

ORBITAL TUMORS AND PSEUDOTUMORS

Jasna Talan-Hranilović and Davor Tomas

Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Twenty-four orbital tumors and 4 pseudotumors diagnosed in biopsy material among 596 ophthalmic tumors examined during the 1998-2003 period are presented according to patient age and sex, tumor histology and immunohistochemistry. The most common orbital tumors were lipomas, meningiomas and lymphomas, with a peak incidence in the seventh decade of life. Most orbital tumors of childhood are distinguished from those occurring in adults. Most pediatric orbital tumors are benign (developmental cysts, capillary hemangioma, hamartoma), with a peak incidence in the first decade of life. Orbital tumors show a bimodal age distribution. Benign orbital tumors are more common than the malignant ones. Rhabdomyosarcoma (embryonal type) is the most common orbital malignancy in childhood, and lymphoma in adults. Orbital pseudotumors is a term that has been widely accepted to describe inflammatory lesions of the orbital tissue with a mixed inflammatory infiltrate with a varying grade of fibrosis. Histologic classification of orbital pseudotumors is presented. Orbital pseudotumors occur predominantly in older individuals and are infrequent in children and young individuals. These imply a nonspecific inflammatory process of unknown etiology, and have been included as part of the differential diagnosis of orbital tumors.

Key words: *Orbital neoplasms – pathology; Orbital neoplasms – classification; Orbit – pathology; Granuloma plasma cell, orbital – pathology*

Introduction

Orbital tumors and related orbital pathology generally require a multidisciplinary approach. Diseases of the orbital cavity call for closer attention due to its specific anatomic structure and location. These diseases need multidisciplinary treatment with cooperation of a number of medical specialties. The World Health Organization classification of the tumors of the orbit provides a framework dividing them into groups according to origin as follows: benign soft tissue tumors of the orbit; malignant soft tissue tumors of the orbit; lymphoid and hematologic tumors; pseudotumors of the orbit; and other primary tumors of the orbit (benign and malignant subgroups). Other tumors of the orbit, secondary and metastatic tumors of the orbit, are a separate group of orbital tumors¹. Metastases are quite infrequent in the ophthalmic region. The most common site of involvement is the uvea, followed by the orbit².

Correspondence to: *Jasna Talan-Hranilović, M.D., Ph.D.*, Ljudevit Jurak University Department of Pathology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: jasna.talan-hranilovic@hg.htnet.hr

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Orbital pseudotumors are a nonspecific inflammatory process that is histopathologically classified into three main types: granulomatous, lymphoid and sclerosing³. This condition was also first described in 1905 by Birch-Hirschfeld⁴. Orbital tumor generally occurs unilaterally (92%)⁵. The most important clinical manifestation of orbital disease is proptosis.

The aim of the present study was to present orbital tumors and pseudotumors diagnosed in the material obtained by ophthalmic biopsy during the 1998-2003 period, and to analyze the overall and histology specific trends in their prevalence. During the study period, 24 orbital tumors and 4 pseudotumors were identified in a total of 624 ophthalmic tumors. Orbital pseudotumors that include a broad category of orbital inflammatory diseases pose a special diagnostic problem. They are defined as nonspecific, idiopathic inflammatory condition of unknown etiology. They mimic true orbital neoplasm, especially lymphoma. Pseudotumors are frequently included as part of the orbital differential diagnosis.

Material and Methods

Twenty-four orbital tumors and 4 pseudotumors, identified out of 624 ophthalmic tumors during the six-year period (1998-2003) were analyzed according to histologic diagnosis, histochemistry and immunohistochemistry analysis, and patient age and sex. Formalin-fixed, paraffin embedded surgical specimens were routinely and immunohistochemically analyzed using the labeled streptavidin biotin method (LSAB). DAKO Tech Mate automated immunostainer was used as a visualization system employing the microwave streptavidin immunoperoxidase protocol (MSIP). Results are presented in tables and figures.

Results

Our survey yielded a total of 624 ophthalmic tumors diagnosed during the 1998-2003 period (Fig. 1). Of these, there were 24 orbital tumors and 4 pseudotumors (Table

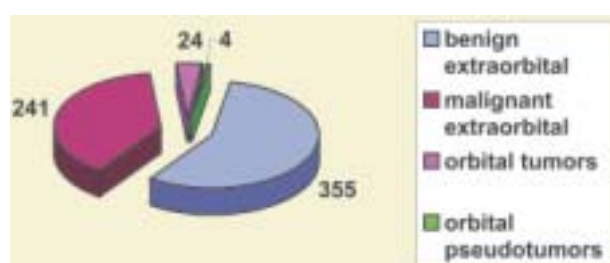


Fig. 1. Ophthalmic tumors diagnosed during the 1998-2003 period.

1). The distribution of orbital tumors according to diagnosis, sex and age is presented in Table 2. Histologically,

Table 2. Distribution of orbital tumors according to diagnosis, sex and age

Diagnosis	No. of cases	Sex/Age (M/F yrs)
Rhabdomyosarcoma	2	1 M 1 yr; 1 F 9 yrs
Epidermal cyst	2	2 M 1 yr, 1 yr
Dermal cyst	1	1 F 6 yrs
Hamartoma (cartilaginous/vascular)	1	1 M 1 yr
Hemangioma	1	1 F 59 yrs
Lipoma	5	4 M 62, 68, 73, 74 yrs; 1 F 69 yrs
Pleomorphic adenoma of lacrimal gland	2	1 M 34 yrs; 1 F 47 yrs
Meningioma	4	2 M 46, 59 yrs; 2 F 33, 49 yrs
Non-Hodgkin's lymphoma (diffuse B phenotype)	4	1 M 80 yrs; 3 M 71, 76, 79 yrs
Secondary tumor	3	2 M 68, 80 yrs; 1 F 80 yrs
Total	24	14 M; 10 F

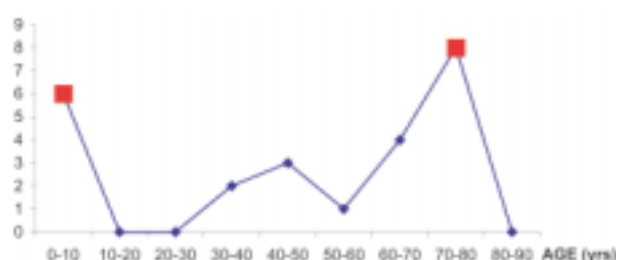


Fig. 2. Orbital tumors according to age groups.

Table 1. Orbital tumors recorded during the 1998-2003 period according to diagnosis

Diagnosis	No. of cases
Rhabdomyosarcoma	2
Lipoma	5
Epidermal cyst	2
Dermal cyst	1
Hamartoma	1
Pleomorphic adenoma	2
Meningioma	4
Non-Hodgkin's lymphoma	4
Metastatic melanoma	1
Metastatic carcinoma	2
Total	24

the following types were identified: rhabdomyosarcoma (n=2), epidermal cyst (n=2), dermal cyst (n=1), cartilaginous and vascular hamartoma (n=1), lipoma (n=5), pleomorphic adenoma of lacrimal gland (n=2), meningioma (n=4), non-Hodgkin's diffuse B phenotype lymphoma (n=4), and secondary tumor (n=3). Secondary orbit-

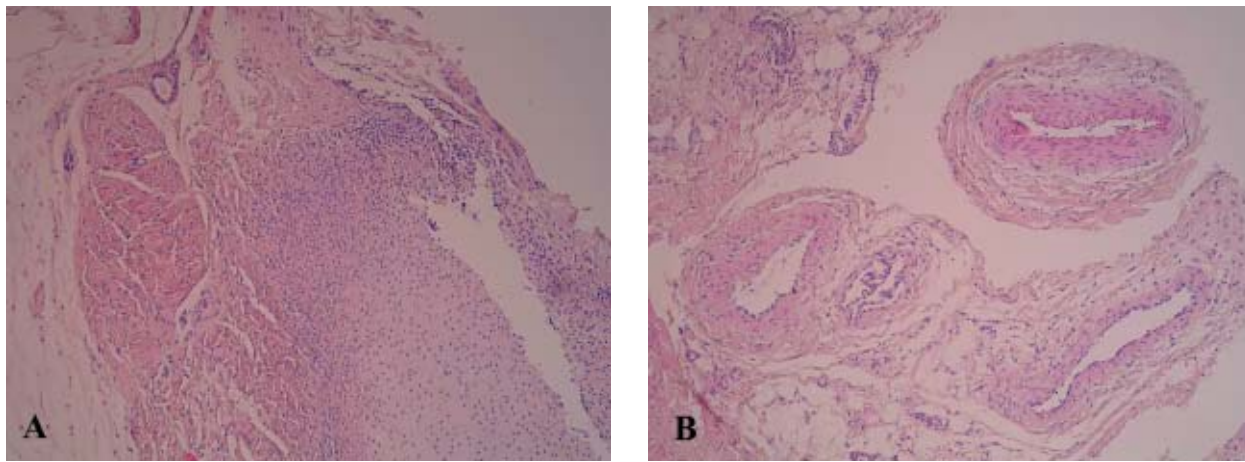


Fig. 3. Hamartoma in a 1-year-old boy: (A) cartilaginous portion of the tumor (HE, X100); (B) tumor portion with vascular and adipose tissue (HE, X100).

al tumors originated from the squamous cell carcinoma of the conjunctiva, basal cell carcinoma of the eyelid, and conjunctival melanoma, one each. The male to female ratio was 14:10. The incidence of orbital tumors showed a bimodal curve of age distribution (Fig. 2). There were 4 cases of orbital pseudotumors: chronic inflammation (n=3) and Kimura's disease (n=1). The male to female ratio was 3:1 (Table 3).

Orbital Tumors

Hamartoma: cartilaginous and vascular hamartoma; n=1, a male aged 1 year; benign mesenchymoma (Fig. 3).

Epidermal cyst: n=2, males aged 1 year; the cyst capsule built of fibrous tissue with squamous epithelial cells and containing amorphous squamous material (Fig. 4).

Dermal cyst: n=1, a female aged 6 years; dermoid cyst lined with keratinizing squamous epithelium, with the presence of skin appendages, frequently surrounded by granulomatous inflammation with foreign body giant cells, the content being squamous and adipose material (Fig. 5).

Table 3. Distribution of orbital pseudotumors according to diagnosis, sex and age

Diagnosis	No. of cases	Sex/Age (M/F yrs)
Chronic inflammation	3	2 M 27, 52 yrs; 1 F 77 yrs
Kimura's disease	1	1 M 15 yrs
Total	4	3 M; 1 F

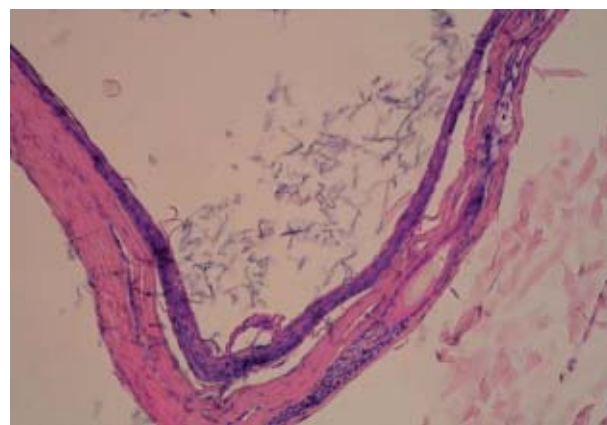


Fig. 4. Epidermal cyst in a 1-year-old boy: fibrous capsule of the cyst with squamous epithelial cells (HE, X200).

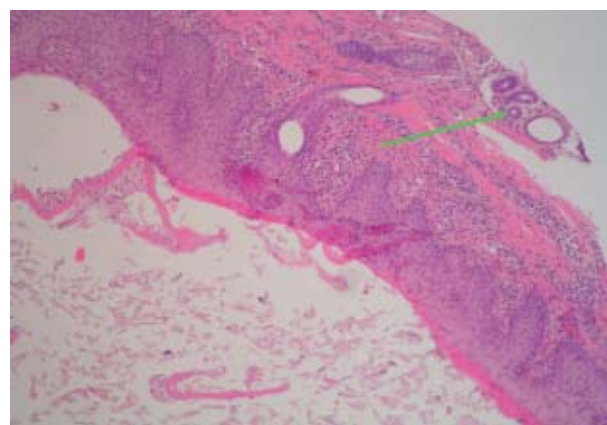


Fig. 5. Dermal cyst in a 6-year-old girl: keratinizing squamous epithelium with additional presence of skin appendages (arrow) (HE, X100).

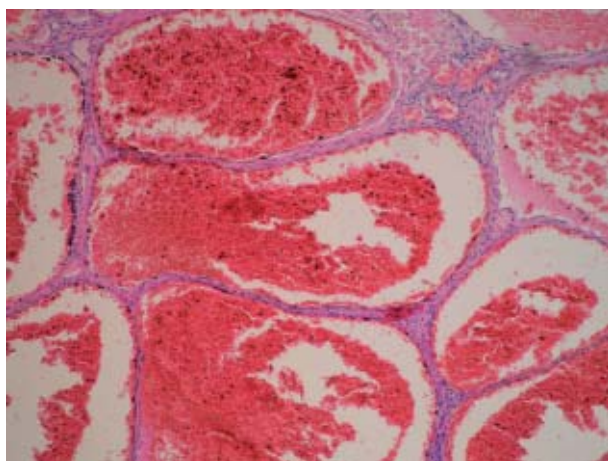


Fig. 6. Cavernous hemangioma in a 59-year-old female: a tumor composed of dilated vascular canals and fibrous stroma (HE, X100).

Cavernous hemangioma: n=1, a female aged 59 years; fibrous capsule surrounding the tumor composed of vascular canals, with fibrous septa between vascular canals of variable thickness, often containing inflammatory cells and hemosiderin-laden macrophages (mean age 42 years, 75% females) (Fig. 6).

Embryonal rhabdomyosarcoma: n=2, a male aged 2 years and a female aged 9 years; it is the most common primary malignant orbital tumor of childhood, with median age at diagnosis of 7 years. Embryonal rhabdomyosarcoma is the most common type of rhabdomyosarcoma in the orbit⁶. The stroma has a myxoid appearance without collagen production. The tumor is composed of small poly-

hedral and spindle cells. The cells have hyperchromatic nuclei with high mitotic activity. Cross striation is rarely found. Trichrom color of the rhabdomyoblast cytoplasm is bright red, and PAS staining shows glycogen within the cytoplasm. Immunohistochemistry: muscle-specific actin consistently positive (it is the most sensitive antibody for the detection of orbital rhabdomyosarcoma), desmin strongly positive, vimentin positive, myosin diffusely positive (Fig. 7).

Lipoma: n=5, four males aged 62, 68, 73 and 74 years, and one female aged 69 years. In some series, lipoma of the orbit has been estimated to account for 9% of all orbital neoplasms. Lipoma is composed of mature adipocytes, has a fibrous capsule and a lobular pattern. The fibrous septa of normal orbital adipose tissue may be confused with the lobular pattern of lipoma (Fig. 8).

Meningioma: n=4, two females aged 49 and 33 years, and two males aged 59 and 46 years. In the orbit, it originates from the optic nerve meninges and is quite rarely seen. In two of our cases, it was found accidentally in eye balls submitted to exenteration for uveal melanoma. Ectopic (extradural) meningioma arising in the orbit is an extremely rare type and is believed to arise from congenitally displaced residues of meningotheelial cells (Fig. 9).

Pleomorphic adenoma of lacrimal gland: n=2, a male aged 34 and a female aged 47 years; mostly arises from deep orbital lobe, and only rarely from accessory or ectopic lacrimal gland. It is a pseudoencapsulated tumor; histologic section reveals a common mixture of epithelial cells, variably sized ducts with inner cuboidal columnar epithelium and mesenchymal-like elements in the outer layer of flat-

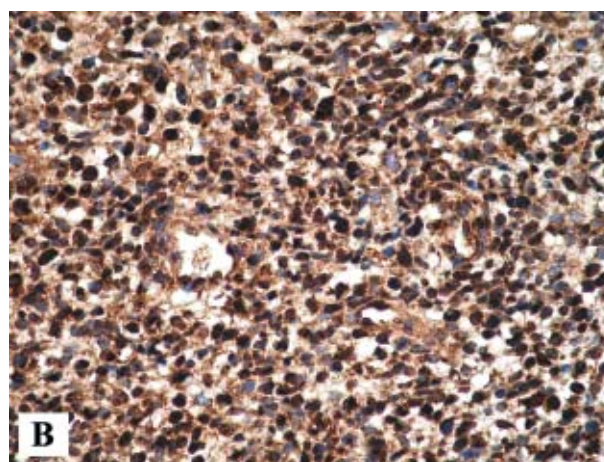
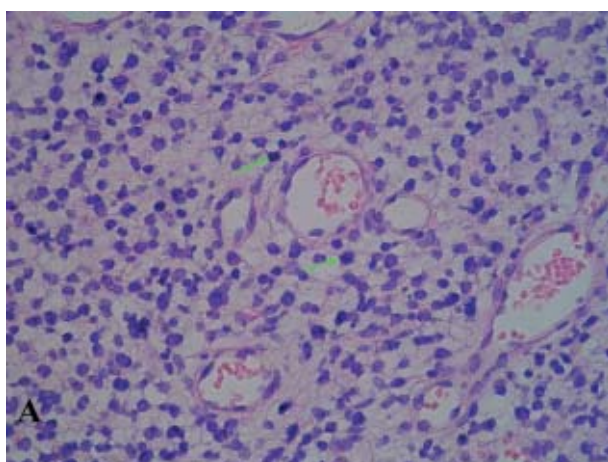


Fig. 7. Rhabdomyosarcoma (embryonal type) in a 9-year-old girl: small, polyhedral, oval and spindle cells, in part of myxoid appearance of the stroma; (A) mitoses (arrows) (HE, X400); (B) immunohistochemistry (myoglobin, X400).

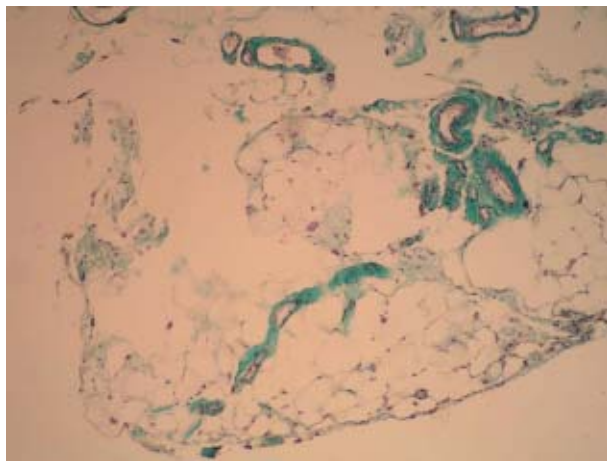


Fig. 8. Lipoma in a 68-year-old male: mature adipose tissue, some blood vessels (Mallory, X100).

tened to spindle shaped cells. The outer layer may undergo unusual metaplasia, particularly into the myxoid tissue, cartilage and rarely bone. Immunohistochemistry: cytokeratin stained myoepithelial cells and occasional stromal cells, muscle-specific actin stained myoepithelium in normal gland and tumor, indicating that benign and malignant pleomorphic adenomas arise from progenitor cells capable of both epithelial and myoepithelial differentiation, or they arise from more than one cell type (Fig. 10).

Lymphoma: n=4, three females aged 79, 76 and 71 years, and one male aged 80 years; lymphomas have now been immunologically classified and this may characterize orbital biopsies. The degree of differentiation is of crucial

importance. Lymphomas of the orbit usually show monoclonal B cell patterns (Fig. 11).

Secondary tumors of the orbit: n=3, a male aged 80 years, squamous cell carcinoma from the conjunctiva; a male aged 68 years, basal cell carcinoma from the eyelid; and a female aged 80 years, melanoma from conjunctival melanoma) (Fig. 12).

Orbital Pseudotumors

The term 'orbital pseudotumors' has been generally accepted to describe inflammatory lesions of orbital tissue. In 1926, Williamson-Noble reported on difficulties encountered in the diagnosis of lymphocytic proliferation due to inflammatory change *versus* neoplastic activity⁷. A mixed inflammatory infiltrate with fibrosis of a varying degree is a histopathologic hallmark of orbital pseudotumor. Orbital pseudotumor is not related to orbital reactive lymphoid hyperplasia (pseudolymphoma), and is not a lymphoid tumor⁸. Additional insight in the classification and etiology of these tumors is obtained from the pathology literature^{8,9}. The histologic classifications of ocular infiltrates proposed by Knowles and Jakobiec in 1980¹⁰, and by World Health Organization in 1993¹ appear to be most acceptable.

Kimura's disease: n=1, a male aged 15 years. Histologically, the lesion contained dense lymphoid aggregates with prominent germinal centers with vascular proliferation and eosinophilia. It is reactive lymphoid hyperplasia with a follicular pattern (Fig. 13).

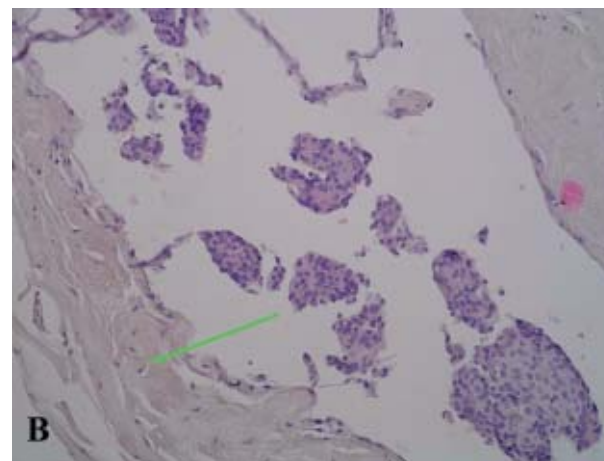
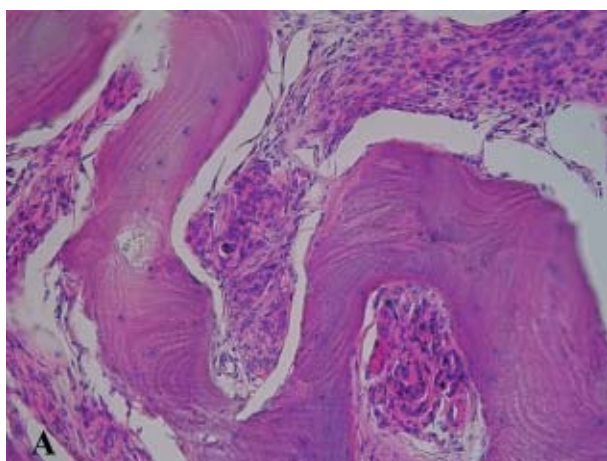


Fig. 9. (A) Orbital meningioma in a 33-year-old female. Meningeothelial cells in haversian canals of orbital bones (HE, X200); (B) meningioma arising from optic nerve meninges (HE, X200).

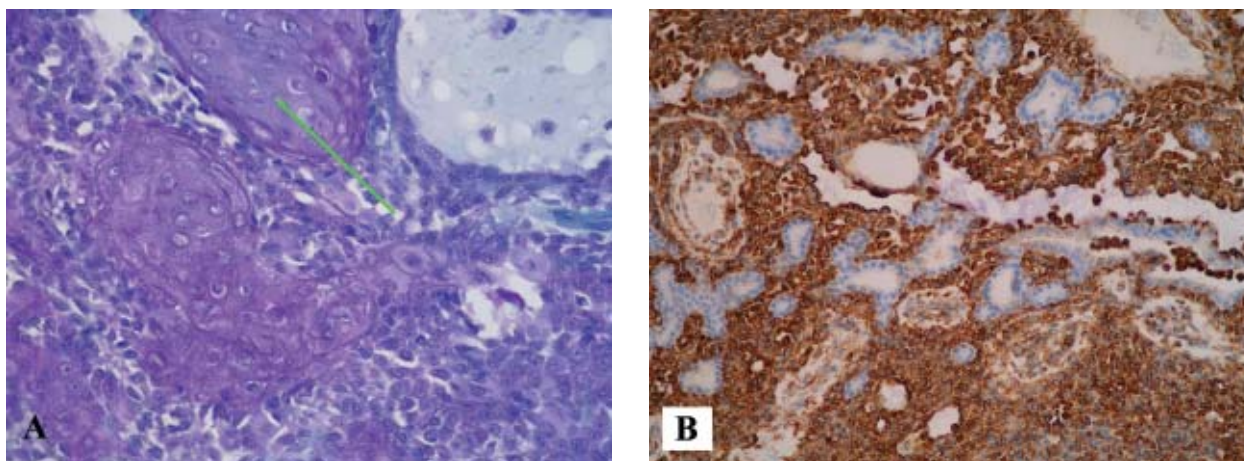


Fig. 10. Pleomorphic adenoma of lacrimal gland in a 34-year-old male: a mixture of epithelial cells, myxoid tissue and cartilage (arrow); A(A) Mallory (X400); (B) immunohistochemistry (vimentin, X200).

Idiopathic chronic inflammation: n=3, two males aged 27 and 56 years; histologically, there were infiltrates of small lymphocytes, plasma cells and eosinophils, with pronounced vascularization. The third patient was a female aged 77 years; histology revealed chronic inflammation with infiltration of lymphocytes, plasma cells, parietal venous thrombosis, necrosis and hematoma. The inflammatory response may be initiated by the hemorrhage itself¹¹ (Fig. 14).

Discussion and Conclusion

The incidence of neoplastic lesions has been found to show a bimodal age distribution curve with peaks in the

first and seventh decades of life¹². Most orbital tumors of childhood are distinct from tumors that occur in adults. The most common orbital malignancy in childhood is rhabdomyosarcoma^{6,13}, however, the majority of pediatric orbital tumors are benign and usually include developmental cysts, capillary hemangioma and hamartoma¹⁴. In our study, the age distribution of 24 orbital tumors showed developmental cysts and mesenchymal tumors to peak in the first decade of life, whereas secondary, metastatic and lymphoproliferative lesions had their maximum incidence after the age of 60. These data are consistent with literature reports. All these tumors were unilateral. In the present study, lipoma was the most common orbital tumor, followed by meningioma and lymphoma. Lymphomas and lipomas

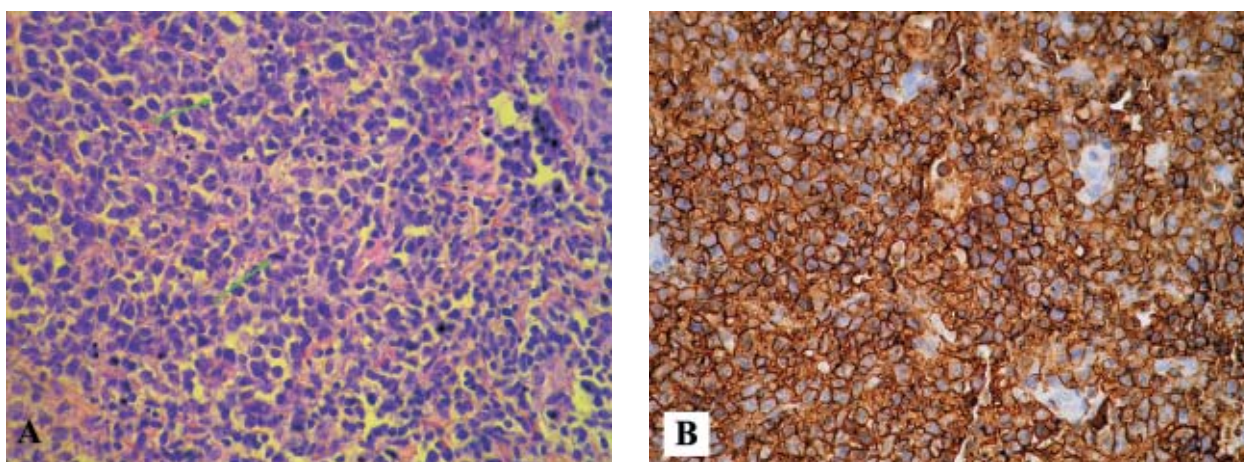


Fig. 11. Lymphoma in a 71-year-old female: monoclonal B cell pattern; (A) lymphoblasts with mitoses (arrows) (HE, X400); (B) immunohistochemistry (CD-20, X400).

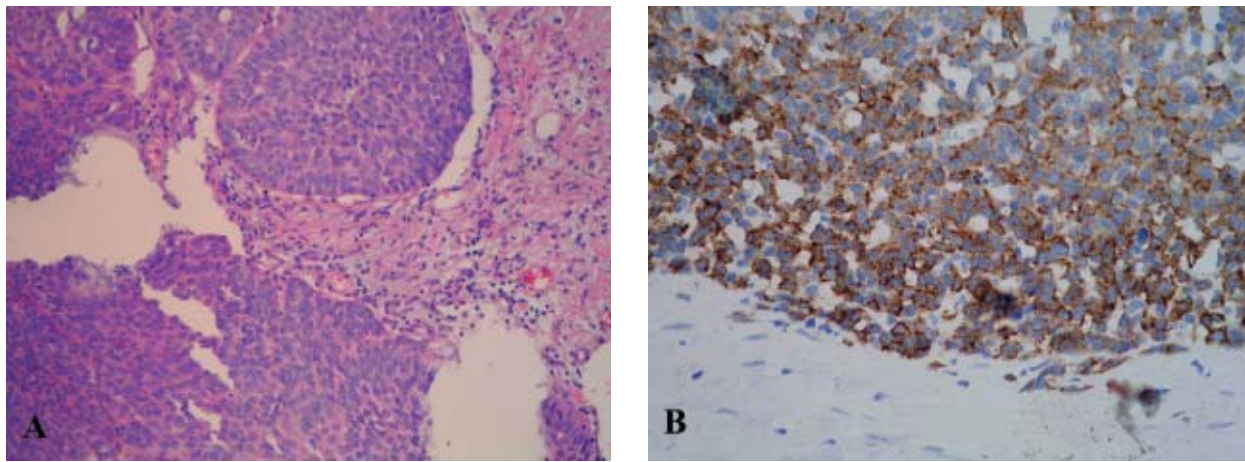


Fig. 12. Secondary tumor of the orbit: (A) squamous cell carcinoma from the conjunctiva in a 68-year-old male (HE, X200); (B) melanoma from conjunctival melanoma; immunohistochemistry (HMB45).

were found in the 7th and 8th, and meningiomas in the 6th decade of life. The two cases of meningioma arising from optic nerve meninges were in the incipient stage. They are considered to be more aggressive tumors than meningiomas of the sphenoid ridges¹⁵.

Orbital pseudotumors occur predominantly in older individuals, and are infrequent in children and young ones¹⁶. Pseudotumors may be the most difficult 'tumors' of the orbit to diagnose clinically and pathologically. The nonspecific, idiopathic types of orbital inflammation, pseudotumors, may be classified into pathologic types such as lymphoid hyperplasia, myositis, vasculitis, lipogranuloma, and dacryoadenitis¹⁶. Kimura's disease, i.e. lymphadenopathy with or without a soft tissue mass, also belongs

to this group, shows a striking male predilection, and is characterized by dense aggregates of lymphocytes with prominent germinal centers. The lesion is benign although recurrence may develop after surgical excision¹⁵. Inflammatory pseudotumors of the orbit are much more common than specific infectious granulomas. Biopsies provide a great deal of information needed in the management of these patients.

In conclusion, orbital lymphoid diseases remain a relatively rare diagnostic and therapeutic challenge even today. Immunohistologic analysis of biopsy specimens helps make an accurate diagnosis and choose appropriate therapy (irradiation dosage).

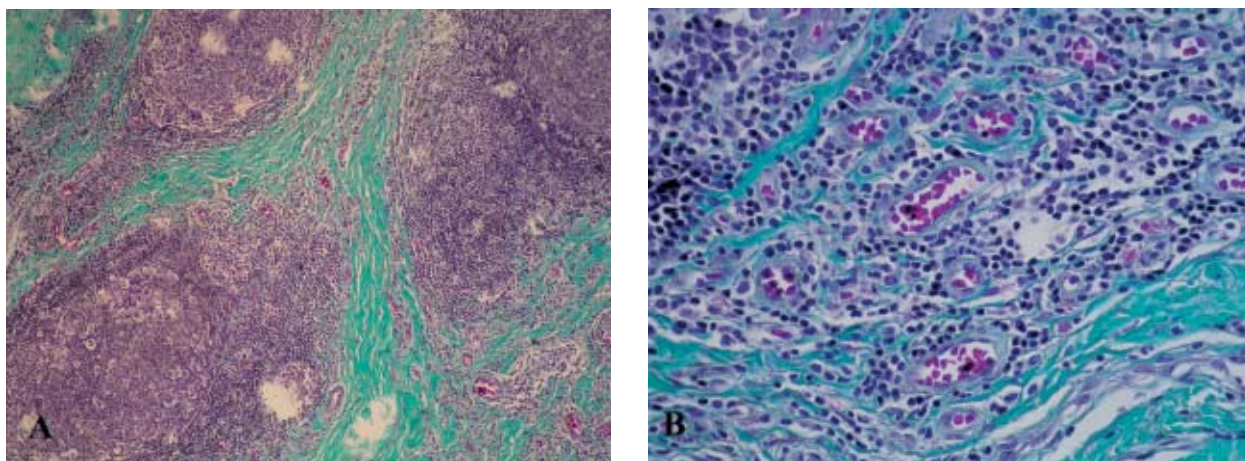


Fig. 13. Kimura's disease in a 15-year-old male: (A) lymphoid aggregates containing prominent germinal centers, follicular hyperplasia (Mallory, X100); (B) germinal centers with vascular proliferation (Mallory, X400).

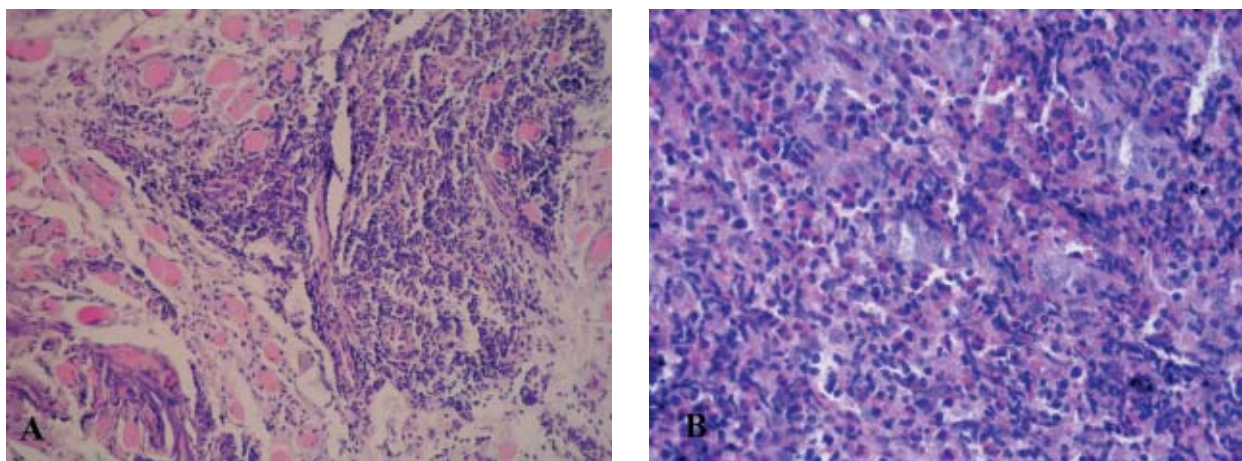


Fig. 14. Idiopathic chronic inflammation: (A) in a 52-year-old male, diffuse infiltrates of small lymphocytes, plasma cells in muscular tissue (HE, X20); (B) in a 27-year-old male, diffuse inflammatory chronic infiltrate with eosinophils (HE, X400).

The following clinical features are suggestive of pseudotumors in cases of exophthalmos: 1) later age at onset than the primary neoplasm; 2) a more acute onset than in primary neoplasm; 3) may be bilateral; 4) pain and edema of eyelids and conjunctiva in 50% of cases; and 5) regression of exophthalmos with steroid therapy¹⁶.

It is concluded that orbital tumors have a bimodal age distribution. Rhabdomyosarcoma is the most common malignant tumor in children, however, benign tumors are more common than the malignant ones. Orbital pseudotumors persist as an etiologic challenge since 1905⁴. They are a nonspecific inflammatory process of unknown etiology, and are included as part of the differential diagnosis of orbital tumors.

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Sažetak

TUMORI I PSEUDOTUMORI ORBITE

J. Talan-Hranilović i D. Tomas

Opisuju se 24 tumora i 4 pseudotumora orbite prema njihovim histološkim i imunohistokemijskim obilježjima, dobi i spolu, dijagnosticirani u biopsijskom materijalu među 624 oftalmičnih tumora u razdoblju od 1998. do 2003. godine. Najčešći orbitalni tumori bili su lipomi, meningeomi i limfomi s vršnom učestalošću u sedmom desetljeću života. Većina orbitalnih tumora dječje dobi razlikuje se od tumora koji se javljaju u odraslih. Tumori dječje dobi većinom su benigni (ciste, kapilarni hemangiomi i hamartomi) s vršnom učestalošću u prvom desetljeću života. Orbitalni tumori imaju bimodalni oblik rasporeda učestalosti. Najčešći zloćudni tumor dječje dobi je rabdomiosarkom (embrionalni tip), a u odraslih limfom. Orbitalni pseudotumori su prihvaćen izraz koji opisuje lezije orbitalnog tkiva s miješanim upalnim infiltratom s različitim stupnjem fibroze. Prikazana je histološka klasifikacija orbitalnih pseudotumora. Orbitalni pseudotumori javljaju se pretežito u starijih osoba, a rijetko u djece i mladih. To su nespecifične upale nepoznatog uzroka koje su uključene kao dio diferencijalne dijagnoze orbitalnih tumora.

Ključne riječi: *Orbitalne neoplazme – patologija; Orbitalne neoplazme – klasifikacija; Orbita – patologija; Plazma stanični granulom, orbitalna – patologija*