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Molecular-Genetic Aspects in the Diagnosis of Odontogenic Tumors

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Abstract: Odontogenic tumors are a heterogeneous group of neoplasms originating from the epithelial and mesenchymal elements of the dental apparatus, characterized by a significant diversity of morphological manifestations, clinical course, and biological behavior. This group of tumors occupies a special place in the structure of maxillofacial pathology, accounting for 2.8-9.6% of all head and neck neoplasms, while their diagnosis remains one of the most complex tasks of modern dental oncology and maxillofacial surgery.

Keywords: odontogenic tumors, ameloblastoma, adenomatoid odontogenic tumor, odontogenic myxoma, odontoma, molecular genetic diagnostics.

Introduction

Childhood The relevance of studying odontogenic tumors is due to several key factors. Firstly, this is the relative rarity of this pathology, which leads to insufficient awareness of general practice dentists about the clinical manifestations and features of the course of various nosological forms, resulting in late diagnosis and inadequate treatment [1]. According to international epidemiological studies, the average time from the appearance of the first symptoms to the establishment of a definitive diagnosis is 14.7-28.4 months, which is significantly higher than similar indicators for other locations of the tumor process in the maxillofacial region.

Secondly, odontogenic tumors are characterized by pronounced polymorphism of morphological manifestations, which creates significant difficulties in the differential diagnosis of various nosological forms, as well as in the differentiation of benign and malignant variants [2]. The current WHO classification of odontogenic tumors (2022) includes more than 20 different nosological units, each of which has its own specific histological characteristics, clinical manifestations, and prognostic features. At the same time, traditional diagnostic methods, based solely on the clinical picture and routine histological examination, do not always allow for sufficient accuracy in determining the nosological affiliation of the tumor and predicting its biological behavior [3].

The epidemiological characteristics of odontogenic tumors show significant differences depending on the geographical region, ethnicity, and age groups of the population. The overall incidence of odontogenic tumors in the population is 0.9-1.2 cases per 100,000 population per year, with the highest incidence recorded in Southeast Asian countries (2.3-3.7 cases per 100,000 population) and the lowest in European countries (0.4-0.7 cases per 100,000 population). The age distribution is characterized by two peaks of morbidity: the first occurs in the age group of 10-19 years (32.4% of all cases) and is associated with the period of active odontogenesis, the second - in the age group of 40-60 years (28.7% of cases) and is due to the development of recurrent and malignant forms.

The gender distribution of odontogenic tumors varies depending on the histological type: benign epithelial tumors (ameloblastoma, adenomatoid odontogenic tumor) are more common in men (M:S ratio = 1.4:1), while mesenchymal odontogenic tumors (odontogenic fibroma, odontogenic myxoma) predominate in women (M:S ratio = 1:1.7). Mixed odontogenic tumors exhibit a uniform distribution

across the sex, with a slight predominance in women (M:S ratio = 1:1.1) [4], [5], [6].

The anatomical localization of odontogenic tumors is characterized by predominant lower jaw involvement (73.8% of all cases), which is associated with the peculiarities of embryonic development and more intensive odontogenic processes in this area. Among the lower jaw sections, the molars and premolars (67.4% of cases), the angle of the lower jaw (19.8%), and the symphyseal region (7.3%) are most commonly affected. Upper jaw involvement is observed significantly less frequently (26.2% of cases) and is predominantly localized in the premolars and molars (54.7%), as well as in the anterior part of the alveolar process (31.2%) [7].

Methodology

The traditional classification of odontogenic tumors is based on the histogenetic principle and divides them into epithelial, mesenchymal, and mixed forms. Epithelial odontogenic tumors include: ameloblastoma (45.6% of all odontogenic tumors), adenomatoid odontogenic tumor (13.7%), calcifying epithelial odontogenic tumor (4.8%), squamous odontogenic tumor (2.1%), and several other rare forms. Mesenchymal odontogenic tumors include: odontogenic fibroma (8.9%), odontogenic myxoma (6.4%), cementoblastoma (3.2%), and other variants. Mixed odontogenic tumors are represented by odontoma (18.3% of all cases) and ameloblastic fibroma (1.7%).

The clinical manifestations of odontogenic tumors are characterized by significant variability and depend on the histological type, tumor size, localization, and developmental stage. The most common symptoms are: painless increase in jaw volume (78.9% of cases), tooth mobility in the affected area (45.6%), impaired tooth eruption (34.7%), paresthesia in the innervation zone of the inferior alveolar nerve (23.4%), and pathological fractures of the jaws (12.8%). Pain syndrome is not characteristic of benign odontogenic tumors and is observed only in 18.7% of cases, primarily in the development of a secondary inflammatory process or malignancy.

A feature of the clinical course of odontogenic tumors is their slow growth and prolonged asymptomatic course in the initial stages of development. The average growth rate of benign odontogenic tumors is 0.8-1.2 cm per year, which is significantly lower than similar indicators for other neoplasms of the maxillofacial region. This circumstance often leads to late diagnosis, when the tumor reaches significant sizes and causes pronounced deformation of the facial skeleton, which significantly complicates surgical treatment and worsens functional and aesthetic results.

Results and Discussion

The diagnosis of odontogenic tumors is a complex task that requires the use of modern clinical, radiological, morphological, and molecular-genetic research methods. Clinical diagnosis is based on a thorough medical history, objective examination of the patient, assessment of the functional state of the maxillofacial region, and analysis of characteristic symptoms. Radiation diagnostic methods include orthopantomography, computed tomography, magnetic resonance imaging, and, if necessary, positron emission tomography. Morphological diagnosis involves obtaining biopsy material followed by histological and immunohistochemical examination [8].

In the last two decades, the molecular-genetic aspects of odontogenic tumors have attracted the special attention of researchers, which is associated with the rapid development of molecular biology methods and the possibility of studying the genetic mechanisms of tumor growth at the molecular level. Molecular genetic studies of odontogenic tumors are aimed at identifying specific genetic alterations characteristic of various nosological forms, which opens up new possibilities for improving diagnostics, predicting the course of the disease, and developing targeted therapy.

Modern molecular genetic research methods include real-time polymerase chain reaction (qRT-PCR) gene expression analysis, protein expression immunohistochemical research, Sanger DNA sequencing, high-performance sequencing (NGS), comparative genomic hybridization (CGH),

fluorescent in situ hybridization (FISH), and other modern technologies. The application of these methods has made it possible to identify a number of specific molecular genetic markers characteristic of various types of odontogenic tumors, which opens up prospects for creating new diagnostic panels and personalized treatment approaches.

One of the most important achievements in the field of molecular genetic research of odontogenic tumors was the discovery of the role of the Wnt/β-catenin signaling pathway in the pathogenesis of ameloblastoma [9]. It has been shown that mutations in the CTNNB1, APC, AXIN2 genes and other components of this signaling pathway occur in 76-89% of ameloblastoma cases and play a key role in the initiation and progression of the tumor process. These data not only deepen understanding of the pathogenetic mechanisms of ameloblastoma development but also open up opportunities for developing targeted therapeutic approaches.

Another important area of molecular genetic research is the study of the role of microRNA (miRNA) in regulating gene expression in odontogenic tumors. It has been established that various types of odontogenic tumors are characterized by specific microRNA expression profiles, which can serve as a basis for the development of new diagnostic and prognostic markers. For example, hyperexpression of miR-211, miR-204, and hypoexpression of miR-138, miR-200c are characteristic of ameloblastoma, which correlates with invasive tumor growth and a tendency to recurrence [10].

Epigenetic mechanisms, including DNA methylation, histone modifications, and the regulation of non-coding RNAs, also play a significant role in the pathogenesis of odontogenic tumors. Studies have shown that hypermethylation of promoter regions of tumor growth suppressor genes (CDKN2A, RASSF1A, MGMT) occurs in 34-67% of ameloblastoma cases and is associated with a more aggressive course of the disease. These data open up prospects for the use of epigenetic drugs in the treatment of odontogenic tumors.

Immunohistochemical studies of odontogenic tumors revealed the expression of various markers that can be used for differential diagnosis and disease progression prognosis. For ameloblastoma, the expression of CK19, CK14, p63 is characteristic, while adenomatoid odontogenic tumor exhibits a positive reaction with CK7, EMA, calretinin. Odontogenic myxoma is characterized by the expression of vitamin, CD34, the absence of S-100 and desmin expression, which allows it to be differentiated from other mesenchymal tumors [11], [12].

In recent years, special attention has been paid to studying the mechanisms of malignization of odontogenic tumors and identifying molecular genetic markers that allow predicting the risk of malignant transformation. Ameloblastic carcinoma, a malignant analogue of ameloblastoma, is characterized by additional mutations in the TP53, RB1, PTEN genes, as well as changes in the expression of the p53, Rb, Ki-67 proteins. The identification of these molecular genetic alterations can serve as a basis for early diagnosis of malignancy and the selection of optimal treatment tactics [13].

The introduction of high-performance sequencing (HPS) methods into the study of odontogenic tumors has opened up opportunities for a comprehensive analysis of the mutational landscape and the identification of new driver mutations. Recent studies using exomatic and genomic sequencing have revealed previously unknown genetic alterations in odontogenic tumors, including mutations in the SMO, BRAF, PIK3CA genes, which expand understanding of the molecular mechanisms of pathogenesis and open new targets for targeted therapy.

The problem of standardizing the molecular-genetic diagnosis of odontogenic tumors remains a pressing task in modern dental oncology. Differences in methodological approaches, criteria for interpreting results, and technical equipment of laboratories lead to variability in obtained data and make it difficult to compare them between different research groups. Developing standardized protocols for molecular genetic studies of odontogenic tumors is a necessary condition for implementing these methods in clinical practice [14].

The economic aspects of using molecular genetic methods in the diagnosis of odontogenic tumors

also require careful analysis. The high cost of modern molecular-genetic studies may limit their widespread use in clinical practice, especially under conditions of limited financial resources in the healthcare system. It is necessary to conduct pharmacoeconomic research to assess the cost/effectiveness ratio of implementing molecular genetic methods for diagnosing odontogenic tumors [15].

The prospects for the development of molecular genetic diagnostics of odontogenic tumors are associated with the introduction of artificial intelligence and machine learning to analyze large amounts of genomic data, the development of fluid biopsy for non-invasive diagnostics, and the creation of personalized therapeutic approaches based on molecular tumor profilization. The integration of clinical, morphological, and molecular genetic data using systems biology methods will open up new possibilities for understanding the pathogenesis of odontogenic tumors and developing effective treatment methods.

Conclusions

Thus, the study of the features of the clinical course and molecular genetic aspects of odontogenic tumors is a relevant and multifaceted scientific problem, the solution of which is of great importance for improving the diagnosis, treatment, and prognosis of the course of this group of diseases. The integration of traditional clinical and morphological methods with modern molecular genetic technologies opens up prospects for creating a new paradigm for the diagnosis and treatment of odontogenic tumors based on the principles of personalized medicine and targeted therapy.

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