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Review

Pathologic aspects of skull base tumors

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ABSTRACT

Skull base tumors form a highly heterogeneous group. As there are several structures in this anatomical site, a large number of different primary malignancies might develop, as well as a variety of secondary (metastatic) tumors. In this article, the most common malignancies are presented, along with a short histopathologic description. For some entities, an immunohistochemical profile is also given that should be helpful in proper diagnosis. As many pathologic diagnoses nowadays also include genetic studies, the most common genetic abnormalities in skull base tumors are presented.

1. Introduction

Tumors of the skull base are a distinct group and, unlike in other cases (e.g. organ specific), they are grouped according to their anatomic location which is used by surgeons. Usually, the pathologic classification refers to tumors' origin, such as the epidermis, bronchial epithelium or soft tissues. Such classification roughly introduces two groups of tumors: epithelial and non-epithelial, according to their origin. In the skull base, one can find bone, peripheral nerves, large vessels and soft tissues from which different tumors could arise. Additionally, as there are plenty of surrounding structures (e.g. the central nervous system, sinuses, pharynx, etc.), the number of possible tumors that could grow into the skull base region, along with their specific diagnoses, increases. Of course, benign as well as malignant tumors could grow in all of the aforementioned situations. Moreover, at the skull base, we may also find metastases. Taking into consideration all of the above, the pathology of tumors in this anatomical region becomes a challenging issue.

From the clinical point of view, tumors are most commonly grouped according to their anatomical occurrence. In the case of skull base tumors, this allows us to group tumors according to whether they grow within or around the anterior, middle or posterior cranial fossa. Such an approach is presented in the majority of clinical descriptions (see Table 1).[1–3] However, specific tumors (e.g. meningioma, neuroma or chordoma) may develop in all the sites and the morphological picture is

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Table 1 – Tumors of skull base and their distribution in relations to anatomic localization (related to anterior, middle and posteriori cranial fossa).

Anterior	Middle	Posterior
Primary and secondary tumors	Chordoma	Paraganglioma
Esthesioneuroblastoma	Chondrosarcoma	Neurilemoma
Chondroma	Meningioma	Meningioma
Chondrosarcoma	Neurilemoma	Chondrosarcoma
Tumors invading from adjacent structures	Paraganglioma	Chordoma
Carcinoma (mainly squamous cell carcinoma from nasal cavity)	Glioma	
Adenoid cystic carcinoma	Teratoma	
Lymphoma	Squamous cell carcinoma	
Plasmocytoma	Plasmocytoma	
Melanoma malignoma	Lymphoma	
Pituitary gland tumors (most common: prolactioma)	Metastatic tumors	
Craniopharyngioma		
Lipoma		
Hemangioma		
Chordoma		
Neurilemoma		
Teratoma		
Metastatic tumors		

similar in all locations. This review is focused on tumors that might develop or invade the skull base region, and where the standard classification would be difficult to apply. In the next section, selected most common tumors are presented with an indication of their most common location.[4,5] As this issue of the journal has a review standard, because of the encyclopedic character of the article, the following tumor descriptions could be given in alphabetic order, although it would perhaps be more appropriate to present lesions according to their histogenesis. As such, the most suitable classification includes tumors grouped as follows: epithelial, soft tissue, tumors of the bones and cartilage, neuroectodermal and hematopoietic.

2. Tumors of epithelial origin

2.1. *Squamous cell carcinoma*

Definition: A malignant epithelial tumor with squamous cell differentiation.

Epidemiology: Depends on the site of the primary tumors (ear or temporal bone, gnathic bones, larynx, oropharynx, sinonasal tract, salivary glands). Usually occurring in middle aged or older adults. Currently, together with the increased incidence of HPV infection, tumors develop in younger patients. Metastatic tumors also occur.[6,7]

Morphologic picture: Histologically, there are recognized subtypes of squamous cell carcinoma such as: squamous keratinized, squamous non-keratinized, basaloid or adenosquamous carcinomas. In all cases, the microscopic features or immunohistochemical profile (expression of cytokeratins and p63) should indicate some degree of squamous differentiation. A full morphological diagnosis should include an examination of HPV infection status, either by direct immunostaining for HPV or for p16 (which is activated in HPV-related tumors).

Differential diagnosis: The presence of keratin (extracellular or intracellular) in some squamous cell carcinomas makes diagnosis easier. In cases with poor differentiation, regardless of the site of origin of the tumor, especially in those cases with predominant spindle cells, differentiation between sarcoma and inflammatory myofibroblastic tumor should be performed. Usually, the application of a panel of immunohistochemical stains using epithelial markers (cytokeratins, p40, p63) and mesenchymal markers (vimentin, CD34, SMA) is sufficient for proper diagnosis.[8–10]

2.2. *Nasopharyngeal carcinomas*

Definition: Carcinoma developing in the nasopharyngeal mucosa with features of squamous cell differentiation, according to the WHO classification.[1]

Epidemiology: The peak incidence is in the 5th and 6th decades, with a twofold male predominance. The risk of tumor development increases with EBV infection.

Morphologic picture: The tumor is composed of areas (islands, sheets or trabeculae) of carcinoma (depending of the subtype, with squamous, basaloid or transitional cell type appearance), which are admixed with variable amounts of lymphocytes (Fig. 1a and b).

Other important notes: Other names used include synonyms: lymphoepithelioma, lymphoepithelial carcinoma or Schmincke type lymphoepithelioma. The same terminology is used for such entities as: nonkeratinizing carcinoma, keratinizing squamous cell carcinoma and basaloid squamous cell carcinoma.

Differential diagnosis: This tumor belongs to a group of poorly differentiated malignancies. The first differentials should be made with diffuse large B cell lymphoma (some cells might have an epithelioid appearance, but express B-cell markers), malignant melanoma (some cases show clearly visible intracytoplasmic pigment and are positive for HMB45, S100 and melan-A), and rhadomyosarcoma (mainly by use of muscle differentiation markers including: desmin, MyoD1 or Myf4). Differentiation with other types of nonkeratinizing carcinoma is done by confirmation of viral infection: nasopharyngeal carcinoma is EBV positive, while other carcinomas could be HPV-related (confirmed by p16 staining).[8,11–14]