Molecular Pathology of Pituitary Adenomas

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Preface

Mainly, the book enriches the previous publications regarding pituitary adenomas by promoting information in new fields, such as signal transduction, stem cell markers, microRNAs, "omics" technologies, and less new ones (proliferation, angiogenesis, and apoptosis).

The first point the book focuses on is the classification of pituitary adenomas, taking into consideration clinical functional aspects and aggressiveness. A chapter on pathology emphasizes the relationship between clinical behavior and proliferation markers/rates. The balance between stimulating and inhibiting factors which determine the final angiogenic phenotype of pituitary adenomas, and the molecular systems that regulate the apoptotic process.

A developing field is represented by the key signaling molecules involved in diagnosis, prognosis, and treatment monitoring of pituitary tumors, while a new area targets the stem cells as originators or markers in pituitary adenomas. "Omics" technologies are undertaken as individual or panels of biomarkers. Individual or group signatures of microRNAs can also qualify as potential biomarkers for diagnosis and prognosis of pituitary adenomas. Last, but not least, a short excursion is being made into the current treatment options for pituitary adenomas, that is, their strength and limitations, and the rational behind designing novel therapies, based on releasing hormones, receptors, and other key signaling molecules.

Molecular Pathology of Pituitary Adenomas brings new data about current progress in the understanding of pituitary adenoma pathogenesis and how it impacts upon current attitude. The book provides useful instruments for research and clinical area; a better understanding of tumor biology, the discovery of molecular events at the basis of tumor development was possible due to the modern approach of immunohistochemistry, now routinely used in clinical pathology, and the advanced techniques of electron microscopy, genomics, and proteomics.

The management of pituitary adenomas in the era of evidence-based medicine changed dramatically; new data appear with an increasing speed, and their selection for being implemented in clinical medicine is a continuous challenge.

Molecular Pathology of Pituitary Adenomas represents an update in the field of pituitary tumor research for scientists, clinicians, and everyone dealing with pituitary tumor patients, that is, endocrinologists, internists, oncologists, neurosurgeons, and pathologists.

All authors had equal contributions to this manuscript.

The Authors

Introduction

The molecular pathology of pituitary adenomas has been approached somewhat differently in this book. It describes an update on the levels achieved so far in this field; while classic areas are reviewed rather briefly, new approaches in the pathology of pituitary adenomas are emphasized. Among these, the most important are signaling pathways, stem cells, mRNA, and "omic" technologies as new generic tools for diagnosis, as well as new therapeutic approaches, involving molecular biomarkers. Our own results regarding some of these biomarkers have been inserted in certain chapters.

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1 Pituitary Tumor Classification: Functionality, Invasiveness, and Aggressiveness

Introduction

Pituitary tumors, often called *adenomas*, are among the most frequent intracranial tumors (10–15%) after meningiomas and gliomas [1,2]. Their epidemiology shows an incidence in postmortem series between 3.2% and 27%, with an average of 10%. A study performed on more than 3000 autopsied pituitaries showed that the great majority of these tumors are obvious only for pathologists (such tumors are called subclinical), and that fewer than 1/600–1/1000 are macroadenomas [3]. Evaluation using high-resolution imaging, like computed tomography (CT) with contrast for reasons unrelated to pituitary disorders due to the importance of the arterial sequence, shows hypodense lesions in 10–25% [4], while the use of magnetic resonance imaging (MRI) of the brain reveals a pituitary mass in 10% [5] or even less, without contrast (0.3%) [6]. A recent metaanalysis estimated the prevalence of pituitary adenomas at 14.4% in postmortem studies, 22.2% in radiological studies, and 16.9% overall [7].

The new imaging technology changed the way we manage these tumors. A sellar mass can harbor many other lesions besides pituitary adenomas, as presented in Table 1.1.

Since most incidentally discovered pituitary lesions do not have any impact on a subject's health, they are called "incidentalomas." These are lesions which do not affect normal pituitary function and do not compress or invade the surrounding structures. Therefore, they do not require any active medical attitude [5]. From the patient's perspective, knowing about a pituitary adenoma causes anxiety despite normal function and lack of symptoms, while most physicians will consider the pituitary incidentaloma for sequential follow-up, as will be presented below.

Beyond any neoplasia, there is a disturbance of normal cell cycle control in terms of oncogene activation or loss of heterozygosity of tumor suppressor genes. Continuous progress has been made in terms of molecular pathogenesis of pituitary adenomas, as reviewed in the subsequent chapters of this book. Stem cells are a source of continuous tissue renewal, as well as a possible source of monoclonal proliferation under environmental disruptors, aided by a certain genetic background. Recent data suggest that stem cells might be involved in this process [8,9].

From their epidemiology to their molecular aspects, pituitary adenomas represent a broad spectrum of disorders that can be analyzed and classified according to autonomous secretion, clinical aspects in diagnosis and treatment, pathology in

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Table 1.1 Pituitary Masses

Physiologic Hyperplasia	Pituitary Tumors	Malignancies	Cysts	Others
Lactotroph in pregnancy	Pituitary adenomas (most frequent)	Ectopic pinealoma (germinoma)	Rathke's cleft	Pituitary abscess
Thyrotroph in myxedema	Craniopharingioma	Granulomatous diseases	Dermoid	Pituitary tuberculosis
Somatotroph hyperplasia (ectopic GH-releasing hormone, GHRH)	Meningioma	Sarcoma, chordoma	Arachnoid	Lymphocytic hypophysitis
Gonadotroph (arguable)		Pituitary carcinoma—rare		Vascular abnormalities
Corticotroph (arguable)		Metastases (lung, breast)		

Table 1.2 Clinical Functional Classification

Pituitary Adenoma	Clinical Signs	Gross Prevalence	Comments
Prolactinoma	Amenorrhea–galactorrhea in women	35%	In men, occur as nonfunctioning adenomas
Acromegaly	Physical changes	20%	Onset much before diagnosis
Cushing's disease	Clinical Cushing's	13%	In adults, more frequent than in children
Thyrotropinoma	Pituitary thyrotoxicosis	2%	TSH inadequate high for increased T3, T4
Nonfunctioning adenoma	Hypopituitarism	30%	Can include prolactinoma in men, gonadotroph adenomas, or other silent adenomas

terms of light microscopy (LM) and electron microscopy (EM) features, and special issues, such as the clinical impact of aggressive pituitary adenomas or rare pituitary carcinoma cases. Despite being histologically benign, they can be severe and life-threatening due to local invasion and compression, metabolic, or cardiovascular complications (Table 1.2).

The World Health Organization (WHO) publication "Histological Typing of Endocrine Tumours" uses a five-tier classification in which endocrine activity, imaging, operative findings, and detailed pathology are integrated [10]. According to the mentioned classification, there are only three accepted types of anterior pituitary lesions: typical pituitary adenoma, atypical pituitary adenoma, and pituitary carcinoma. A step forward in classifying pituitary tumors was the use of tumor markers after 2005–2006. The Ki-67 labeling index (LI) is widely used due to its correlation with invasiveness, and probably prognosis as well. While adenomas showing increased (>3%) LI and extensive p53 immunoreactivity are considered "atypical adenomas," suggesting an aggressive potential or malignant transformation, the term *pituitary carcinoma* is applied exclusively when cerebrospinal and/or systemic metastases are identified [11].

As most of the tumors are subclinical and they never get removed by the neurosurgeon, it is important to focus on required medical attitude and dividing them into incidentalomas, which do not require treatment, and pituitary adenomas, which impose detailed diagnosis and active pharmacological, surgical, or radiation therapy. The variation in pathology, despite significant progress in this area, seldom influences the clinical decision in a significant manner [12].

The wide variation in human resources and technical facilities, as well as financial constraints, can affect the high-detail characterization (genetic and molecular level) of pituitary tumors. However, the clinical and basic research pituitary community can bring together resources in difficult, rare cases, ensuring an adequate clinical approach as well as research material.

Clinical Presentation and Classification

Upon clinical presentation, pituitary adenomas can be classified as secreting tumors (such as growth hormone (GH), adrenocorticotropic hormone (ACTH), prolactin (PRL) in women, or the rare thyroid-stimulating hormone (TSH)–secreting adenomas) or clinically nonfunctional adenomas. Tumor secretion is autonomous, which triggers various clinical syndromes and allows for appropriate testing. In addition to tumor secretion, pituitary adenomas might compress the neighboring structures, with optic chiasma or cavernous sinus syndrome, sphenoid sinus invasion or extension toward the base of the brain, all included in the mass effect. Last but not least, normal pituitary function can be impaired, leading to various degrees of pituitary failure.

The most common adenomas (30–35%) are PRL-secreting tumors. GH-secreting adenomas cause acromegaly and gigantism. Less common are ACTH-secreting adenomas, which cause Cushing's disease and TSH-secreting tumors, triggering pituitary hyperthyroidism. The remaining pituitary adenomas, representing approximately a third, are clinically silent and are known as nonfunctioning pituitary adenomas (NFPAs), meaning that they only cause symptoms due to tumor growth. However, the last category is subdivided after detailed immunopathology into gonadotropinomas, tumors with secretion of "mute" hormones, and null cell adenomas, which are devoid of immunoreactivity for classic anterior pituitary hormones.

Prolactinomas

Prolactinomas are adenomas associated with increased PRL levels usually above 100 ng/ml; the serum PRL levels usually correlate with the tumor size [13]. PRL-producing tumors show the highest incidence among pituitary adenomas in childhood and adolescence [14]. They represent the most common neoplasm of the anterior pituitary in clinical series and in autopsy material [3]. Although they were among the first type of pituitary adenomas included in surgical series three decades ago, their operating frequency has decreased dramatically after the introduction of dopamine agonist therapy, which has proved to be more effective.

Owing to clinical manifestation mostly presenting as amenorrhea–galactorrhea, PRL-secreting adenomas are usually microadenomas in females. Due to the high frequency of hyperprolactinemia as isolated endocrine disorder on one hand and pituitary microincidentaloma on the other, it is sometimes difficult to sustain the diagnosis of microprolactinoma. PRL might be increased due to drugs (such as neuroleptics, antidepressants, estrogens, and metoclopramids), pituitary stalk syndrome, local thoracic or breast lesions, or even postpartum or postabortum hyperprolactinemia [15]. High PRL levels without any effect upon gonadal function can be observed in macroprolactinemia [16]. In contrast, they present in males as macroadenomas in the majority of cases because of delayed diagnosis due to their modest clinical symptoms, such as decreased libido and sexual dysfunction [13].

Clinical Syndrome of Prolactinomas

The clinical syndrome of prolactinomas is highly suggestive when amenorrhea and galactorrhea occur in women, as Chiari in 1832 and Fromel in 1882 had described [17]. Disorders of ovulation involve PRL more than in the frame of prolactinomas, higher PRL levels being attributed to many disorders [18] (Table 1.3). Pituitary adenomas can be associated with hyperprolactinemia (HPRL), either by tumor-autonomous secretion of PRL (prolactinomas, acromegaly) or by lack of inhibitory control in the macroadenomas with suprasellar extension (SSE) and pituitary stalk syndrome [19]. In addition, HPRL can be triggered by drugs that interfere with dopaminergic control, decreased removal in kidney failure, as well as reflex mechanisms [20].

Sometimes galactorrhea is obvious, spontaneous, and in high amounts, while it might be present only upon careful breast clinical examination, and sometimes it may even be absent. Although most prolactinomas occur in adults, puberty can be delayed and associated with primary amenorrhea in a childhood-onset prolactinoma. While prolactinomas are microadenomas or macroadenomas in women, they are mostly macroadenomas in men, therefore being associated with low libido and impotence, mass lesions (optic chiasma, cavernous sinus syndrome), and global hypopituitarism. Rarely, galactorrhea may occur in men, but this is related more to the degree of breast development due to estrogens than to PRL.

Hyperprolactinemia is defined as a fasting PRL level above 20 ng/ml in men and 25 ng/ml in women, using immunoassays. Various methods have been used in PRL assays. Compared with the first competitive radioimmunoassay, the introduction of the two-site monoclonal “sandwich” assays, immunoradiometric assay (IRMA) and