Does Hormonal IHC have Clinical Relavance in Pituitary Adenomas?

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Abstract

Background: Pituitary adenoma represent the third most common primary intracranial tumor in neurosurgical practice constituting about 10% of intracranial neoplasm. In accordance to the new WHO classification pituitary adenoma is classified according to the cell of origin which is detected immunohistochemically. Some of the pituitary adenomas may show features associated with recurrence and resistance to conventional therapy. Serological and IHC correlation helps in separating these high risk adenomas.

Aim: 1. to determine clinical relevance of IHC in pituitary adenomas. 2. Identification of high risk pituitary adenomas based on immunohistochemically

Materials and Methods: 30 surgically resected specimens. Sections were stained for H&E and immunostained for GH, PRL, ACTH, TSH, FSH, LH.

Results: Tumor mainly affected the age group between 24 to 66 years. Most cases presented as non functioning macroadenomas. Based on serological and immunohistochemical profile of pituitary adenomas we found the following results: Plurihormonal adenomas-18cases (60%), Silent corticotroph adenoma-5cases (16.67%), Lactotroph adenoma in men-3cases (10%), Null cell adenoma-2cases (6.67%), Functional thyrotroph -1cases, non-functional gonadotroph -1case.

Discussion: The tumors were common between age group of 41-45 yrs, incidence in men were higher. In our study most of the cases were nonfunctional and diagnosed as macroadenomas resulting in pressure effects. The need of the hour is to subtype PA of clinical relevance. With the new WHO classification histological typing, based on immune markers is essential and older classifications of adenomas based on tictorial stains are obsolete.

Prognostication based on proliferation markers remains a major challenge in pituitary pathology. Hence high risk category has been identified with the aid of immune markers.

Conclusion: Earlier the diagnosis of adenoma was considered sufficient for many cases. With new classification based on IHC, it is recommended to correlate the estimated hormones levels with immune markers in routine diagnosis. As this helps in identifying the high risk groups which require intensive investigations and closer follow up.

Keywords: Pituitary Adenoma; Immunohistochemistry; High Risk.

Introduction

Pituitary adenoma represent the third most common primary intracranial tumor in neurosurgical practice constituting about 10-15% of intracranial neoplasm [1]. Pituitary adenomas are classified with functional classification using histology, immunohistochemistry (IHC), ultrastructure, biochemical, imaging and surgical
findings [1]. The consensus and editorial meeting for Tumors of Endocrine Organs, April 2016 made several changes and brought innovations in classification of pituitary adenoma. New WHO classification of pituitary adenoma is according to the cell of origin labeled as somatotroph, lactotroph, corticotroph, thyrotroph, gonadotroph. The IHC panel includes the use of antibodies to growth hormone (GH), prolactin (PRL), adrenocorticotropic (ACTH), thyroid stimulating hormone (TSH), follicular stimulating hormone (FSH), lutenizing hormone (LH).

Some of the pituitary adenomas may show features associated with recurrence and resistance to conventional therapy such tumors are identified as high risk adenomas. Serological and Immunohistochemical correlation helps in separating these high risk adenomas.

The following are recognized as high risk adenoma sparsely granulated somatotroph adenoma, lactotroph adenoma in men, Pit-1 positive plurihormonal adenoma, Crooke’s cell adenoma and silent corticotroph adenoma.

Materials and Methods

Surgically resected specimens of pituitary adenomas of patients admitted to our hospital, between the period 2013-2015. Tissue specimen were fixed in 10% buffered formalin for 48 hours and paraffin embedded. 4-5 micrometer thick serial sections were stained for Hematoxylin and Eosin, and immunostained using primary antibodies against the following pituitary hormones: GH, PRL, ACTH, TSH, FSH and LH. (monoclonal antibodies, PathNSit). The presence of near diffuse cytoplasmic staining was interpreted as positive. Same tumor cells showing staining for more than one antibody was considered as co-expressive.

Cases which were functional somatotroph were classified as sparsely or densely granulated based on light microscopy. In addition the clinical presentation and serological levels were tabulated.

Results

30 cases of PA were studied. Tumor mainly affected the age group between 24 to 66 years. Incidence in men were higher (63.34%) when compared to women (36.66%) and most of the cases were non-functioning macroadenomas.

Based on serological and immunohistochemical profile of pituitary adenomas we found the following results: Plurihormonal adenomas-18cases (60%), Silent corticotroph adenoma-5cases (16.67%), Lactotroph adenoma in men-3cases (10%), Null cell adenoma-2cases (6.67%), Functional thyrotroph -1cases, non-functional gonadotroph-1 case.

Discussion

Pituitary adenomas are heterogenous tumors due to different cell of origin. Patients were of the age group of 24 to 66yrs with peak of incidence between 41-55yrs. The incidence in men (63.34%) were higher in accordance to Alma et al. [2]. In terms of functional classification, PA are grouped as functional and non-functional PA. In our study around 18 cases (60%) cases were functioning pituitary adenomas which is supported by balinisteau et al.[3]. Despite the secretory nature, majority of the cases seeked clinical attention due to pressure effects such as diminishing vision or headache. Radiologically most of the cases were diagnosed as macroadenomas.

Adenomas are the most common tumors arising in the pituitary gland and it is the need of the hour to subtype PA of clinical relevance. With the new WHO classification histological typing, based on immune markers is essential and older classifications of adenomas based on tictorial stains should be abandoned as these terms do not correlate with functional or immunohistochemical findings.

Following IHC and serological correlation around 8cases (26.67%) belonged to high risk category: Sparsely granulated pituitary adenoma, Silent corticotroph adenoma-5cases (16.67%), Lactotroph adenoma in men-3 cases (10%). 3 cases operated for recurrence out of which 2 were reported as silent corticotroph adenomas, however the previous surgical and histopathological reports were unavailable.

Silent corticotroph adenomas are thought to arise from cells that fail to process the ACTH precursor, proopiomelanocortin, into the biologically active 1-39 ACTH. These lesions are generally much more aggressive than other silent adenomas, and recurrence is extremely common [4].

According to WHO recommendations, tumors expressing both FSH and LH or GH and PRL were not considered as plurihormonal. Silent corticotroph expression was commonest co-expression in plurihormonal cases.

As immunohistochemical markers become more sophisticated, the number of truly unclassified adenomas is falling. The rare tumour that is completely negative for all hormones and transcription factors is classified as a null cell adenoma is 2cases (6.67%) and usually behaves like a gonadotroph adenoma [4].

Prognostication remains a major challenge in pituitary pathology. The proliferative activity using markers such as proliferating cell nuclear antigen, Ki67/MIB 1, and anti apoptotic Bcl 2 has unfortunately shown no consistent correlation with tumour invasiveness or recurrence [6-8].

The best predictive marker remains the tumour classification based on hormone content and cell structure. For example, among people with acromegaly
who fail surgical resection, response to long acting somatostatin analogues is best predicted by the subtype of somatotroph adenoma as densely or sparsely granulated [9,10]. This finding renders the value of a Cam 5.2 keratin stain more important than almost any other immunostain in this setting.

Immunohistochemistry can accurately identify the full spectrum of pituitary hormones produced by adenoma cells, enable more defined configuration of cell morphology and reveal several structural elements and cytoskeleton components, such as cytokeratin filaments and mitochondria. Recognition of these elements, which could previously only be identified by electron microscopy, and application to the current diagnostic approach has facilitated the classification of pituitary adenomas [11].

**Conclusion**

Earlier the diagnosis of adenoma was considered sufficient for many cases, but with better understanding of cytogenetics of pituitary adenomas, and molecular evidence supporting the role of transcription factors in differentiation of stem cells into respective cell types, it becomes essential to provide a “clinicopathological diagnosis”. Majority of the cases are diagnosed due to pressure effects rather than endocrine manifestation. In this scenario, IHC is essential in ascertaining the clinical behavior of the tumor.

With new classification based on IHC, it is recommended to correlate the estimated hormones levels with immune markers in routine diagnosis. As this helps in identifying the high risk groups which require intensive investigations and closer follow up.

**References**