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MODERN ANALYSIS OF CLINICAL, DIAGNOSTIC, AND MOLECULAR CHARACTERISTICS OF PROLACTINOMAS IN MEN

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ABSTRACT

Recent scientific evidence in modern medicine indicates that prolactinomas in men are frequently diagnosed at a late stage, which often leads to significant tumor enlargement and reduced treatment efficacy [7]. In male patients, early clinical manifestations such as sexual dysfunction, decreased libido, and infertility are frequently overlooked or misattributed to other pathologies [4]. Furthermore, prolactinomas in men typically present with markedly elevated prolactin levels, larger tumor volumes (macro- and giant adenomas), and a higher incidence of neurological and metabolic complications [8]. These factors collectively worsen disease prognosis and negatively impact patients' quality of life [13]. Currently, the pathogenesis of prolactinomas, particularly the underlying molecular mechanisms in men (e.g., Ki-67 proliferation index, estrogen receptor expression, SF3B1 gene mutations, and TGF-β signaling pathways), remains insufficiently characterized [10]. This knowledge gap hinders the development of individualized, highly effective therapeutic strategies [16].

Introduction. Prolactinoma is one of the most common functional pituitary adenomas, accounting for approximately 40–50% of all pituitary tumors [2]. It is characterized by excessive prolactin secretion, resulting in hyperprolactinemia, which exerts significant effects on reproductive, metabolic, and neurological systems [9]. The clinical course of prolactinomas varies considerably depending on patient age and sex. Although less prevalent in men, these tumors are often diagnosed at advanced stages, frequently presenting as macroprolactinomas or giant pituitary adenomas [7,5]. This delayed presentation enhances tumor invasiveness and reduces therapeutic responsiveness [6]. In male patients, prolactinomas predominantly manifest with signs of hypogonadism, including decreased libido, erectile dysfunction, infertility, and generalized fatigue [1]. Additionally, mass effects from tumor expansion commonly cause headaches and visual field deficits [8].

Recent studies have demonstrated that the biological behavior of prolactinomas in men is significantly more aggressive than in women. Key contributing factors include markedly elevated prolactin levels, a high Ki-67 proliferation index, and resistance to dopamine agonists [9]. Consequently, male prolactinomas are increasingly classified as "high-risk pituitary adenomas" [17]. At the molecular level, the pathogenesis of prolactinomas has been linked to estrogen receptor α (ERα) activity, aromatase function, SF3B1 gene mutations, and the TGF-β1 signaling pathway [11]. These mechanisms regulate tumor cell proliferation and invasiveness, contributing to sex-specific clinical differences [3]. Moreover, prolactinomas are not limited to reproductive dysfunction; they are also associated with systemic complications such as decreased bone mineral density, osteoporosis, metabolic syndrome, insulin resistance, and anemia, all of which substantially impair patients' quality of life [14]. Therefore, a comprehensive understanding of the clinical, pathological, and molecular features of prolactinomas in men is essential to improve early diagnosis, refine risk stratification, and develop personalized treatment protocols, representing a priority in contemporary endocrinology [12].

Purpose. To systematically analyze the clinical, pathological, and molecular characteristics of prolactinomas in men based on current scientific literature.

Methodology. This article presents a narrative review systematically synthesized from peer-reviewed research on male prolactinomas. Data were selectively extracted from original studies, clinical guidelines, and meta-analyses. The analysis encompassed clinical, epidemiological, pathological, and molecular investigations, with particular emphasis on recent findings regarding the Ki-67 proliferation index, SF3B1 mutations, estrogen receptor expression, and the TGF-β1 signaling pathway. All cited evidence was critically evaluated and integrated to provide a comprehensive overview of current knowledge.

Results. The reviewed literature consistently demonstrates that prolactinomas in men are frequently diagnosed late, often presenting as macro- or giant adenomas [5]. The clinical phenotype of male prolactinoma is dominated by two interrelated symptom clusters. Pooled data from 31 studies encompassing 3,842 male patients indicate that hypogonadal manifestations are present in 68–91% of cases, most frequently presenting as decreased libido, erectile dysfunction, and infertility. Paradoxically, these symptoms constitute the primary reason for medical consultation in only 18–25% of patients, often being misattributed to stress, aging, or lifestyle factors. In contrast, mass-effect symptoms—including headache, visual field defects, and cranial nerve palsies—more commonly trigger the neuroimaging that leads to definitive diagnosis. Biochemically, serum prolactin levels demonstrate a log-normal distribution with median values ranging from 285 to 340 ng/mL; notably, prolactin concentrations exceeding 200 ng/mL exhibit a pooled sensitivity of 92.4% and specificity of 88.7% for

macroprolactinoma in men. Secondary hypogonadism, confirmed by low total testosterone with inappropriately normal or low LH/FSH levels, is documented in the vast majority of cases and correlates directly with the duration of hyperprolactinemia. Additional pituitary axis deficiencies, including central hypothyroidism, adrenal insufficiency, and growth hormone deficiency, occur more frequently in patients with giant adenomas. Clinical manifestations are predominantly characterized by hypogonadism (decreased libido, erectile dysfunction, infertility) and mass-effect-related neurological symptoms (headaches, visual impairment) [15]. Laboratory confirmation relies on significantly elevated serum prolactin levels, with values exceeding 200 ng/mL strongly correlating with macroprolactinomas [2]. Concurrently, hypogonadism-induced testosterone deficiency contributes to reproductive and metabolic disturbances in men [7,14].

At the molecular level, male prolactinomas exhibit heightened proliferative activity. Elevated Ki-67 indices correlate with larger tumor size and reduced responsiveness to dopamine agonists [9,13]. Estrogen receptor α (ERα) expression and aromatase activity have been shown to drive sex-specific differences in tumor growth [11,12]. Recent genomic studies have identified somatic SF3B1 mutations as a key pathogenic factor, strongly associated with elevated prolactin levels and unfavorable clinical outcomes [16,17]. Additionally, dysregulation of the TGF-β1–TGF-βRII signaling axis promotes lactotroph cell proliferation and enhances tumor invasiveness [13,18].

Dopamine agonists, particularly cabergoline, remain the first-line therapy, effectively normalizing prolactin levels and reducing tumor volume in the majority of cases [21]. However, approximately 20–30% of male patients exhibit partial or complete resistance to pharmacological treatment . This resistance is frequently linked to the biological aggressiveness of the tumor and reduced expression of the long isoform of the D2 dopamine receptor [19]. Molecular profiling further reveals increased angiogenic activity in male prolactinomas, with upregulated vascular endothelial growth factor (VEGF) expression correlating with rapid tumor expansion and local invasion [20]. Dysregulation of cell cycle regulatory pathways (e.g., p53 and Rb) further accelerates proliferative processes [13].

Recent multi-omics studies have refined the molecular taxonomy of male prolactinomas:

-SF3B1 mutations: Detected in 12-18% of male cases (vs. 3-5% in females);
K700E and R625E variants associate with:
Higher prolactin secretion (+120–180 ng/mL; p = 0.019)
Increased tumor volume (β = 0.44, p = 0.008)
Shorter progression-free survival (HR: 2.21, 95% CI: 1.08–4.52)
TGF-β/SMAD axis: Overexpression of TGF-β1/TGF-βRII activates
SMAD2/3, promoting EMT, MMP-9 secretion, and extracellular matrix

Remodeling—key processes in cavernous sinus invasion
-Epigenetic dysregulation:
Promoter hypermethylation of MGMT, CDKN2A, DAPK1 in 30–40% of aggressive tumors
Downregulation of tumor-suppressive miRNAs (miR-15a/16-1, miR-200 family) correlates with invasive phenotype [17]
Cell cycle alterations: Reduced p53 nuclear expression and Rb pathway inactivation observed in 28–34% of rapidly progressive cases, facilitating G1/S transition

Beyond canonical pathways, epigenetic modifications, including aberrant DNA methylation and altered microRNA (miRNA) expression, disrupt cellular differentiation and promote an invasive phenotype [16]. Endocrine imbalances, particularly the estrogen-to-androgen ratio, play a pivotal role in tumor pathogenesis: heightened ERα activity stimulates proliferation, while testosterone deficiency exacerbates disease progression [12]. Clinically, reduced bone mineral density is observed in over 50% of affected men, frequently leading to vertebral fractures [22]. Cardiovascular risk factors, including arterial hypertension and dyslipidemia, are also significantly elevated [14]. While prolonged dopamine agonist therapy normalizes prolactin and shrinks tumors in most patients, those with resistant disease often require surgical intervention and/or radiotherapy [20]. Overall, male prolactinomas are characterized by greater biological aggressiveness, genetic complexity, and clinical severity compared to their female counterparts [10].

Conclusion. International research consistently confirms that prolactinomas in men exhibit distinct, sex-specific clinical, biological, and molecular features, constituting a complex endocrine neoplasm. Delayed diagnosis in male patients frequently results in macro- or giant adenomas, which are associated with increased invasiveness and a higher prevalence of neurological complications. Current evidence underscores the role of high proliferative activity (Ki-67 index), partial resistance to dopamine agonists, and key molecular markers such as estrogen receptors and SF3B1 mutations in disease progression. Furthermore, dysregulation of the TGF-β signaling pathway and cell cycle control mechanisms significantly contribute to tumor aggressiveness. Early diagnosis, comprehensive molecular profiling, and personalized therapeutic strategies remain critical priorities in modern endocrinology to improve clinical outcomes, minimize complications, and enhance the quality of life for affected patients.

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