Malignant Tumors of the Eyeball and its Appendixes

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In pathology of tumors, there are several reasons in favour of immunology. Spontaneous regressions of malignant tumors and their metastases have been reported, as well as an increased incidence of neoplasia in immunodepression (in subjects who suffered a renal transplantation, the incidence of neoplasms is 5%, compared to 0.05% in general population). One of the main functions of the immunity system in neoplastic pathology consists of detection and purging of the new tumoral cells. The paradox of the immunology is that often the immunity system favours the tumoral development rather than inhibit it. One of the possible explanations is the absence or the very low titre of the tumoral antigens (which would "escape" the immunocompetence), contrary to experimental data. Histologically, we noticed the abundance of lymphocytes and inflammatory cells around and inside the tumor. Similar to malignant tumors of other organs and tissues within the body, the malignant tumors of the eye and its appendages must be early detected and rapidly approached. This is a well-known fact, especially since everyone agrees on the fact that antitumor therapy is generally relatively effective and the early surgical intervention is the only way to effectively resolve tumors, supplemented by chemotherapy, radiation and non-specific immunotherapy.

Keywords: orbital tumors, exophtalmos, treatment protocol, enucleation.

Malignant tumors of the eye and its appendages can be classified, considering certain particularities, as:

· *Tumors of epithelial origin* (epithelioma). Epithelioma is a superficial neoformation with a tendency to ulcerate, neighbouring destructions and superinfections with adenopathy after superinfections, rarely with metastases;

· *Tumors of connective origin* (sarcoma), neoformations with a rapidly expanding evolution, with a high metastatic potential (local, regional and general metastases). They can be made of fusiform, globus or polymorphic cells. It is remarkable that every organ forms its own type of sarcoma, depending on its own connective tissue: myosarcoma, osteosarcoma, reticulosarcoma, retinoblastoma – retinocytoma (derived from the visual cell, not having a connective origin, as initially thought). In general, the term *blastoma* is used for tumors developed from precursor cells (blast cells), therefore with a very high potential for proliferations, but also very sensitive to therapy with physical agents (radium, cobalt, and especially betatron - generated high energy electrons).

· *Pigmented tumors (malignant melanomas).* Once considered as epetheliomatous, sarcomatous or mixed type, nowadays regarded as a particular variant of sarcoma, with the stem cell formed by melanoblast, therefore an extremely malignant variant of tumors.

Malignant tumors of the appendages

Malignant tumors of the eyelids and conjunctiva

Eyelids and conjunctiva may develop all three types of malignant tumors: malignant epithelioma, sarcoma, and melanoma (fig.1).

Epithelioma of the eyelids involves the cutaneous layers; it is the most frequent malignant tumor in ophthalmology. Histopathologically speaking, it is classified as basal cell and squamous cell epithelioma.

Fig.1. Basocellular epithelioma of the upper eyelid - suture

Basal cell epithelioma clinically presents in ulcerous, papillomatous form, or as a so-called scarring plane epithelioma.

Ulcerated epithelioma presents as a profound cutaneous ulceration, hardened at the base, with a tendency to heal on one side and extend on the other side (it spreads itself like *prairie fire*).

The treatment of noninfiltrating epitheliomas which are not prone to metastases is based on the plain resection with the scalpel or the laser scalpel with CO_2 followed by the suture Epitheliomas in general, especially the small ones, are sensitive to contact radiotherapy.

A particular form of this tumor is *epithelioma terebrans,* which spreads itself in depth, rather than in surface, being able to propagate on the eyeball and the orbit. The palpebral ulceration is always covered by dirty gray tissue detrituses. Despite its evolution, the ulcerated epithelioma does not develop remote metastases; it might involve the ganglia a result of suprainfection, therefore satellite adenopathy, but it doesn't develop ganglionic metastase.

Papillomatous epithelioma presents as a small papilloma with a hardened base, sometimes pigmented; its evolution is much slower than the evolution of the ulcerated form. If treated as a plain wart and destroyed by diathermy, it relapses.

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Scarring plane epithelioma presents as a keratosis area, surrounded by a reddish halo, hardened, with a tendency to spontaneously heal and relapse.

Squamous cell epithelioma shows as a cutaneous protuberance, hard during palpation, with a tendency to spontaneously ulcerate and bleed. It evolves both on the surface and in depth. The superinfection leads to pre-auricular satellite adenopathy. Only the histopathologic examination can definitely differentiate between this form and the basal cell epithelioma.

Conjunctival epithelioma is a rare tumor, mostly located on the sclerocorneal limbus. The clinical appearance consists of papillomatous formations of 2-3 mm in diameter, with a bleeding surface, possible pigmented. At palpation, the formation feels hard. It evolves at the surface, being able to spread on the cornea and very rare, in depth. Conjunctival epithelioma can rarely develop ganglionic metastases (in pre-auricular or maxillary ganglia).

Palpebral sarcoma is a rare tumor that develops in extreme ages, especially in young or old subjects. It arises as a nodular formation of the upper eyelid, adherent to tarsus and the overlying skin, prone to ulceration. It has a high evolutionary potential, invading the bulbar conjunctiva and spreading to the eyeball and orbit, developing metastases via the blood. In the initial stage, it can be easily mistaken for chalazion, while in chalazion, the skin is free at the surface of the tumor. It differs from chalazion by the fact that the eyelid cannot be rolled on Desmarres roller.

Conjunctival sarcoma is an extreme rare tumor, located on the tarsal conjunctiva in the proximity of the cul-de-sac with the appearance of small white-yellowish formation.

Melanic tumors of the eyelid are cutaneous pigmented nevi which, in certain situations (traumas, surgical interventions, inflammation without an obvious reason) expand, become pruruginous, surround themselves by an intensely vascularised halo and exulcerate; these are symptoms of malignancy. Before ulceration, surgical exeresis of at least 0.5 cm is indicated, either with electric scalpel, or with laser scalpel with CO_2. Infiltration with local anaesthesia is not recommended, due to the possibility of dissemination of melanic cells. In case of lack of a larger substance, replacement plasty is necessary. Melanoma is radioresistant to X-Rays, but not to Cobalt or Radium; if the result of anatomic-pathological examination is abnormal, a nonspecific desensitising treatment with BCG vaccine and cytostatic is used.

Treatment principles of palpebral cutaneous malignant tumors

In mutilations after cancerous exeresis and the outer half of the lower eyelid, the upper eyelid is dualized, by suturing its tarsus in colobomatous area. Pediculated plasty from the upper eyelid, with excessive skin (fig.2).

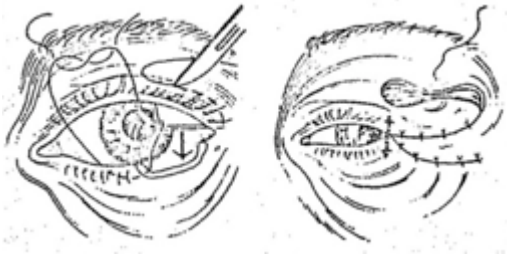

Fig.2. Surgical lower paracantal subtotal coloboma

In the exeresis of the inner half of the lower eyelid, after the external release of the eyelid, there will be a complete plasty through gliding, obturating the initial coloboma. There will be an external palpebral lack, which will be treated by tarsal-conjunctival and cutaneous plasty from the opposite eyelid (fig.3).

Fig.3. Surgical subtotal and inner coloboma of the lower eyelid

An original method when lacking the palpebral substance consists of blepharoptosis by Teflon implantation (fig.4).

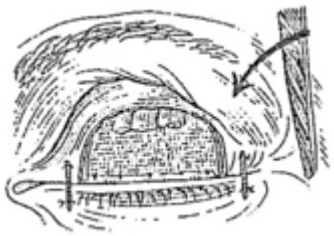

Fig.4. 2/3 palpebral lack, grasping the entire tarsus – Teflon plasty dressed in upper conjunctiva and pediculated cutaneous plasty

Other types of plasty can be performed on the lower eyelid or mixed – upper palpebral translation towards the middle and pediculated plasty on the opposite eyelid, entirely, completing the remaining upper coloboma (fig.5).

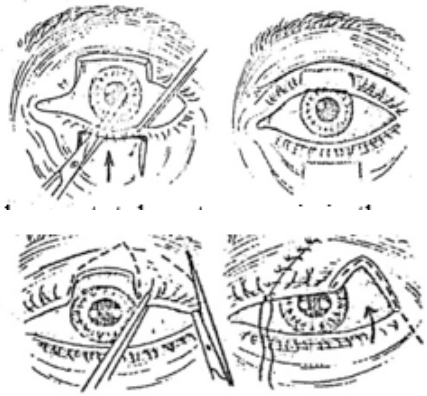

Fig.5. Revealed coloboma, total post-exeresis in the middle area of the upper eyelid – graft of the lower eyelid towards the upper

Fig.6. Total mild degree coloboma of the upper eyelid; Esser-Abbe-Mustarde method

In bilateral ablepharia, reconstructive surgery is even more urgent, since the eye with dehiscence is exposed to dryness. That is why, after a protective conjunctival movement of the eyeball, cutaneous plasty by sliding from proximity or pediculated plasty are performed (fig.7).

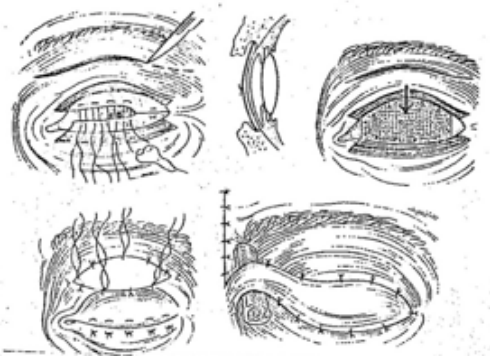

Fig.7. Reconstruction of bilateral ablepharia (blepharoptosis) – Teflon graft covered by cutaneous sliding from neighbouring area after incision clearance and free upper eyebrow autograft; with frontal pediculated flap.

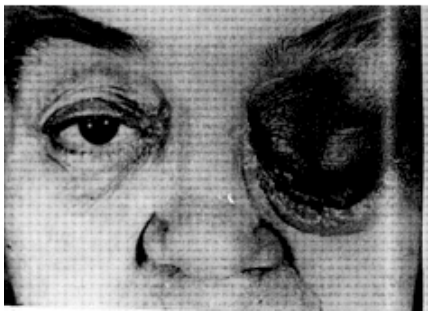

Fig.8. Malignant melanoma

Malignant melanoma of conjunctiva occurs by malignant degeneration of conjunctival pigmented nevus or of a conjunctival melanosis. Malignization of a *pigmented* nevus consists of growth, signs of acute inflammation, intensified pigmentation, and abnormal neovascularization.

The preferred localition of the melanoma of conjunctiva is on the sclerocorneal limbus or on caruncle. The tumor easily bleeds if touched. It has an extremely high evolution potential, with frequent metastases in liver and brain.

The tumors of conjunctiva and eyelids benefit from wide surgical exeresis, in healthy tissue, preferable with electric scalpel to prevent the spread of tumor cells via hematogenic path and then cutaneous grafts via sliding, pediculated or free grafts. In eyelid plasty, with integration of the inner angle, the cul-de-sac will be removed in the same session, to prevent the breaking of the suture wires by proximity suprainfection.

In case of corneal damage, besides the conjunctival pasty, lamellar corneal homograft is practised. In advanced stages with expansion to orbit of the proximity areas, one needs to cooperate with the ENT specialist, maxillofacial surgeon and the neurosurgeon. If needed, also the damaged ganglia can be removed.

After surgery, especially in melanic tumors, de-sensitization with increasingly higher doses of BCG, and immunostimulation with levasimole and even interferon are recommended.

Noli me tangere principle is applicable to all pigmented formations of the eyelids or conjunctiva, as long as they do not show signs of activity and progress; in these situations, one should monitor the lesion, intervening surgically only in obvious signs of progress.

Malignant tumors of the lacrimal glands

Even if the tumors of the lacrimal glands are quite frequent, only some of them are malignant. Clinically, the tumors of the lacrimal glands show unilateral exophtalmos, pushing the eyeball downwards and towards the inner side, and limiting the movement of the globe upwards and on the outer side. Palpation of the superexternal angle of the orbit is sensitive, painful and it shows a renitent or even hard formation. Other symptoms are diplopia and excessive unilateral production of tears. The diagnosis is complete by echography, orbital scintigraphy, and computer tomodensitometry. From an anatomopathological point of view, there are adenoid cystic carcinoma, mucoepidermoid carcinoma, infiltrative carcinoma and, rarely, lymphoreticular sarcoma. Sarcoma shows acute inflammation.

The tumors of the lacrimal gland are easier approached when they reach the palpebral area or by means of Kronlein approach, when the orbital part is involved. The treatment with cytostatics and immunostimulants is both recommended and useful, since the recurrences are quite frequent.

Tumors of the orbit

Tumors of the orbit have epithelial or conjunctival origin, with a clear development towards *sarcoma*. The presence of several tissues in the orbit – vessels, muscles, cellular tissue – create the possibility to develop several types of sarcoma: fibrosarcoma, myosarcoma, lymph sarcoma, osteosarcoma, etc.

The clinical picture of the intraorbital tumors overlaps the clinical picture of *unilateral exophtalmos*.

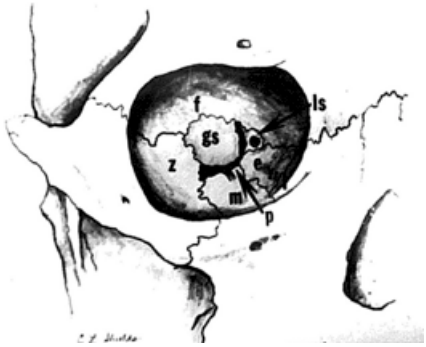

Fig.9. Structure of the orbit (f-frontal bone, gs – great wing of the sphenoid bone, ls – little wing of the sphenoid bone, p - palatine bone, m – maxillary bone, e – ethmoid bone)

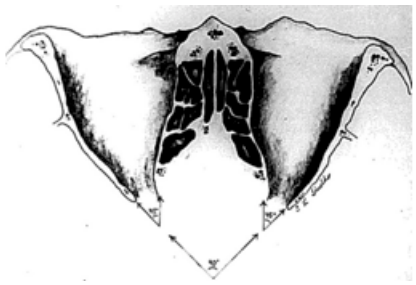

Fig.10. Cross section of the two orbits

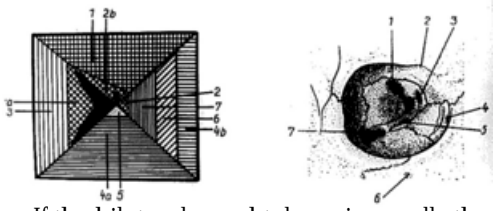

Fig.11. Topography of the orbit – Benedict division

If the bilateral exophtalmos is usually the expression of an endocrine disease – Graves' disease and rarely the expression of other diseases like lymphoma, leukemia, scurvy – diseases which are easy to diagnose and which do not raise issues to the physician, it is caused by a wide array of conditions, some of them extremely difficult to be diagnosed and which need to be treated as emergencies.

Checking a patient with unilateral exophtalmos must follow the scheme: complete anamnesis, thorough clinical, ENT, maxillo-facial, and neurological examination, simple radiography, and echography.

When there are suspicions of an orbital tumor, perform tomodensitometry or NMR, orbital arteriography, orbital phlebography, orbital scintigraphy, cutaneous thermography.

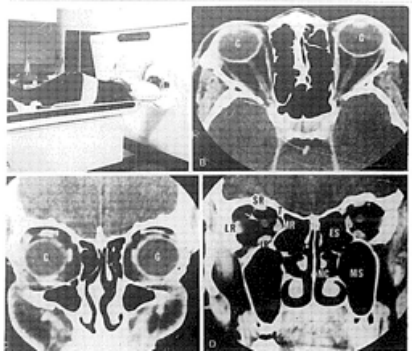

Fig.12. Orbital tomodensitometry
A - T.D.T scanner; B – image of the normal orbit – axial section; C- frontal section of the eyes; D – retrobulbar frontal section

The tumor shows tumoral exeresis with anatomo-pathological examination and by scanning electron microscopy. For malignant tumors, perform chemotherapy, radiation and immunotherapy (non-specific BCG desensitization and immunostimulation with Levasimole).

The anamnesis of the patient suffering from unilateral exophtalmos should monitor: onset circumstances; presence or absence of the pain, changes in visual acuity or visual field, presence or absence of diplopia, chronology of the symptoms, progress of the exophtalmos (progressive or remittent).

Attention should be paid to ocular-orbital or cranial traumas, inflammatory or tumoral processes of the facial sinuses, endocrine diseases (especially thyroid diseases), and neurologic conditions.

In terms of therapy, cancer of the orbit asks for neurosurgery, by means of a transfrontal flap.

The patients showing signs that lead to the suspicion of a malignant tumor should be immediately referred to a specialty service.

Malignant tumors of the eyeball

Malignant tumors of the eyeball include malignant tumors of the retina, optic nerve and uvea. Unlike other tumors, intraocular tumors have a special status, given by the particular structure of the eyeball, with its fibrous tunic, sclera, which makes the programming of the tumor difficult and late. The extraocular propagation of the intraocular tumor via lymphatic path is practically neglectable, due to little lymph tissue within the eyeball.

Intraocular tumors can propagate via hematogenic path or step by step. Situated inside the sclerotic coat, intraocular tumors spread very late, step by step.

Sclera has three areas of minimal resistance: orbital lamina, where the fibers of the optic nerve exit the eyeball; the equatorial area, where the sclera is pierced by the four vortex veins; the perilimbal area, with numerous piercing vessels that make the anastomosis between the episcleral circulation and the great irian circle.

For tumors situated in the neighbourhood of these places of minimal resistance, the expansion risk is much higher than for the ones located further.

As long as the macular area is not involved and the patient is not alarmed by a poor vision, early detection of the intraocular tumors is extremely difficult.

Early detection of the extramacular tumor is completely random, usually it happens only late, even when complications arise.

Malignancy of intraocular tumors (retinal, uveal, made of very young cells, with an extremely high power of proliferation) has a special status.

Malignant tumors of the retina

Retinoblastoma

Next to the uveal malignant melanoma, retinoblastoma is the most frequent intraocular tumor of childhood. Heredity plays an important part in the onset of retinoblastoma; most of the cases are or appear unilateral and erratic.

The tumor arises in children with normal eyeballs, more frequent in posterior pole. The typical pattern consists of multiple burning points of variable sizes, sometimes a larger tumor surrounded by several smaller ones, probably independent, in most of the cases.

It is believed that the disease is the result of the loss or mutation of RB1 gene, a suppressor oncogene located in chromosome 13q14. Genetics of retinoblastoma also influences the therapy ways.

When the tumor is larger, the clinical picture differs, depending on the development type, leading to several clinical forms: endophytic, exophytic, diffuse infiltrative, and combined forms.

Retinoblastoma has a heritable (40% cases) and a non-heritable form (60%). Heritable cases imply mutations of the germinal line, while the non-heritable ones imply somatic mutations.

Histologically, there are two types of retinoblastoma, undifferentiated with cells with reduced cytoplasm and hyperchromatic nuclei, and differentiated, with large cells, with Flexner-Wintersteiner rosettes.

The indications of the clinical diagnosis of retino-blastoma are: leukocoria (white pupillary reflex), amaurotic cat's eye, strabismus, secondary glaucoma, changes of the pupil or iris, hypopyon or hypema, and mydriasis.

Early diagnosis is crucial for an effective treatment, that could preserve the vision as much as possible.

Pre-therapy studies in retinoblastoma should describe the extension of intraocular tumor, the presence or absence of orbital extension, as well as the presence or absence of metastatic disease.

The treatment is complex, depending on several factors. It must be combined with the family's genetic counsellor, as well as with early detection of new cases in families at risk; it depends on the site, size and number of tumors, laterality, histological form, association with other eye conditions, age and heath of the child and her compliance to treatment or the parents' understanding of the treatment.

There are conservative treatment methods: external radiotherapy, scleral plaque radiotherapy, laser photocoagulation, thermotherapy, transscleral cryo-coagulation, local chemotherapy, systemic chemotherapy, and genic therapy.

Enucleation is a radical treatment method used for patients with extensive retinoblastoma.

Malignant tumors of the uvea

Involving the iris, ciliary body or choroid, malignant uveal melanoma is the most frequent tumor; its preferred location is the choroid, then the ciliary body and rarely, the iris.

Malignant iris melanoma is an emergency, since the surgical intervention – sectorial iridectomy – performed in time leads to the preservation of the eyeball and the patient's survival, a favourable chance.

Malignant choroidal melanoma or choroidal mean-sarcoma is the most frequent and severe tumor of the eye.

Angiography allows the differentiation of the melanoma from the choroidal pigmented nevus, but it can hardly differentiate it from the appearance of the hemangioma.

Enucleation seems to be the best solution when intraocular tumors are believed to be malignant.

Although choroidal metastases are rare, there are certain forms of cancer, especially liver and breast carcinoma, as well as uterine, and pulmonary cancer, which lead quite frequently to choroidal metastases; they can be bilateral or, more frequent, unilateral; but if the patients survive, the cases with unilateral metastases usually develop neoplastic buds also in the second eye.

Choroidal metastases are unique or multiple tumors, preferably located in the posterior pole, in the proximity of the optic nerve papilla or at the inferonasal periphery of the fundus. They are round or oval, with margins that are difficult to define, and are little pigmented.

Their angifluorographic picture resembles the one or primary melanoma. Almost always there is a certain element, difficult to define, that differentiates a primitive

choroidal tumor from a choroidal metastase; alternating the hyperfluoroscence phenomenon with hypo-fluorescence reveals the kaleidoscope of choroidal metastases. Investigations on the general health of the body might guide the diagnosis towards a primitive tumor of another organ with metastases in the eye.

Unlike the approach of a choroidal melanoma, in metastatic tumors, enucleation is not indicated; perform treatment with cytostatics, immunostimulants, eventually physiotherapy, but the results are not encouraging due to the reserved chances.

Conclusions

The main goal of the treatment of a tumor, regardless of location or sometimes evolution, is to remove, as much as possible, the entire tumor mass. To reach this goal, advanced tumors need more complex and numerous interventions.

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