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EDITORIAL

Biomarkers of acromegaly

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The papers of Kiseljak-Vassiliades et al. [1] and Selek et al. [2] published in this issue are significant because they focus on an important and unresolved problem of pituitary tumor prognosis, progression, and treatment. Many years ago, pituitary tumors were classified based only on their tinctorial properties using the hematoxylin—eosin stain and were classified as acidophilic, chromophobe, or basophilic adenomas. At that time, blood hormone levels could not be measured and the clinical diagnosis was based on a simple classification, namely acromegaly, gigantism, Cushing's disease, or endocrinologically inactive tumors. The introduction of immunohistochemistry (IHC) and electron microscopy (EM) resulted in revolutionary changes in the understanding of pituitary tumors. Blood hormone levels became possible to measure and correlate the clinical findings with the results of hormone measurements and morphology.

It became evident that there are many more separate entities [3]. Pituitary tumors could be mono-hormonal, producing only one hormone, bi-hormonal, or multi-hormonal producing two or more hormones, respectively. Using IHC and EM, it became possible to identify silent tumors which are immunoreactive for one or more hormones but not associated with increased hormone activity. Later studies revealed that there is plasticity within the pituitary cells, changing their hormone production and release that govern the key physiological processes they are involved in. With the introduction of molecular and genetic techniques, several new activities have been described and correlation, or lack of, has been documented in several patients with pituitary tumors.

Despite the significant progress made since the early 1970s, currently, not enough is known regarding the histogenesis, progression, and malignancy associated with pituitary tumors. Although several biomarkers have been tested and have shown a capacity to predict the clinicopathological behavior of pituitary tumors [4, 5], we still have difficulty identifying which tumors are slow growing or aggressive or which tumor has the potential for invasiveness, rapid growth, and metastases. According to the World Health Organization (WHO), pituitary carcinoma can only be diagnosed if cerebrospinal and/or systemic metastases can be documented [6]. The criteria to diagnose aggressive pituitary tumors are still not conclusively decided.

Kiseljak-Vassiliades et al. [1] reviewed the medical charts of 111 pituitary tumor patients diagnosed with acromegaly. The patients were operated by one neurosurgeon. The authors correlated the clinical data with histological subtype and disease control as defined by IGF-1 levels and random blood growth hormone levels in response to surgery and/or medical therapies. Results clearly indicate that sparsely granulated pituitary tumors occurred in younger patients and were larger compared with the densely granulated subtype. While the densely granulated tumors had a higher rate of remission after surgery, as well as, to medical therapy, their findings confirm that densely and sparsely granulated GH-producing pituitary adenomas differ in clinical behavior, treatment, and prognosis. Furthermore, their data validate the use of cam5.2 as a useful biomarker of response to therapy and overall prognosis in the management of acromegalic patients.

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Selek et al. [2] investigated 95 surgically removed tumors of patients consisting of 38 acromegaly, 26 prolactinoma, and 31 non-functioning pituitary adenomas, as well as 11 normal pituitary glands obtained at autopsy. They evaluated aromatase and estrogen receptor-alpha (ERα) immunoexpression, as well as, demographic, pre- and post-operative features of these patients. The results showed that aromatase expression was noted in all pituitary tissues studied and that immunoexpression was significantly higher in GH adenomas and negatively correlated with estrogen receptor-alpha (ER-α). Although aromatase H-score did not correlate significantly with post-operative remission status, patients with higher aromatase H-scores achieved complete remission. These findings suggest that aromatase expression may be a new prognostic marker for GH-producing pituitary adenomas.

Despite major progress achieved in the clinical and morphologic diagnosis of pituitary tumors, we have to shed more light on their pathogenesis, cell proliferation, progression, causes of invasion, and therapeutic options. Current oncology research is focused on finding reliable biomarkers that can predict tumor behavior. This work is in progress all around the world, in many universities, hospitals, and research institutes.

In pituitary adenomas, the best biomarker currently being used is the Ki-67, nuclear labeling index. It is expressed throughout the cell cycle and is detected routinely using the MIB-1 monoclonal antibody. This assay is useful but not perfectly reliable. p53, a cellular tumor antigen involved in cell cycle regulation, has also been used as a possible biomarker for identifying pituitary adenomas. In the WHO Classification, for identifying atypical pituitary adenomas, ki-67 nuclear index and immunopositivity for p53 are used as criteria [6]. Atypical adenomas are tumors that disclose "atypical morphological features suggestive of aggressive behavior," such as invasive growth, elevated mitotic index, a Ki-67 labeling index greater than 3 %, and extensive nuclear staining for the p53 protein [6]. The WHO classification of typical and atypical adenomas does not correlate straightforward with tumor clinical behavior. Neither all typical adenomas have a benign clinical evolution nor do all atypical adenomas have the tendency to recur or invade surrounding structures. Furthermore, there are pituitary tumors which grow rapidly but the Ki-67 nuclear labeling index is not high (<3 %), while others grow slowly and the Ki-67 nuclear index is high (>3 %). Lack of standardization of a reliable method for quantifying p53 expression and the fact that its detection can be inconclusive has limited the validity of p53 as a possible biomarker for pituitary adenomas [7].

It is a crucial element that an ideal biomarker for use in the diagnosis and prognosis of disease be highly specific and sensitive. Unfortunately, biomarkers are also influenced by type of fixative, technical differences, and by the fact that tumor cell proliferation is obviously affected by many events, thus making biomarkers with ideal specificity and sensitivity difficult to find.

More studies are needed to ascertain the role of microRNA, angiogenesis, genetic, and epigenetic factors in pituitary tumor development and progression. Looking for new biomarkers is a very important area of oncology and much more work is required to permit us to draw definitive conclusions.

Conflict of interest The authors wish to declare that they have no conflict of interest.

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