2**, the molecular oncogenesis of PTC is mainly related to deregulation of mitogen-activated protein kinase (MAPK) signaling pathway and involves point mutations in *BRAF* and *RAS* genes and *RET/PTC* gene rearrangements [21, 22]. Analysis of these molecular markers can have diagnostic and prognostic implications in thyroid cancer.

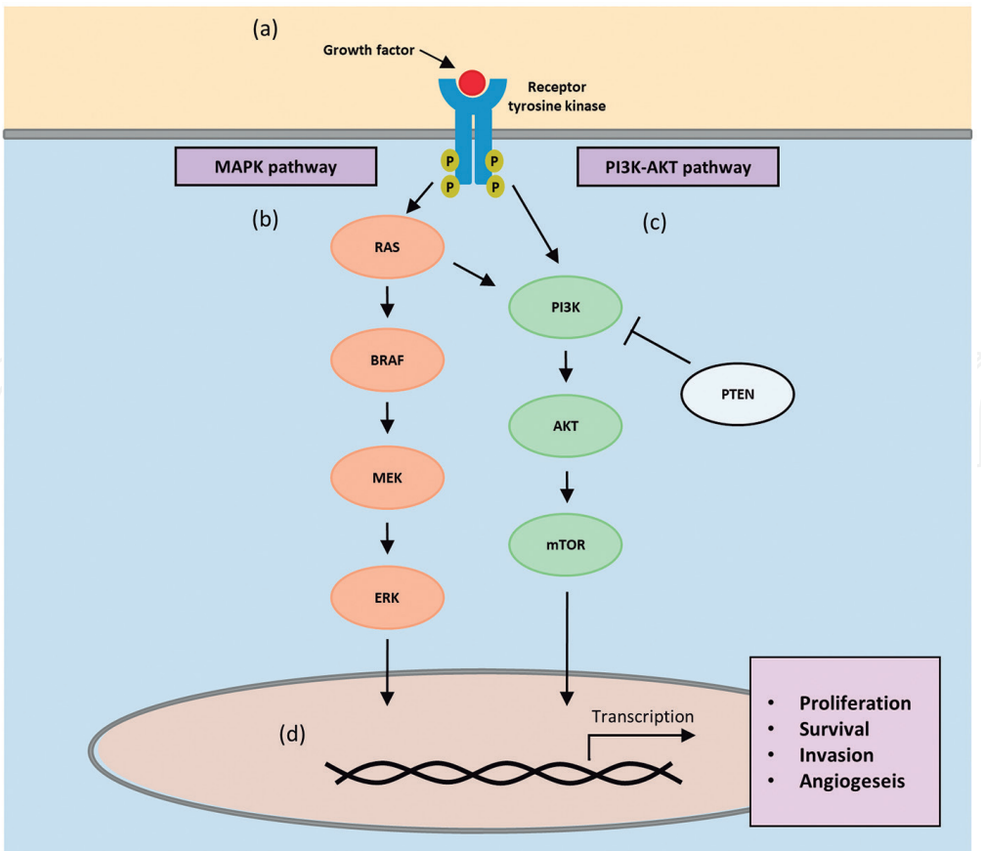

Figure 2.
MAPK and PI3K pathways. (a) Growth factors bind to receptor tyrosine kinase and trigger the activation of (b) MAPK and/or (c) PI3K-AKT. (d) The signaling mediated to both pathways promotes the transcription of gene associated to different cellular processes such as proliferation and survival.

3.3.1 BRAF mutation

BRAF (B-type RAF kinase) is a serine threonine kinase considered the most potent MAPK activator. This protein regulates important cellular processes such as proliferation, differentiation, and apoptosis [1].

In PTC, the main mechanism for activation of *BRAF* gene is a point mutation that promotes a substitution of nucleotide thymine by adenine at position 1799. This single nucleotide change promotes the replacement of valine by glutamate at protein residue 600 (V600E). The *BRAF* V600E mutation is the most frequent genetic abnormality reported in thyroid carcinomas in the general population, particularly in PTC [21].

In acromegalic patients, the importance of *BRAF* V600E mutation on PTC carcinogenesis is still not well defined. In an Italian cohort of acromegalic patients, the *BRAF* V600E mutation was detected in 70% of cases with PTC, suggesting that this mutation is the main genetic driver of neoplastic transformation of thyroid cells in acromegaly [23]. On the other hand, other studies have demonstrated that the *BRAF* V600E mutation is infrequent in patients PTC with and without acromegaly [20, 24]. In these reports lower prevalence of this genetic alteration in acromegalic patients with PTC than non-acromegalic cases with PTC was verified. These results suggest that *BRAF* V600E mutation may not be a main mechanism of malignant transformation of thyroid cells in patients with acromegaly.

3.3.2 RAS mutations

The *HRAS*, *KRAS*, and *NRAS* are homologous gene members of the *RAS* (retrovirus-associated DNA sequences) family. These genes encode GTP-binding

proteins localized at the inner superficial of the cell membrane involved in signaling MAPK and PI3K-AKT pathways [1]. Together, *RAS* mutations are the second most frequent molecular alteration found in thyroid cancer, occurring in 10–20% of PTC cases and 40–50% of follicular carcinomas [22].

Point mutations are commonly restricted at codon 61 of the *HRAS* and *NRAS* genes and at codons 12 and 13 in the *KRAS* gene. *RAS* mutations in thyroid cancer have been associated to favorable prognosis such as tumor encapsulation and absence of metastases but also may represent a poor prognostic factor predisposing to cellular dedifferentiation and anaplastic transformation [22]. *NRAS* codon 61 mutation has been referred as the most frequent genetic alteration in PTC patients with acromegaly. Aydin et al. pointed out that patients with *NRAS* codon 61 mutation have aggressive histologic features such as vascular and capsular invasion [24]. However, another study revealed no case in a cohort of acromegalic patients with PTC-harbored *RAS* mutations [23]. These contradictory findings indicate that the importance of *RAS* mutational status in thyroid oncogenesis in acromegaly remains to be clarified.

3.3.3 RET/PTC rearrangements

The *RET* is a proto-oncogene that encodes a receptor-type tyrosine kinase with three domains: extracellular, transmembrane, and intracellular tyrosine kinase. The activation of this gene can contribute to the development of several neoplasms [25]. Rearrangements of *RET* that originated from fusion with unrelated genes (RET/PTC rearrangements) have been reported in thyroid follicular cells [26]. This genomic alteration can produce a chimeric oncoprotein with inappropriate tyrosine kinase activity able to continually stimulate the MAPK and PI3K-AKT pathways [26]. Among the fusion variants of *RET*, the rearrangements RET/PTC1 and RET/PTC3 are the most frequent in thyroid cancer. Whereas in RET/PTC1 the *RET* gene is fused to *CCDC6* (known as *H4*), in RET/PTC3 the rearrangement occurs with *NCOA4* (known as *ELE1* or *RFG*) [25]. RET/PTC rearrangement appears to be an important mechanism of thyroid carcinogenesis, but its frequency has oscillated in different reports. This genetic abnormality was not detected in PTC patients with acromegaly [24], although studies with this approach are rare in acromegaly.

3.3.4 Other molecular alterations

Besides the potential classic marker, other molecules have been evaluated in relation to their implication on PTC development in acromegaly, among them are IGF-I, IGF-IRβ, AIP, AHR, and galectin-3 (Gal-3) [20, 23–24, 27].

The analysis of immunohistochemical staining for IGF-IRβ revealed a high expression of this receptor in PTC samples [20]. Although differences in IGF-IRβ tumoral staining between PTC patients with and without acromegaly have not been observed, this marker had significantly less expression in adjacent normal tissue of patients with acromegaly. These data suggest that high GH levels may trigger autocrine and paracrine effects of IGF-I in thyroid follicular cells resulting in overexpression of IGF-IRβ in tumor tissue of acromegalic patients. In line with these results, it was observed that PTC patients with acromegaly have higher expression of IGF-I than PTC cases without acromegaly [27]. Additionally, an intense expression was verified of Gal-3 in PTC with acromegaly, speculating a possible influence of this protein on thyroid carcinogenesis.

As previously mentioned, inactivation of *AIP* gene is frequently reported in pituitary tumors. However, this genetic abnormality seems not to be determinant to thyroid carcinogenesis in acromegalic patients [23]. Furthermore, there are no

differences in AIP protein expression between PTC in patients with and without acromegaly. Although immunohistochemical analysis for AIP receptor (AHR) has shown strong staining of PTC samples carrying *BRAF* V600E compared with wild type, differences were not found in AHR staining between PTC in acromegalic and non-acromegalic patients [23]. Thus, molecular alterations in AIP and AHR cannot be related to PTC carcinogenesis in acromegaly.

4. How to screen NTD in acromegalic patients

NTD seems to be significantly more frequent in patients with acromegaly. Even palpable thyroid nodules occur significantly more often in these patients [9, 13].

Periodic thyroid ultrasound (US) and careful evaluation of detected lesions are important parts in the follow-up of acromegalic patients. The sonographic characteristics considered to be suspicious of TC, such as microcalcifications, irregular margins (infiltrative and microlobulated), taller than wide shape, and rim calcifications with small extrusive soft tissue component (evidence of extrathyroidal extension), are the same of the general population with NTD [5, 9].

Fine-needle aspiration (FNA) is the procedure of choice in the evaluation on NTD, and it should be performed when clinically indicated according to nodule's size and US appearance. The FNA cytology result must be reported using the Bethesda System for Reporting Thyroid Cytopathology [9, 28].

In summary, as the risk of malignancy in thyroid nodules in these patients is about 8%, which is in the range considered for the general population, the management of NTD should follow the current guidelines [9, 28].

5. How to treat TC in acromegalic patients

Although there is a risk of TC in acromegalic patients, its clinical behavior does not seem to be different [5]. Therefore, acromegalic patients with TC may be treated with total thyroidectomy or hemithyroidectomy according to its FNA result and size and the presence of clinically apparent metastatic lymph nodes [28].

Before surgery, we suggest that all acromegalic patients should do a preoperative voice assessment (preoperative laryngeal exam—laryngoscopy) because they frequently have soft tissue thickening and edema of the tongue, pharynx, and upper airways [3]. Also, they must have a careful evaluation of comorbidities as hypertension, diabetes mellitus, and cardiovascular disease [3].

After surgery, these patients may or may not receive radioiodine depending, if it is a differentiated TC, on its risk of recurrence [28]. Studies about the relationship between medullary thyroid cancer (MTC) and acromegaly are lacking.

The frequency of US and laboratory tests during TC follow-up should follow the current guidelines.

6. Conclusion

NTC and TC are more frequent in acromegalic patients. On the other hand, the studies about potential mechanisms involved in this association between TC and acromegaly are still scarce, and besides they include small sample sizes. Furthermore, in these few reports, there is no marker clearly implicated on diagnosis or prognosis of PTC. Thus, further studies with this approach are needed.

We suggest that acromegalic patients should be routinely screened by thyroid ultrasound and during their follow-up as necessary. Its management should follow the current guidelines. This is very important because it may allow early diagnosis and treatment of TC.

Acknowledgements

We would like to thank Doctor Gilvan Nascimento Cortês for the review of the manuscript.

Conflict of interest

There is no conflict of interest.

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