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Orbital tumors: the relationship of histopathological examination results and clinical characteristics: A literature review

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Abstract

Orbital tumors, which can be neoplastic or non-neoplastic, vary in their clinical impact, ranging from cosmetic concerns to severe complications like vision loss or death in metastatic cases. These tumors are classified based on their cellular origin, including hematolymphoid, vascular, neurogenic, and others, to aid in diagnosis, prognosis, and treatment. Clinically, orbital tumors present with symptoms such as proptosis, decreased visual acuity, diplopia, pain, and inflammation, which are key diagnostic indicators. Early detection through imaging techniques like MRI and CT scans, along with histopathological examination, is crucial for effective management and preserving vision. Globally, benign orbital tumors are more common than malignant ones, with idiopathic orbital inflammation being the most frequent benign tumor. However, the prevalence and characteristics of orbital tumors are underreported in regions like Indonesia, indicating a need for better regional awareness. Histopathological examination is the gold standard for diagnosis, and its integration with clinical evaluation improves tumor identification and management. The review emphasizes the need for further studies to explore the relationship between clinical features and histopathology, which could improve early detection, diagnostic accuracy, and treatment strategies for orbital tumors.

Keywords: Orbital Tumor; Clinical Characteristics; Histopathology; Neoplasm; Screening

1. Introduction

Orbital tumors are abnormal growths located within the orbital cavity, encompassing both neoplastic and non-neoplastic origins. These tumors can have significant clinical implications, ranging from cosmetic concerns to severe complications such as visual impairment or even mortality in cases of metastasis. Histopathologically, orbital tumors are categorized into various groups based on their cellular origin, including hematolymphoid, vascular, neurogenic, soft tissue, secondary, metastatic, and other types. This classification aids in understanding the tumor's behavior, prognosis, and appropriate treatment options.

Clinically, orbital tumors present with diverse symptoms such as proptosis, decreased visual acuity, diplopia, pain, lacrimation, chemosis, and inflammation. These manifestations not only affect the patient's quality of life but also serve as important diagnostic markers. Early detection of orbital tumors is crucial, as timely and accurate diagnosis followed by effective treatment can preserve vision and prevent complications. Imaging techniques such as MRI and CT scans are invaluable for localizing and characterizing these tumors, while histopathological examination remains the gold standard for definitive diagnosis.

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Globally, the prevalence of orbital tumors varies, with benign cases being more common than malignant ones. For instance, a study in Japan by Goto (2021) reported that 72% of orbital tumors were benign, with idiopathic orbital inflammation (IOI) being the most common type, while lymphoma accounted for most malignant cases. In Indonesia, however, the incidence and characteristics of orbital tumors remain underreported, reflecting a gap in regional data and awareness.

Histopathological examination, as the gold standard for diagnosis, combined with clinical evaluation, improves the accuracy of tumor identification. This integrated approach ensures responsive management of orbital tumors. These considerations highlight the importance of further studies to elucidate the relationship between clinical characteristics and histopathological findings, facilitating earlier detection and better outcomes for patients. Understanding this correlation is critical for developing early detection strategies, improving diagnostic accuracy, and optimizing patient outcomes. This review aims to address the existing knowledge gaps by synthesizing findings on the clinical and histopathological aspects of orbital tumors.

2. Review Content

2.1. Orbital Tumor

2.1.1. Etiology

Orbital tumors refer to abnormal growths that occur within the orbital cavity. The orbital cavity is a complex area consisting of the eye, muscles, nerves, blood vessels, and connective tissue. It is widest at the front and narrows towards the back, where the optic nerve exits the orbit and connects to the brain. Tumors in the orbital cavity can cause a range of cosmetic and visual problems (Tailor et al., 2013).

2.1.2. Epidemiology

Most primary orbital tumors are benign, but the risk of malignancy increases in patients over 60 years old. In adults, benign primary orbital tumors are diagnosed equally in men and women, although some subtypes are more common in women, such as cavernous hemangiomas and optic nerve sheath meningiomas. A large retrospective study involving 2,480 orbital tumors found that 68% of cases were benign masses. The most common benign tumor was dermoid cysts (14%), followed by cavernous hemangiomas (9%) (Murdock et al., 2022). In East Java, Soebagjo et al. (2013) reported 44 cases of retinoblastoma at RSUD Dr. Soetomo, Surabaya, from 2010 to 2012. The patient characteristics showed 61.36% were male and 38.64% were female, with an average age of 3.72 years.

2.1.3. Clinical Characteristics

Clinical characteristics of orbital issues include eyelid swelling, eye displacement, pressure sensations, discomfort from exposure and dryness of the eyelids, and excessive tearing. Proptosis (the eye bulging forward) is a common sign caused by masses behind the eyeball, such as cavernous hemangiomas or optic nerve tumors. Eye movement problems can lead to double vision (diplopia) due to pressure on the nerves or increased orbital pressure. This may cause blurred vision, loss of color perception, difficulty seeing distances, limited vision, or early presbyopia. Pain, usually from inflammation, is rare but an important sign of malignant orbital tumors. As a tumor grows, surrounding soft tissues expand, and in some cases, orbital pressure increases (Hintschich et al., 2019).

The eyeball may shift vertically or horizontally, for example, moving downward and inward due to a mass in the lacrimal gland or a dermoid cyst. Shifting downward and outward is often caused by a frontoethmoidal mucocoele, vascular lesions, nerve tumors, or dermoid cysts. Masses at the front of the orbit often cause eye displacement and double vision before affecting visual acuity, while tumors at the orbital apex may cause vision loss with little or no double vision or proptosis. Conjunctival chemosis, or swelling of the conjunctiva, can result from ocular surface dryness (Baba et al., 2017). Watery eyes (lacrimation) are another sign of orbital tumors. Other signs include eye movement disturbances, eyelid asymmetry, inflammation, optic nerve swelling, choroidal folds, and sensory loss around the eye (hypoesthesia) (Hintschich et al., 2019).

Additional signs include "corkscrew" blood vessel dilation on the conjunctiva (episcleral vessels), changes in eye appearance, itching or pain at the lesion site, and salmon patches (pink spots) on the conjunctiva, indicating vascular abnormalities. Port wine stains, due to capillary vascular malformations, appear as flat pink spots that later turn purple. These birthmarks, often linked to the trigeminal nerve, are also known as nevus flammeus. Strawberry hemangiomas are raised, red lesions on the skin that resemble strawberries, formed by clusters of small blood vessels (Soebagdjo, 2019).

2.1.4. Diagnostics

This clinical evaluation involves the use of the "7 P" mnemonic, which includes 3 P's from the orbital history through anamnesis (pain, progression, and patient's history) and 4 P's from the physical examination (proptosis, periocular changes, palpation, and pulsation) (Mombaerts et al., 2019).

History Taking

A comprehensive medical history provides insight into the disease and its progression, helping with diagnosis. It includes information about current health, past sinus issues or surgeries, endocrine dysfunction (especially thyroid), immunological diseases, cancer, infections, injuries, and abnormal skin pigmentation. The onset of proptosis, which can occur at any age, is a key factor in diagnosis, with attention given to whether the onset is acute, subacute, chronic, or acute on chronic. Slow disease progression might go unnoticed by the patient, making comparison with old photos useful. The sequence of symptoms can also indicate the location of a mass in the orbit. Accurate communication of symptoms is crucial for early diagnosis. In cases of optic neuropathy, patients might notice color imbalance between eyes, reduced color brightness, or difficulty with depth perception and coordination. Blurred vision when looking at extreme angles or standing can occur with optic nerve circulation issues, as seen in optic nerve meningioma, large retrobulbar masses, or severe thyroid eye disease. The nature of pain also helps identify the cause: dull or pressure-like pain is often caused by a mass, while sharp pain is linked to exposed corneal issues. Orbital myositis causes persistent periorbital pain, particularly when moving the affected eye muscle. Persistent, severe pain, often due to inflammation, can indicate a rare malignant orbital condition, and some patients may also experience loss of sensation around the eye (Hintschich et al., 2019).

Physical Examination

Physical examination includes 4 P's: proptosis, periocular changes, palpation, and pulsation. Proptosis refers to the eye displacement, which can indicate the tumor's location. While measurements above 22 mm on an exophthalmometer might suggest abnormality, the key indicator is a difference of more than 2 mm between the eyes. Periocular changes start with a general patient examination, preferably under sunlight, looking for facial asymmetry, eye displacement, or orbital masses. Skin changes like color changes may indicate vascular issues or neurofibromas, while infiltration and thickening could point to systemic lymphoma or sarcoidosis. The eyelids should also be examined for masses, prolapsed fat, or enlarged lacrimal glands, and a "salmon patch" on the conjunctiva could indicate lymphoma (Hintschich et al., 2019).

Palpation checks for any lumps, grooves, or foreign objects, assessing the shape, size, texture, and attachment of any masses. Masses can be well-defined or irregular, soft or hard, and either painful or not. Size changes with Valsalva maneuver or signs of "filling and emptying" with pressure can indicate low-pressure vascular malformations or meningocele. Palpating the preauricular, submandibular, and clavicular lymph nodes is crucial in assessing orbital masses, especially if cancer is suspected. Pulsation checks for pulsations in proptosis. A bruit (sound) suggests vascular obstruction and could indicate thyroid eye disease (Topilow et al., 2020).

Biopsy Examination

Fine Needle Aspiration (FNA) involves taking tumor cells with a hollow needle, which are then stained for cytology or immunocytochemical analysis. FNA can accurately diagnose systemic diseases and certain malignant orbital lesions, with an accuracy of up to 87%. It's useful for tumors like pleomorphic adenomas and hypervascular malignant tumors where blood loss must be limited. FNA is a quick, often needle-only procedure, usually performed without anesthesia. Open Biopsy is used for detailed pathological analysis, including immunohistochemistry (IHC) and molecular tests, with specimens ideally sized at least 6x6 mm for the best results. The tissue should not be damaged during the procedure. Open biopsy is minimally invasive, typically safe with low morbidity, and can be performed with local anesthesia. It's often used for biopsying deeper orbital tissues, such as the lacrimal gland or extraocular muscles, through various approaches (anterior, lateral, or medial) (Mombaerts et al., 2019).

FNA can replace open incisional biopsy for certain accessible lesions. For hard-to-reach tumors, CT or ultrasound guidance may be used. Tumors mostly made of fluid, like cysts or vascular tumors, may provide less accurate results. Core needle biopsy is similar to FNA but uses a larger needle to preserve tissue architecture, allowing for histological and IHC analysis. While FNA and core needle biopsy are less invasive, open biopsy via a small incision in the orbit is preferred for the most accurate diagnosis (Mombaerts et al., 2019).

2.2. Histopathology Classification of Orbital Tumor

2.2.1. Hematolymphoid Tumor

B-cell lymphoma

Lymphoma is a cancer of the lymphocytes, which can start from B cells, T cells, or natural killer (NK) cells. It is classified into Hodgkin lymphoma and Non-Hodgkin lymphoma (NHL), with NHL making up about 80% of all cases (Xie, Pittaluga, and Jaffe, 2015). In the U.S., the rate of non-Hodgkin lymphoma is about 7 cases per 100,000 people each year (Swerlow et al., 2016). Diffuse Large B Cell Lymphoma (DLBCL) is the most common type of NHL, followed by Follicular Lymphoma (FL) (van Leuween et al., 2014).

The symptoms of B cell lymphoma vary depending on whether the tumor is aggressive or slow-growing. Aggressive types, like DLBCL and Burkitt lymphoma, grow quickly and form large masses (Padalla and Kallam, 2023). Slow-growing types, like FL and marginal zone lymphoma, develop gradually and cause intermittent or worsening swelling of lymph nodes. FL often shows painless swelling and nearly normal blood test results. DLBCL often causes rapid swelling of lymph nodes or masses with symptoms like fever, night sweats, and weight loss, which occur in about 30% of patients (Conlan et al., 1990). Histopathology of B cell lymphoma shows distorted lymph nodes replaced by abnormal cells with large nuclei and high rates of growth (Padalla and Kallam, 2023).

2.2.2. T-cell lymphoma

T-cell lymphoma is a rare subtype of non-Hodgkin lymphoma (NHL) with a poorer prognosis compared to B-cell lymphoma. It accounts for 12% of all NHL cases and is more common with age. Geographical location and ethnicity also affect the distribution of the disease (Varghese and Alsubait, 2024). Clinical manifestations of T-cell lymphoma depend on the subtype. CTCL appears as skin lesions, with MF starting as patches and progressing to plaques or tumors, often in sun-protected areas. Peripheral T-cell lymphoma (PTCL) commonly involves nodes, organs like the liver and spleen, and sometimes the skin. Patients may show B symptoms (fever, night sweats, weight loss), and paraneoplastic syndromes like eosinophilia and hemophagocytic syndrome are common (Park et al., 2017).

Histopathological findings of CTCL may resemble benign inflammation, with features like epidermotropism, Pautrier microabscesses, and tangled, hyperchromatic lymphocytes in the epidermis. PTCL has varied histology, with overlapping features of B-cell lymphoma and Hodgkin disease. Adult T-cell lymphoma shows abnormal peripheral circulating lymphocytes. Anaplastic large cell lymphoma (ALCL) is marked by horseshoe-shaped nuclei. Common findings include polymorphous infiltrates with tumor cells, eosinophils, plasma cells, histiocytes, and blood vessels (Weiss et al., 1985).

2.2.3. Vascular Tumor

Cavernous hemangioma

Cavernous hemangioma is the most common vascular orbital tumor in adults, especially in women (70% of cases). It usually occurs in the intraconal space between the rectus muscles and is characterized by axial proptosis without pain or inflammation. Since the tumor grows slowly, double vision (diplopia) is rare, but hypermetropia and choroidal folds are common due to the anterior displacement of the posterior pole (Castela et al., 2016). Microscopically, cavernous hemangiomas are large, fibrous, and encapsulated, with cavernous vascular channels separated by minimal connective tissue stroma. The vascular spaces are lined by a single layer of endothelial cells, with smooth muscle varying in the walls. Differential diagnosis includes other vascular tumors showing mitotic activity, pleomorphism, or atypia (Vogele et al., 2022).

Lymphangioma

This tumor can be limited to the orbit or extend to the conjunctiva, eyelids, and periorbital tissues. It typically appears in the first decade of life, sometimes at birth, but may be detected later, especially after trauma or bleeding. When it involves multiple orbital structures (muscles, optic nerve), it can cause limited eye movement, proptosis, ptosis, or appear as an elastic, floating mass filled with lymphatic material. Spontaneously or following trauma or viral infection, the tumor may fill with blood (forming a "brown cyst"), leading to acute proptosis that can press on the eyeball or optic nerve (Castela et al., 2016). Histologically, lymphangiomas typically consist of large lymphatic cysts located in the subcutaneous area, connected by expanded dermal lymphatic vessels lined with endothelial cells. These tumors are often macrocystic or microcystic, showing large, irregular vascular spaces lined with a single layer of endothelial cells within a fibroblastic or collagen stroma (Miceli et al., 2022).

2.2.4. Neurogenic Tumor

Neurofibroma

Neurofibromas are made up of a combination of Schwann cells, perineural cells, and fibroblasts, and often contain axons in localized, diffuse, or plexiform lesions. Plexiform neurofibromas, the most common and complex type of orbital peripheral nerve tumor, grow along nerves and form a characteristic "bag of worms" appearance. These tumors are highly vascular and are diffusely connected to normal tissue. The skin over them thickens and they usually affect the upper eyelid and lacrimal gland. Although benign, plexiform neurofibromas can cause significant issues, including continuous growth, vision problems or blindness, and, rarely, death due to damage to vital intracranial structures (Hintschich et al., 2019). Histologically, neurofibromas show non-encapsulated lesions in the dermis. These tumors consist of all elements of peripheral nerves. The cells have wavy, serpentine nuclei with pointed ends. There is mucin deposition in the stroma and fibroplasia, with mast cells commonly present. Axon pathways are often difficult to see in routine sections but can be highlighted with immunohistochemical staining for neurofilaments (Vogele et al., 2022).

Meningioma

Orbital meningiomas are benign tumors that originate from the meninges, with two common forms: optic nerve sheath meningiomas and sphenoid wing meningiomas, both of which frequently occur in middle-aged women. Optic nerve meningiomas cause minimal proptosis but significantly affect vision due to impaired optic nerve perfusion (Hintschich et al., 2019). When located on the optic nerve, these tumors can lead to vision loss, optic nerve edema or atrophy, often accompanied by a chorioretinal vascular shunt at the optic nerve edge (Castela et al., 2016). Histopathologically, the tumor has large, irregular cells with abundant cytoplasm. A whorled pattern is formed by flattened cells surrounding large round cells. Psammoma bodies, which are calcified spherical collections of meningeal cells, may occasionally appear in the tumor (Vogele et al., 2022).

Primitive neuroectodermal tumor

In 2016, the WHO published a revised classification of central nervous system (CNS) tumors using molecular parameters. Some tumors that were previously recognized in the 2007 classification have been renamed or removed. The primitive neuroectodermal tumor (PNET) is no longer recognized as such and is now classified under embryonal tumors (Rios and De Jesus, 2023).

Patients with embryonal tumors usually present with signs of increased intracranial pressure, such as headaches, nausea, vomiting, irritability, and lethargy, in decreasing frequency (Maaz et al., 2021). They may also have vision problems, seizures, hemiparesis, cerebellar signs, and cranial nerve paralysis. Supratentorial embryonal tumors are found in older children, with an average age of 8.4 years, and females are more affected than males in a 2.3:1 ratio (Banan and Hartmann, 2017; Jaju et al., 2019). Embryonal tumors with layered rosettes show abundant neuropil and true rosettes, and have amplification of the C19MC region on chromosome 19 (Gupta and Dwivedi, 2017). Histology shows small, round, layered blue cells with pseudostratified neuroepithelium around a central lumen, which may be empty or contain eosinophilic debris. The cell nuclei are located far from the lumen (Rios and De Jesus, 2023).

Pilocytic astrocytoma

Glioma, or Juvenile Pilocytic Astrocytoma, is the most common optic nerve tumor, but it makes up only 3% of orbital tumors. Gliomas typically cause painless proptosis and vision loss, ranging from mild to severe. According to G. Castela, gliomas can also lead to eye movement issues (Castela et al., 2016). Most orbital gliomas remain stable for a long time, but some, even though benign, may show infiltrative growth and systemic spread (Hintschich et al., 2019). Histologically, optic nerve gliomas have a distinct appearance, with pilocytic astrocytoma (hair-like appearance) and Rosenthal fibers, showing moderate anisokaryosis and slightly elongated nuclei (Vogele et al., 2022).

Schwannoma

Orbital neurilemoma, or schwannoma, is a benign tumor originating from Schwann cells and is typically encapsulated. It can be located in the orbit or reach the orbit through nearby peripheral nerves. Clinically, it resembles a solitary orbital tumor, causing proptosis and eye displacement (hypoglobus), depending on its location. Schwannomas do not cause pain despite originating from nerve sheaths (Castela et al., 2016). Histologically, schwannomas consist of spindle-shaped cells with wavy or bent nuclei, arranged in dense and loose areas, known as Antoni A and Antoni B regions. The dense, eosinophilic Antoni A area contains spindle cells in intersecting fascicles. The loose, hypodense Antoni B area has scattered cells separated by prominent myxoid extracellular matrix, which may form microcysts. Verocay bodies, areas with no nuclei, are also present (Vogele et al., 2022).

2.2.5. Soft Tissue Tumor

Solitary Fibrous Tumor

Solitary fibrous tumors of the orbit (previously called fibrous mesothelioma), including hemangiopericytoma and fibrous histiocytoma, are more common in the extraconal space. These tumors are located in the anterior orbit and can grow quite large. They have a slow growth pattern and rarely cause double vision (diplopia). Macroscopically, solitary fibrous tumors are well-defined, grayish, and typically do not recur after complete excision (Castela et al., 2016). Hemangiopericytomas arise from mesenchymal perivascular cells that resemble pericytes and have few cytoplasmic organelles. They are characterized by thin-walled, branching blood vessels, known as "staghorn" vessels. The nuclei are often oval or spindle-shaped. The mass is usually well-defined or encapsulated (Nguyen et al., 2023).

Leiomyosarcoma

Leiomyosarcoma is the most common soft tissue sarcoma seen in hereditary retinoblastoma and the second most common secondary cancer after osteosarcoma. Orbital leiomyosarcoma typically presents as painless proptosis, but it can also cause vision loss or be felt as a mass. This tumor is thought to originate from the smooth muscle of blood vessels or the Muller muscle (Chen et al., 2015). Histopathologically, leiomyosarcomas are characterized by bundles of cells, abundant eosinophilic cytoplasm, pleomorphism, elongated, hyperchromatic nuclei, and often positive staining for smooth muscle actin, desmin, and h-caldesmon (Garcia et al., 2020).

Synovial sarcoma

Synovial sarcoma makes up about 10% of all soft tissue sarcomas (STS) (Mastrangelo et al., 2012), with an age-adjusted incidence rate in the US of 0.177 per 100,000 people (around 580 new cases annually). It typically arises from soft tissues in the limbs but can also occur in the torso, chest, neck, and rarely in other organs like the lungs, heart, or digestive system (Gazendam et al., 2021). In the limbs, patients often present with a firm, enlarging mass that is usually movable within the muscle and not painful. In cases involving internal organs, symptoms are localized to the affected organ, such as urinary retention in the prostate or pneumonia-like symptoms in the lungs (Zhang et al., 2014; Rajeev et al., 2017).

Diagnosing synovial sarcoma clinically can be difficult. However, it should be suspected in young, healthy patients showing hard masses in the limbs or other body areas. Synovial sarcoma is a heterogeneous tumor with uncertain origins, divided into two main subtypes: monophasic and biphasic. The monophasic subtype is typically spindle cell (more common), while the biphasic subtype contains both spindle-shaped cells and epithelial cells. Rarely, poorly differentiated, ossified, or myxoid subtypes are seen. Due to its varied appearance, a pathologist specializing in sarcoma histology is often needed for diagnosis (Mangla and Gasalberti, 2023).

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is a malignant soft tissue sarcoma that is believed to originate from primitive mesenchymal cells, which typically differentiate into skeletal muscle tissue (Kaseb et al., 2024). RMS is the most common soft tissue sarcoma diagnosed in children, with only 1% of cases found in adults (Amer et al., 2019). The exact cause and risk factors are mostly unknown. While most RMS cases are sporadic, it can be linked to familial syndromes (Li et al., 2021). RMS is usually asymptomatic, but symptoms vary based on the tumor's location, size, and metastasis. The most common sites for RMS tumors are the head, neck, and genitourinary areas. Patients with tumors in the head and neck (such as the orbital sinuses, nasopharynx, and paranasal regions) may experience symptoms like mucopurulent nasal drainage, sinus congestion, or proptosis. Additionally, symptoms caused by the mass effect of the tumor, such as proptosis, dizziness, nausea, or headaches, can occur (Skapek et al., 2019).

RMS cells show minimal muscle development and include undifferentiated mesenchymal cells, elongated myoblasts, and poorly differentiated myofibers (Parham and Barr, 2013; Lav, Heera, and Cherian, 2015). Alveolar RMS typically has medium-sized cells in large groups separated by fibrovascular septa, with scattered giant cells. Embryonal subtypes usually have small, round blue cells and rhabdomyoblasts loosely packed in a myxoid matrix. Spindle cell types are arranged in a pseudovascular pattern and are more differentiated. Pleomorphic subtypes are identified by undifferentiated cells of various shapes with enlarged, hyperchromatic nuclei (Agaram, 2022; Kashi, Hatley, and Galindo, 2015).

2.2.6. Secondary Tumor

Squamous cell carcinoma

Squamous cell carcinoma (SCC), or ocular surface squamous neoplasia (OSSN), is the most common secondary epithelial tumor of the orbit, often originating from the paranasal sinuses or pharynx. The incidence of OSSN is strongly linked to factors like intense sun exposure (UV radiation), HIV infection, and Human Papillomavirus (HPV). The nasal limbus, receiving the highest light exposure, is the most common site for these tumors due to concentrated limbal epithelial crypts in this area. SCC typically spreads through lymphatic channels, invading lymph nodes, which may become firm and difficult to move. This can be detected through digital palpation, where the lymph nodes are enlarged and immobile. The invasion can extend contralaterally and bilaterally (Soebagdjo, 2019).

The clinical presentation varies based on the tumor type and location. Patients often have a history of prior periorbital surgeries (for eyelid, conjunctiva, perinasal, or intracranial tumors) (Castela et al., 2016). Histologically, SCC shows atypical cells throughout the epithelium, with individual tumor cells or nests extending into the underlying stroma. The epithelium may become keratinized, with eosinophilic or clear cytoplasm, intercellular bridges, dyskeratosis, coarse chromatin, and prominent nucleoli. In some patients, cells may contain pigment, especially in those with highly pigmented skin (Blandford et al., 2017).

Basal cell carcinoma

Basal Cell Carcinoma (BCC) is an external tumor that grows on the eyelid. The prevalence of BCC is higher in populations near the equator compared to those near the poles, indicating that sun exposure, particularly ultraviolet radiation, is a major risk factor. BCC is the most common type of skin cancer, making up over 70% of all malignant skin tumors.

Clinically, BCC appears as an ulcerated, slightly rough surface with induration, irregular borders, and destruction at the eyelid margin. It rarely metastasizes or invades deeper areas due to a fascia barrier. The tumor is often painless when pressed, and can cause epiphora (excessive tearing), leading to vision problems if left untreated. The nodular type, which is the most common (60-80% of cases), has a smooth surface with clear borders and small dilated blood vessels. It grows slowly, taking 1-2 years to reach about 0.5 cm in diameter (Soebagdjo, 2019).

Adenoid cystic carcinoma

Adenoid cystic carcinoma (ACC) is a rare cancer that originates from secretory glands, most commonly the salivary glands (Ammad Ud Din and Shaikh, 2023). It is slightly more common in women, with an incidence rate of 4.5 cases per 100,000 people (Chae et al., 2015). ACC is locally aggressive, and while metastasis can occur, it typically presents as a slow-growing, firm, and painless swelling in the head and neck. Pain and paresthesia can also occur due to the tumor's tendency to invade nerves, particularly in tumors arising from the parotid gland (Chummun et al., 2001; Martínez-Rodríguez et al., 2011). Tumors near the skull base can cause eye movement issues or paralysis of cranial nerves IX, X, XI, and XII. Cases of Horner's syndrome have also been reported (Pushpanjali et al., 2014).

ACC was originally named "cylindroma" by Billroth in 1859 due to its characteristic cylindrical cell arrangement in a hyaline stroma (Azumi and Battifora, 1987). Histologically, ACC cells have hyperchromatic, angular nuclei and minimal cytoplasm. It has three main histological patterns: tubular, cribiform, and solid, often mixed, with cribiform being the most common. The tumor contains cyst-like spaces between basaloid cell islands, though these are not true cysts. The tubular pattern features tubular cell nests in the hyaline stroma, while the solid subtype shows dense basaloid cell sheets, often with prominent mitosis and central necrosis (Azumi and Battifora, 1987).

Sebaceous cland carcinoma

Sebaceous gland carcinoma (SGC) is a malignant tumor originating from the sebaceous glands, most commonly from the meibomian glands in the tarsal plate. It can also develop in the Zeis glands near the eyelashes or in sebaceous glands around the caruncle, eyebrows, or facial skin. The exact cause of SGC is largely unknown, but risk factors include race and sun exposure. SGC often spreads superficially, known as pagetoid spread (Soebagdjo, 2019).

The nodular form of SGC appears as a firm, non-movable yellowish nodule, typically located in the tarsal plate. Pagetoid SGC involves intraepithelial infiltration at the eyelid or conjunctival margin, leading to invasion and madarosis, which can resemble chronic blepharoconjunctivitis. Histopathological examination is the standard method for diagnosing and confirming SGC. Most patients have well-differentiated tumors, with tumor cells arranged in sheets or lobules with central necrosis. The cytoplasm is pale, foamy, and contains vacuoles, while the nuclei are hyperchromatic, and staining shows positivity for lipids, such as oil red O stain (Soebagdjo, 2019).

2.2.7. Metastatic Tumor

Melanoma

Malignant melanoma is a type of cancer that develops in pigment-producing cells, which give color to tissues such as skin, hair, and eyes. Periocular malignant melanoma most commonly occurs in the uveal tissue and conjunctiva. Uveal melanoma symptoms include blurry vision, though many patients are diagnosed before symptoms appear. Other symptoms may include photopsia, floaters, reduced visual field, visible tumors, eye pain, metamorphopsia, and glaucoma. Choroidal melanoma often presents with complications like retinal detachment, intraocular bleeding, and extraocular extension, which can lead to perforation.

Conjunctival melanoma is typically noticed as a thick, dark lesion on the conjunctiva with feeder vessels and surrounding black areas. It usually occurs in adults and is unilateral, with or without irritation and pain. Sometimes, the lesion may not be dark-colored (amelanotic). Choroidal melanoma can have dome-shaped (75%), mushroom-shaped (19%), or diffuse (6%) appearances, and the lesions can be dark-colored (55%), non-pigmented (15%), or mixed (30%). Histopathologically, malignant melanoma is classified into three types: spindle cell, epithelioid, and mixed (Soebagdjo, 2019).

Ca Mammae

The most common primary sites for metastatic tumors are the breast, prostate, lungs, kidneys, and digestive system. These lesions often present with proptosis and painful diplopia, sometimes mimicking orbital inflammation. A notable exception to the usual clinical sign of proptosis is spontaneous enophthalmos in cases of scirrhous metastatic breast cancer (Hintschich et al., 2019). Enophthalmos, ptosis, periorbital skin induration, limited eye movement, and incomplete eyelid closure can also occur (Novitskaya et al., 2013). Histologically, breast adenocarcinoma varies, and orbital metastasis may differ from the primary tumor. All metastatic breast carcinomas are invasive. The invasive types include ductal, lobular, and mixed carcinomas. Metastatic breast cancer in the orbit shows neoplastic cells arranged in single-file strands with focal ductal differentiation, surrounded by fibrotic stroma (Nguyen et al., 2023).

2.2.8. Others

Inflammatory Pseudotumor

Non-specific orbital inflammation (NSOI) or idiopathic orbital inflammation (IOI) is a benign, non-infectious orbital inflammation characterized by polymorphic lymphoid infiltration with varying degrees of fibrosis, and no known local or systemic cause. NSOI typically presents with sudden pain, proptosis, and other signs of inflammation such as swelling and erythema. Unilateral presentation is more common, but bilateral cases also occur. Pain is the most common symptom in adults (58-69%), followed by diplopia (31-38%). Other common signs include periorbital edema/swelling (75-79.2%), proptosis (32-62.5%), extraocular muscle involvement (54.2%), red eyes (48%), chemosis (29%), vision loss (20.8%), and ptosis (16.7%). Histopathological examination in pseudotumors shows severe inflammation around the tissues, which may suggest a systemic disease. Immunohistochemical staining is used to differentiate malignant lymphoma and autoimmune diseases related to immunoglobulin G4 (Isse et al., 2013).

2.3. Relationship of Histopathological Examination Results and Clinical Characteristics

Orbital tumors present a variety of clinical manifestations, with some tumors having distinct characteristics. Based on various collected journals, orbital tumors show certain tendencies in their manifestations, allowing them to be classified as either malignant or benign. For example, malignant tumors tend to have characteristics such as pain around the eye and periocular changes, like paresthesia and hypoesthesia. Additionally, malignant tumors often cause systemic symptoms like fever, weight loss, and fatigue. Some malignant tumors have distinct features, such as enophthalmos in breast cancer metastases or heterochromia and pupil distortion in uveal melanoma. In contrast, benign tumors usually manifest unilaterally with proptosis, both axial and non-axial, without pain. For example, benign neurofibromas often present with a characteristic eyelid thickening resembling a "bag of worms." Tumors can also be differentiated by the onset of symptoms, with benign tumors typically having a slower or chronic onset, while malignant tumors tend to present acutely. A tumor may not always be confined to one area, so various clinical symptoms may appear depending on its spread.

Determining whether an orbital tumor is benign or malignant cannot rely solely on its clinical characteristics; additional diagnostic tests, such as histopathological examination, are necessary. Histopathology helps identify differences in cell type, cell differentiation, and specific features found in biopsy samples. Vascular and neurogenic cells rarely become malignant, while mesenchymal and lymphatic cells tend to be malignant. Epithelial cells can be either benign or

malignant and are distinguished by the specific features of each tumor type. Cell differentiation also helps determine the tumor's nature. For example, anaplasia, a hallmark of malignancy, helps confirm whether a tumor is malignant. The presence of pleomorphism and abnormal cell nuclei are signs of anaplasia

3. Conclusion

Orbital tumors exhibit a wide range of clinical manifestations, with distinct differences between benign and malignant types. Malignant tumors are often associated with pain, periocular changes, systemic symptoms, and specific features like enophthalmos or pupil distortion, whereas benign tumors tend to show gradual, unilateral proptosis without pain. Histopathological examination plays a crucial role in confirming the nature of the tumor, as it provides detailed information on cell differentiation, the presence of anaplasia, and specific tumor characteristics. The combination of clinical manifestations and histopathology is essential for determining whether a tumor is benign or malignant and understanding its clinical behavior. However, further studies are needed to explore the relationship between clinical features and histopathological findings in greater depth. Such research could enhance diagnostic accuracy and help establish more effective treatment strategies for orbital tumors.

Compliance with ethical standards

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No conflict of interest to be disclosed.

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