Pituitary acromegaly: not one disease

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Abstract

Acromegaly has traditionally been regarded as a monomorphous disorder resulting from a benign pituitary adenoma. Increasing evidence, however, is highlighting that this disorder is associated with a spectrum of morphologically distinct pituitary tumors with variable clinical, biochemical and radiologic features and differing therapeutic outcomes that are attributed to different genetic and epigenetic changes. These data underscore the need for developing a more refined clinicopathological risk stratification system and implementing personalized targeted therapeutic approaches.

We read with interest the recent article ‘T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly’, published in the November 2016 issue of Endocrine-Related Cancer (Potorac et al. 2016). The authors concluded that ‘The T2-weighted signal intensity of GH-secreting adenomas at diagnosis correlates with hormone reduction and tumor shrinkage in response to primary SSA treatment in acromegaly’.

This report confirms the previous work of Hagiwara and coworkers (Hagiwara et al. 2003) who reported that with respect to pituitary somatotroph tumors, low signal on T2-weighted MR imaging is almost exclusive to the densely granulated variant, and our data indicating that hormone and tumor response to somatostatin analogs correlate with densely granulated tumor morphology in acromegaly (Ezzat et al. 1995, Bhayana et al. 2005). Others have confirmed the predictive value of tumor histologic subtyping with respect to somatostatin responsiveness (Fouger et al. 2012, Heck et al. 2012, Kato et al. 2012, Brzana et al. 2013, Larkin et al. 2013, Kiseljak-Vassiliades et al. 2015a). We have been applying this principle to our patient management for several years (Asa & Mete 2016, Bakir et al. 2016) and discuss it frequently in our multidisciplinary pituitary tumor case conferences. We have also found that densely granulated corticotroph and lactotroph tumors tend to exhibit low signal on T2-weighted MR imaging (Bakir et al. 2016).

This work emphasizes that pituitary tumors associated with various clinical entities do not represent a single disorder but rather a group of morphologically and functionally distinct entities (Asa 2011). Although most clinicians are now aware that rare cases of acromegaly are due to pituitary hyperplasia that represents a response to excess secretion of growth hormone-releasing hormone (GHRH), usually by an extracranial neuroendocrine tumor (Sano et al. 1988), many seem to be unaware that primary pituitary endocrine neoplasms that cause acromegaly represent a spectrum of lesions. Some may be hereditary and when they present in childhood, the manifestations of gigantism are distinct (Hannah-Shmouni et al. 2016). The vast majority, however, are sporadic and develop in adults.

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Pituitary GH-secreting lesions are divided by histopathological classifications into multiple variants. Somatotroph neoplasms may be composed of densely or sparsely granulated somatotrophs based on keratin patterns (Asa 2011); the importance of accurate interpretation of keratin staining patterns was emphasized by Obari and coworkers who showed clearly that mixed or intermediate staining patterns reflect a densely granulated tumor and only neoplasms with a pure pattern of ‘fibrous body’ keratin staining should be classified as sparsely granulated somatotroph tumors (Obari et al. 2008). Although sparsely granulated tumors are usually monohormonal, densely granulated somatotroph tumors often produce alpha-subunit (Asa 2011). Less frequent plurihormonal neoplasms may be composed of mammosomatotrophs that synthesize and secrete prolactin as well as GH and alpha-subunit and may occasionally co-secrete TSH also (Asa 2011); these are usually densely granulated and resemble densely granulated somatotroph tumors. Rarely, acromegaly may be caused by poorly differentiated tumors of Pit-1 lineage (Mete et al. 2016).

There are differences in the clinical presentations of these various neoplasms, and they exhibit different behaviors (Asa 2011). In general, densely granulated somatotroph and mammosomatotroph tumors tend to be associated with high levels of GH and IGF-1 and florid symptomatic (Trouillas 1996, Fougner et al. 2012, Heck et al. 2012, Kato et al. 2012, Brzana et al. 2013, Larkin et al. 2013, Kiseljak-Vassiliades et al. 2015a); perhaps because of this hypersecretory status, they are occasionally diagnosed as intrasellar tumors that can be surgically resected and cured (Asa 2011). In contrast, sparsely granulated somatotroph tumors tend to be associated with less obvious clinical symptomatology and more subtle biochemical alterations; they are usually large and invasive at diagnosis (Obari et al. 2008, Brzana et al. 2013, Larkin et al. 2013, Kiseljak-Vassiliades et al. 2015b). Clinically, mammosomatotroph tumors are associated with hypersecretion of prolactin and/or TSH; interestingly, patients with pure somatotroph tumors are significantly more likely to present with diabetes mellitus or impaired glucose tolerance than those with plurihormonal tumors (Cheng et al. 2013). Poorly differentiated tumors of Pit-1 lineage represent an extreme variant that is more likely to be diagnosed when large and more highly invasive (Mete et al. 2016). Although molecular alterations are rare in pituitary tumors (Asa & Ezzat 1998, 2002, 2009), the densely granulated somatotroph and mammosomatotroph tumors represent a subset in which there may be a characteristic genetic alteration; a subset of these tumors harbor the activating GNAS mutations that constitutively upregulate cyclic adenosine monophosphate (cAMP) signaling (Spada et al. 1990, Asa et al. 2007, Mayr et al. 2013). In contrast these mutations are usually not found in sparsely granulated somatotroph tumors with rare exceptions (Larkin et al. 2013). The molecular alterations in these more aggressive tumors remain unclear, but seem to involve GH receptor and STAT signaling (Asa et al. 2007, Tateno et al. 2011) that result in the manifestation of cytoskeletal dysfunction seen as keratin aggregation into fibrous bodies (Asa & Ezzat 1998, 2002, 2009). Patients with AIP germline mutations tend to harbor sparsely granulated tumors (Daly et al. 2010) and sparsely granulated somatotroph tumors are overrepresented among sporadic somatotroph neoplasms with low AIP expression (Denes et al. 2015), suggesting that loss of AIP may play a role in their development. Although the pathogenesis of poorly differentiated tumors of Pit-1 lineage is not known, some of these patients were members of MEN1 kindreds (Mete et al. 2016).

Given the differences in pathogenesis that give rise to distinct clinical, biochemical, radiological and morphological features of the various tumors associated with acromegaly, it is no surprise that their responses to targeted therapies are different. Tumors that are dependent on cAMP signaling would logically be responsive to the inhibition of this pathway that is mediated by somatostatin analogs, especially those that target the somatostatin receptor type 2 (SSTR2). Those receptors are highly expressed in most somatotroph tumors, but recent studies have suggested that SSTR2 may be downregulated in the sparsely granulated tumors (Kato et al. 2012, Brzana et al. 2013, Casar-Borota et al. 2013, Mayr et al. 2013, Kiseljak-Vassiliades et al. 2015b, Iacovazzo et al. 2016).

It should be noted that the same distinctions are even more pronounced in Cushing disease where densely granulated tumors tend to be small and associated with florid clinical and biochemical features, whereas sparsely granulated tumors are often more subtle, and although not silent, have been described as ‘whispering’ (Asa 2011). Mutations in the ubiquitin-specific peptidase USP8 (Ma et al. 2015, Reincke et al. 2015, Hayashi et al. 2016) have been identified in small tumors that were almost certainly densely granulated; these mutations may predict response to the somatostatin analog pasireotide (Hayashi et al. 2016). Therefore, our ability to detect densely granulated tumors in Cushing disease, which we have experienced, may also prove to have therapeutic significance.
In the era of precision medicine, it is critical that endocrine oncology maintain its position as a leader in understanding the importance of tumor classifications based on pathology and the value of biomarkers that predict appropriate therapeutic responsiveness. In other tumors, it has become a standard of care to ensure accurate subclassification before determining therapeutic approaches. One would never consider treating a breast cancer patient for ‘infiltrating ductal carcinoma’ or a lung cancer patient for ‘adenocarcinoma’ as we used to 20 years ago; instead, we classify every tumor based on the biomarkers that define pathogenesis and predict therapeutic efficacy. Similarly in the pituitary, we often see a diagnosis of ‘pituitary adenoma’ or perhaps ‘pituitary adenoma producing GH’. However, in patients with acromegaly, the most important immunostain that pathologists should evaluate is the keratin stain that at least allows the distinction of the two most important subclasses of GH-producing tumors. If this approach identifies abundant and distinct fibrous bodies, instead of the usual pattern of perinuclear filaments, the diagnosis is more likely to be that of a sparsely granulated tumor that is typically aggressive and resistant to somatostatin analog therapy.

The ability to predict cellular morphology on pre-operative imaging adds another dimension to the complexity of personalized pituitary medicine. Potorac and coworkers have underscored the value of this little known but important structure-function correlation in pituitary oncology.


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