Editorial

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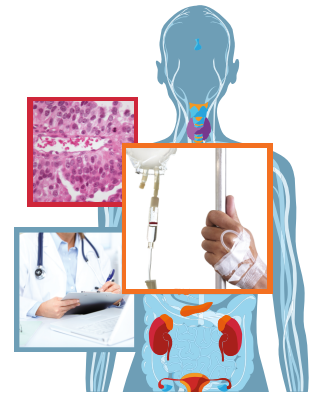

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Somatotroph adenomas: histological subtypes and predicted response to treatment

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Pituitary adenomas are now described as pituitary neuroendocrine tumors (PitNets) [1]. A large proportion, approximately 22–54%, is clinically defined as nonfunctioning pituitary adenomas and will present with signs and symptoms of mass effect, rather than excessive hormone secretion. 'Silent pituitary adenomas' are tumors that express one or more of the anterior pituitary hormones or their transcription factors, which can be visualized by immunohistochemical analysis. Although, they do not secrete hormones at a clinically relevant level. Silent pituitary adenomas can be further sub categorized into totally silent or clinically silent tumors [2].

A null cell adenoma that is restricted to a primary anterior pituitary tumor, is hormone negative (determined by immunohistochemistry) and does not express any of the pituitary transcription factors. The clinical picture of pituitary adenomas reflects a continuum between functional adenomas and 'totally silent' adenomas. The functional status of the tumor can change throughout the disease course [3].

Somatotropic tumors are growth hormone (GH) producing tumors. These account for approximately 20% of surgically treated pituitary tumors and more than 95% of cases of acromegaly. Very rare cases of acromegaly are due to an excess of the GH-releasing hormone (GHRH). This may be associated with neuroendocrine tumors of lung, pancreas, medullary thyroid cancer, pheochromocytomas and hypothalamic gangliocytomas. Ectopic production of GH has been reported from rare cases of pancreatic neuroendocrine tumor or lymphoma [4,5].

Many familial syndromes have been reported to predispose to acromegaly or gigantism. These include multiple *MEN1* and *MEN4*, familial isolated pituitary adenoma and Carney complex. A sporadic germline mosaic disorder McCune-Albright disease can also result in GH excess [6]. A rare genetic syndrome, X-linked acrogigantism has been described in early-onset childhood gigantism [7]. In familial cases, onset is in young age with florid presentation due to high GH levels. The response to medical treatment is poor [7].

Silent somatotroph adenomas lack clinical and biological signs of acromegaly but are GH-immunoreactive tumors. They represent approximately 2–4% of all pituitary adenomas in surgical series. Patients with truly silent somatotroph adenomas have normal preoperative GH and IGF-1 levels; some cases can be clinically silent but demonstrate a lack of GH suppression and elevated IGF-1 levels (whispering adenomas) [8].

Growth hormone excess can be due to pure somatotroph adenomas and these can be densely granulated (DGSA) or sparsely granulated (SGSA).

DGSA are present in 30–50% of acromegaly cases. The cells are eosinophilic and are strongly as well as diffusely positive for GH and α-subunits. They resemble normal somatotrophes. DGSA is usually present in older patients and are slow-growing lesions. Patients have typical features of acromegaly and high levels of GH and IGF-1 and imaging demonstrates characteristic bone changes of acromegaly and is associated with low intensity tumors on T2-weighted MRI scans. The disease shows an excellent response to somatostatin analogs (SSAs).

SGSA accounts for 15–35% of patients with acromegaly. The cells are lightly eosinophilic or chromophobic. The tumors identified usually demonstrate focal or weak *GH* expression and no α-subunit expression. SGSAs have

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characteristic fibrous bodies. A variant of somatotroph tumors may have occasional fibrous bodies. This is classified as an intermediate type but behaves like a DGSA.

SGSAs can be more aggressive and in most cases, the Ki67 proliferation index is greater than 3%. SGSA is more common in patients of younger age, presenting with rapidly growing tumors, which are large at the time of diagnosis. The clinical presentation is subtle and the tumor may be classified as a silent tumor. Silent somatotroph adenomas are more frequently sparsely granulated. Compared to DSGA, the levels of GH and IGF-1 are not high. On MRI scans, SGSAs have a characteristic T2 hyperintensity and are found to have frequent cavernous sinus invasion. SGSAs are often resistant to treatment with SSAs. SGSA are also associated with recently recognized histological variants of GH excess such as plurihormonal tumors. This group of tumors expresses multiple hormones. Every tumor type has distinct pathophysiology, resulting in variations in clinical manifestations, imaging and responses to therapies [9].

These include:

- Mammosomatotrophs, which are composed of single population of Pit-1 cells. These express GH and prolactin and α-subunit, estrogen receptor-α (ERα). Their clinical and biological features are very similar to the DGSA. However, prolactin levels are generally higher than 4000 mU/l and are more frequently diagnosed in young patients who initially present with acromegaly and gigantism. High levels of GH/IGF-1 can lead to earlier diagnosis even in patients with relatively small tumors. They respond to SSAs and to dopamine agonists.
- Mixed somatotroph–lactotroph tumors are composed of two different cell populations, somatotrophs and lactotrophs. Either of the cell population can be densely or sparsely granulated with various combinations occurring. These tumors are distinct from mammosomatotrophs, composed of a single monomorphous cell population that expresses both hormones. The tumors express Pit1 in all tumor cells, but ERα is only expressed in cells that also express prolactin. The clinical characteristics of mixed somatotroph–lactotroph tumors are dependent on the composition and the relative proportions of the two cell types. The behavior of these tumors is uncertain because of a lack of clear pathology and different patterns of histological subtypes. More recently, research has suggested that mixed somatotroph–lactotroph tumors are more likely to invade into the surrounding tissue and are difficult to treat with a low surgical cure rate. However, it has been suggested that this may be due to the sparsely granulated somatotroph component in many of these tumors [10].
- Mature plurihormonal Pit1-Lineage tumors resemble mammosomatotroph tumors, however, these tumors can synthesize GH, prolactin, thyroid stimulating hormone, as well as express the transcription factor GATA3. The patients may also have hyperthyroidism and goiter.
- Acidophil stem cell tumors consist of a single immature cell type, which are precursors of GH and prolactin cells. Upon histological analysis acidophil stem cell tumors demonstrate characteristic oncocyte with occasional fibrous bodies. They mainly express prolactin and GH only focally. Mostly patients present with hyperprolactinemia and acromegaly are less obvious as GH levels are mildly elevated. Acidophil stem cell tumors are more aggressive than common prolactinomas. The prolactin levels are disproportionally low for the size of the tumor and are frequently resistant to dopamine agonists treatment.
- Poorly differentiated Pit1-Lineage tumor is a neoplasm, which is composed of poorly differentiated, chromophobic cells that express Pit-1, as well as focal estrogen receptor and GATA3. These tumors can produce different combinations of GH, prolactin, α-subunit and/or thyroid stimulating hormone. Originally, this group was described as silent tumors, but patients may manifest with acromegaly, hyperprolactinemia, and/or hyperthyroidism. The tumors are mostly macroadenomas, aggressive and invasive, with increased risk for recurrence following surgery and lower rates of disease-free survival. Radiologic imaging frequently identifies cavernous sinus invasion with clivus and suprasellar growth involvement. Such tumors have been reported in members of MEN [10,11].

The diagnosis of pituitary hyperplasia is usually made on histology. It should result in the investigation of a GHRH-secreting tumor. If a GHRH secreting tumor is not identified, then the possibility of an underlying genetic syndrome, such as *MEN1*/*MEN4*, Carney Complex, McCune Albright and X-linked acrogigantism syndrome, should be considered [12].

Currently available treatments for the GH-secreting tumors include surgery, medical therapy with SSAs, dopamine agonists, and/or a GH receptor antagonist (Pegvisomant) and radiotherapy. The treatment results in remission of disease in approximately half of the patients. Dopamine agonists are a possible treatment op-

tion for acromegaly, this is due to mammosomatotroph tumors, mixed somatotroph–lactotroph tumors and pure somatotroph tumors presenting dopamine receptors on their surface.

In conclusion, the clinical spectrum of acromegaly varies from florid to subtle features and the diagnosis may be missed in some patients who are presumed to have clinically nonfunctioning pituitary tumors or no pituitary disorder. The various histopathological tumors resulting in acromegaly provide an explanation for the different clinical, biochemical and radiological characteristics of these patients and may provide valuable information to both researchers and clinicians as to why there is such varied response rate to different therapeutic approaches [10].

The classification of the granular pattern on histological subtypes has clinical relevance because it can be used as a predictor of somatoroph adenoma response to medical therapies.

There is a significant difference in the rate of remission between DGSA and SGSA. SGSAs have higher rates of incomplete resection and reoperation. They also tend to be unresponsive to therapy, particularly to SSAs and can be associated with disease persistence. DGSAs are reported to have a higher rate of remission in response to surgery as well as to medical therapy with SSAs. There is no difference in response to Pegvisomant between DGSA and SGSA. Most of the patients with SGSA normalize IGF-1 levels on Pegvisomant [13].

The reported response rate to stereotactic radiosurgery in patients with DGAS and SGSAS is similar, between 70 and 80%, within 4 years of therapy.

In somatotrope adenoma associated with genetic syndromes, treatment with SSAs are usually ineffective. Dopamine agonists can control prolactin levels but have no effect on GH and IGF-1 levels. Pegvisomant can be used with good results in patients with pituitary hyperplasia. Acromegaly, caused as a result of pituitary hyperplasia, either primary or due to ectopic GHRH, also has unique clinical and radiographic features, which may result in an alternative therapeutic approach being required [10].

Pituitary adenoma diagnosis is variable. It mainly relies on pathologists, who use electron microscopy and experimental antibodies. The research field is moving to improve the understanding of pituitary specific transcription factors to compliment immunohistochemistry (IHC) analysis. Identifying silent PitNET is essential, because these tumors could be treated with cabergoline or SSAs and these tumors are more prevalent than currently believed. Molecular studies are more sensitive than IHC in detecting the silent variants. Exploiting the underlying biology of pituitary adenoma, combined with IHC stains for transcription factors would, therefore, improve the classification of PitNET subtype, develop algorithms for individualized treatment of the subtypes and predict the long-term outcome of these tumors. Such framework will provide a more efficient, rational and clinically diagnostic approach. Most diagnostic laboratories are not equipped for this comprehensive diagnostic approach, as yet.

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References

1. Mete O, Lopes MB. Overview of the 2017 WHO classification of pituitary tumors. *Endocr. Pathol.* 28(3), 228–243 (2018).
2. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin. Endocrinol.* 72(3), 377–382 (2010).
3. Nishioka H, Inoshita N, Mete O *et al.* The complementary role of transcription factors in the accurate diagnosis of clinically nonfunctioning pituitary adenomas. *Endocr. Pathol.* 26(4), 349–355 (2015).
4. Sano T, Asa S, Kovacs K. Growth hormone-releasing hormone-producing tumors: clinical, biochemical, and morphological manifestations. *Endocr. Rev.* 9, 357–373 (1988).
5. Puchner MJ, Kudecke DK, Saeger W, Riedel M, Asa SL. Gangliocytomas of the sellar region – a review. *Exp. Clin. Endocrinol. Diabetes* 103, 129–149 (1995).
6. Ribeiro-Oliveira A, Barkan A. The changing face of acromegaly – advances in diagnosis and treatment. *Nat. Rev. Endocrinol.* 8, 605–611 (2012).

7. Trivellin G, Daly AF, Faucz FR *et al.* Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. *N. Engl. J. Med.* 371, 2363–2374 (2014).
8. Korbonits M, Carlsen E. Recent clinical and pathophysiological advances in non-functioning pituitary adenomas. *Horm. Res.* 71(Suppl. 2), 123–130 (2009).
9. Asa SL, Kucharczyk W, Ezzat S. Pituitary acromegaly: not one disease. *Endocr. Relat. Cancer* 24(3), C1–C4 (2017).
10. Amit A, Sylvia LA, Lama A, Ilan S, Shereen E. The clinicopathological spectrum of acromegaly. *J. Clin. Med.* 8(11), 1962 (2019).
11. Drummond J, Roncaroli F, Grossman AB, Korbonits M. Clinical and pathological aspects of silent pituitary adenomas. *J. Clin. Endocrinol. Metab.* 104(7), 2473–2489 (2019).
12. Rick J, Jahangiri A, Flanigan PM *et al.* Growth hormone and prolactin-staining tumors causing acromegaly: a retrospective review of clinical presentations and surgical outcomes. *J. Neurosurg.* 131(1), 147–153 (2018).
13. Fougner SL, Casar-Borota O, Heck A, Berg JP, Bollerslev J. Adenoma granulation pattern correlates with clinical variables and effect of somatostatin analog treatment in a large series of patients with acromegaly. *Clin. Endocrinol.* 76(1), 96–102 (2012).