

MALIGNANT CHOROIDAL MELANOMA IN T4 ORBITAL STAGE; PROSTHESIS OF THE ORBIT

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SUMMARY

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Aim: Diagnosis and treatment of tumors of the eye is extremely difficult; surgical treatment in advanced stages, when the tumor grows in the orbit, leads to extensive radical surgery of the face. The extent and nature of surgical procedures depends on the nature of the tumor process, in advanced stages is indicated mutilating surgery – exenteration of the orbit. Exenteration of the orbit due to the extrascleral extension of malignant melanoma of the uvea is very rare, unfortunately, even today in certain cases it is necessary to make such a mutilating surgery.

Materials and Methods: Case report – 65 year old female patient, sent to our Department in 2008 with the finding of the pigment deposits on the posterior pole of the left eye. Ultrasound study found elevations of up to 3 mm, she was asked to come for further control in three months interval. She did not come, furthermore she sporadically attended another eye clinic. In 2011 she was treated for secondary glaucoma – cyclocryopexia. Due to pain another surgery – tarzorrhaphia was indicated.

In 2012 she underwent surgery at St. Elisabeth Cancer Institute in Bratislava – Nephrectomy transperitoneally l. dx., excision hepatis. Histological examination in addition to the primary papillary renal carcinoma – mucinous tubular T1 Nx Mx type, found the metastasis of malignant melanoma to the liver and right kidney.

She underwent the diagnostic procedure to find the origin of the melanoma.

The patient was subsequently admitted to our clinic with blind painful eye for enucleation. During the surgery the tumor was found retrobulbar tumor ingrowth. Histopathological findings confirmed malignant melanoma. Indicated was exenteration of the orbit due to malignant melanoma T4 N0 M2 stage in June 2012. After healing of the cavity she was recommended to design an individual prosthesis.

After completing several courses of palliative chemotherapy during a recent review in January 2015 the patient is without recurrence of the melanoma in the orbit

Results: Histological examination confirmed malignant melanoma in stage G2, predominantly epithelioid type, spindle cell type in part B of pips, tumor fills the entire back and part of the anterior chamber, grows through the sclera and optic nerve is completely overgrown by tumor mass and spreads into orbit. The immunophenotype is suggesting a better prognosis (S100 +, melanoma +, + HMB45, cyclin D1 3%, 10% of p53, Ki67 3%). Tissue eyelashes were infiltrated by numerous micrometastases.

The patient after exenteration of the orbit after 3 months got an individual epithesis. Local orbit cavity is more than 24 months after exenteration without recurrence of melanoma. The patient is still undergoing outpatient chemotherapy and feels good.

Conclusion: The treatment of malignant tumors of the orbit and the eye is difficult, in most cases surgical treatment is indicated, with the additional radiation therapy and chemotherapy. Malignant tumors at an advanced stage should be solved radically. Exenteration of the orbit leads to produce a large defect in the orbit and this part of the face. Patients in the active age after surgery followed by facial defects after such procedures have disadvantage in work and this defect leads to serious socio-economic challenges. Patients with individually made prosthesis comprising a refund of the eyeball and the surrounding soft tissues allow active life and full application of the private as well as professional life.

Key words: malignant choroidal melanoma, exenteration of the orbit, prosthesis of the orbit

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INTRODUCTION

Tumours of the orbit, extraocular and intraocular tumours form a broad area of ophthalmology. The diagnosis and treatment of tumours in the ocular region is extremely demanding and complex. Clinical symptoms are also present according to the character of the tumour and its localisation. Of diagnostic procedures, ultrasound examination is significant, and computer tomography and magnetic reso-

nance imaging play an irreplaceable role. Serious socio-economic problems ensue for patients following surgical procedures and general therapy. Surgical treatment in advanced stages, when the tumour grows into the surrounding area, leads to extensive radical operations in the facial area. The extent and character of surgical procedures depends on the character of the tumour process, in advanced stages mutilating procedures are frequently indicated – exenteration of the orbit (3, 5, 11, 12).

Treatment of malignant melanoma of the uvea (MMU) in principle requires a causal approach in an endeavour to completely remove the tumour as a whole, and also procedures in order to prevent fatal connections (or consequences) of the development of metastases in the surrounding structures – in the orbit and in the whole organism. In connection therewith, it is necessary to emphasise that more effective results are being achieved with the introduction of new technological possibilities in therapy (light and laser coagulation, local therapy by ionising radiation, photon and proton radiation therapy, microsurgical methods of excision of MMU etc.). However, neither timely removal nor the complete destruction of the tumour (with “clinically healed” MMU) provide a guarantee that metastases will not appear (4, 14).

At the beginning of the 1960s, a finding of development of primary MMU in the eye almost exclusively meant enucleation, motivated by the fact that:

1. increased mortality was expected following a deferral of enucleation;
2. there was not a sufficient level of knowledge concerning the character of growth of fuso-cellular sarcoma tumours (especially fuso-cellular sarcoma type A tumours do not have a tendency to metastasise);
3. there was not sufficient knowledge about the effectiveness of “conservative” therapy by ionising radiation (and the degree of risk of postradiation complications), chemotherapy, methods of photocoagulation, laser coagulation, microsurgical approaches and combined procedures.

In the last quarter of the 20th century, the approach to the treatment of MMU changed fundamentally. Nevertheless, to this day situations still arise where it is necessary to enucleate the afflicted eyeball at the time of diagnosis due to the volume of the MMU in connection with the imprecision or incompleteness of diagnostic procedures. Even today, we encounter the incidence of MMU in stage T4, when a mutilating surgical procedure is indicated (6, 7, 8).

CASE REPORT

A 65 year old patient was sent to our clinic in 2008 with a finding of a pigment deposit on the posterior pole of the left eye. An ultrasound examination determined an elevation of up to 3 mm, and the patient failed to report for a follow-up examination 3 months later. She also sporadically visited another outpatient eye clinic. 3 years later, from 2011, she was treated for secondary glaucoma – cyclocryopexia, tarzorphia of the eyelids. In 2012 she was operated on at the St. Elizabeth Oncological Institute in Bratislava – Nefrectomia transperitonealis l. dx. exciso hepatis. A histological examination, in addition to determining primary papillary renal carcinoma – mucinous tubular T1 Nx Mx type, determined metastasis of malignant melanoma into the liver and right kidney. An investigation was conducted into the origin of the melanoma.

The patient was subsequently admitted to our clinic due to the histological finding in the orbital region. Enucleation was indicated, retrobulbar outgrowth of the tumour was determined perioperatively (fig. 1-3). After verification of

malignant melanoma, the patient agreed to the indicated exenteration of the orbit in malignant melanoma stage T4 NO M2 (fig. 4-7).

The histological examination confirmed malignant melanoma in stage G2, predominantly of epitheloid type, in part fuso-cellular sarcoma type B with nucleii, the tumour fills the entire posterior and part of the anterior chamber, grows through the sclera, and the optic nerve is completely overgrown by tumour masses and spreads into the orbit. The immunophenotype attests to a better prognosis (S100 +, melanoma +, + HMB45, cyclin D1 3%, 10% of p53, Ki67 3%). The tissue of the eyelids is infiltrated by numerous micro-metastases.

The histological examination of the originally determined metastasis of the liver before confirmation of the finding in the eyeball and orbit correlated with the finding of malignant melanoma in the orbit.

After healing of the orbital cavity (fig. 8-11) the patient was fitted with an individual prosthesis (fig. 12-17).

After exenteration the local orbital cavity is without recurrence (fig. 18), the patient is continuing to undergo outpatient chemotherapy, and has completed several cycles of palliative chemotherapy for metastases of malignant melanoma in the liver and right kidney, progression of pulmonary metastases has been determined (chemotherapy Paclitaxel, Carbocisplatin 5AUC).

At the last follow-up examination in January 2015, the patient is without recurrence in the region of the orbit (fig. 19).

Technique of producing prosthesis in orbital region

At present in Slovakia, we use a complete program by the BREDENT company for the production of facial prostheses, from the imprinted silicone material to the final colouring and fixation of colours. In the initial phase we make a precise double imprint of the afflicted area (or the area we shall replace, eye, ear, nose or cheeks). We make a plaster cast of this imprint (hardness 3), by which we obtain a realistic model on which we can model the replacement part of the face from wax.

If this concerns an eye prosthesis, we insert a produced acrylate eye of identical colour precisely into the wax model. In this phase the modelled wax prosthesis is tested directly on the patient, and individual details are perfected (wrinkles, porosity of skin, directness of gaze, opening of eye etc.). After perfecting, plaster is poured onto the wax model, and after hardening the wax is washed out and the cavity is filled with silicone material in a colour mixture according to the colour of the patient’s skin, precisely in layers so as to ensure that the resulting effect is as realistic as possible in comparison with the healthy part of the patient. Subsequently after pressing and under pressure, the silicone hardens after 2 hours at a temperature of 70°C. The silicone prosthesis is subsequently given finishing treatment, and details of the skin are coloured in. In the case of a prosthetic eye, after final colouring, special eyelids and eyebrows made of natural human hair are sewn on.

In the final phase, the affixing of the prosthesis is resolved. At present we use three methods of affixing. The first option is adhesion to the skin using a special glue. The se-



Fig. 1 Macro-photo of enucleated eyeball after enucleation



Fig. 2 Cross-section of enucleated eyeball – retrobulbar outgrowth

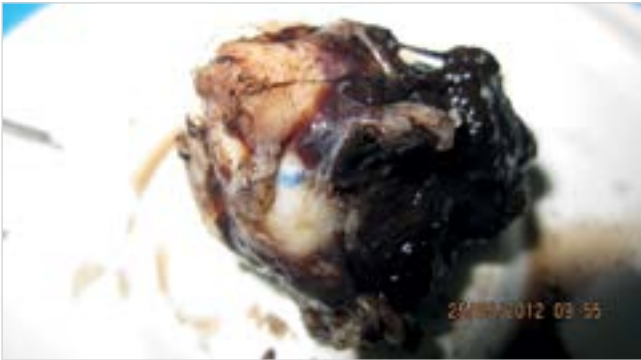


Fig. 3 View of posterior part of eyeball with retrobulbar outgrowth of melanoma

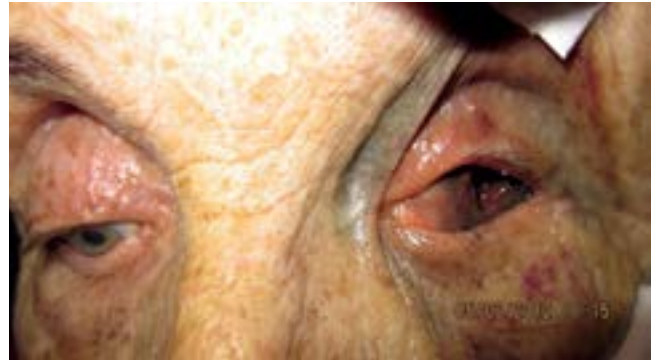


Fig. 4 Clinical picture of patient after enucleation with masses of melanoma in apex of orbit and infiltration of soft tissues with micrometastases



Fig. 5 Detail of conjunctival sac and eyelids with micrometastases and infiltration of tissues in orbit



Fig. 6 Perioperative finding during exenteration of orbit (6/2012)

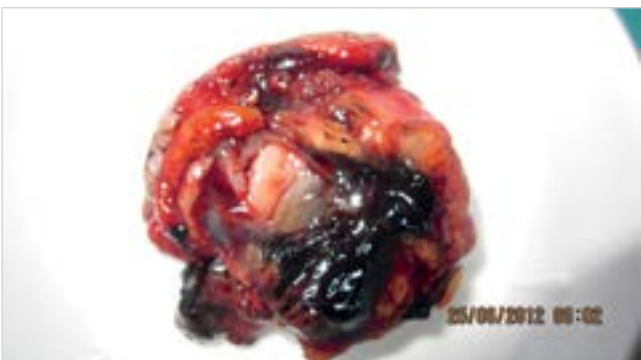


Fig. 7 Macro-photo of tissues after exenteration

cond, most frequently used option, upon which everyday adhesion of the prosthesis is no longer necessary, is fixation of the prosthesis to the frame of the eye glasses, and the patient puts the prosthesis itself in place when donning the glasses. The third, most comfortable option, is affixing the prosthesis with magnetic implants. However, this option is conditional upon the primary operation, in which titanium screws with a magnetic head are applied into the bone; in the case of malignant tumours of the orbit we cannot use this option, because in future the patient would be restricted by obstacles upon imaging examinations in the region of the head and orbit (e.g. in the case of the necessity of determining potential outgrowth of the process into the region of

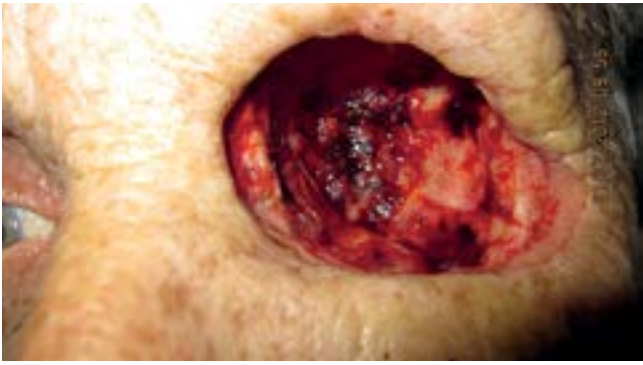


Fig. 8 Orbital cavity 1 months after exenteration (7/2012)



Fig. 9 Orbital cavity with progressing granulation

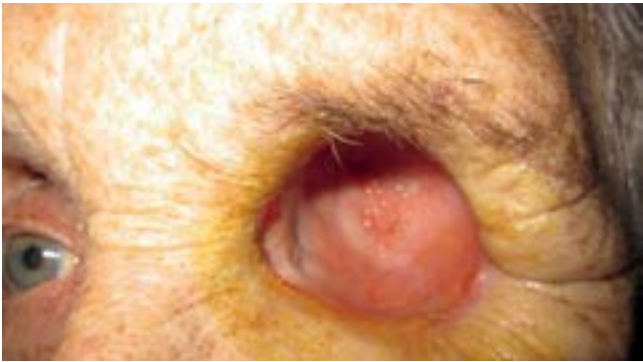


Fig. 10 Healing without complications more than one month after exenteration of the orbit

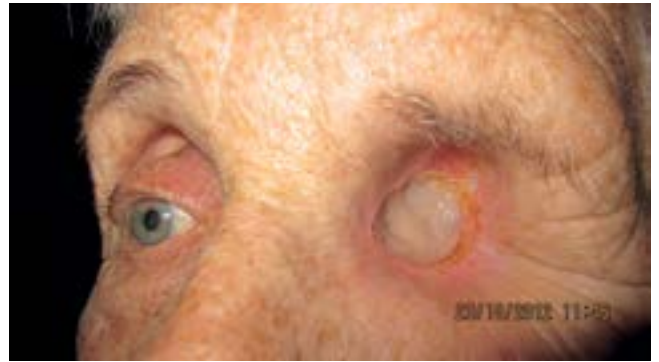


Fig. 11 Cavity without recurrence six months after exenteration of the orbit (10/2012)



Fig. 12 Individually produced prosthesis of left orbit of patient



Fig. 13 Patient with fitted left orbit prosthesis



Fig. 14 Detail of face with fitted left orbit prosthesis



Fig. 15 Detail of orbital region upon downward gaze of eye in patient with fitted left prosthesis



Fig. 16 Photograph of patient after fitting of prosthesis and glasses



Fig. 17 Photograph of patient after fitting of prosthesis and sunglasses

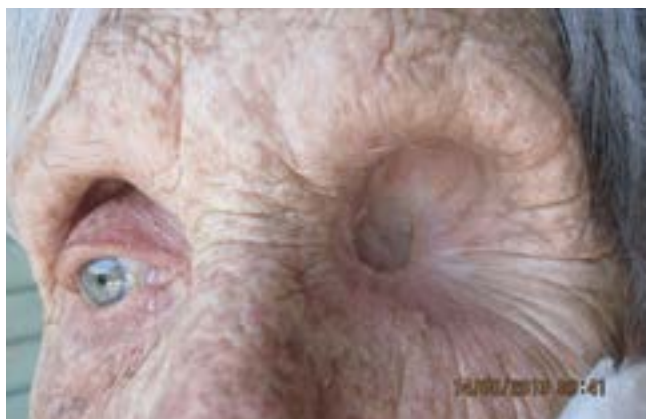


Fig. 18 Detail of orbit 1 year after exenteration (5/2013), without recurrence of malignant melanoma



Fig. 19 Detail of orbit at last follow-up examination (1/2015); patient is more than 2.5 years after exenteration, without recurrence of malignant melanoma in the orbital region following exenteration of the orbit, cavity without recurrence (10/2012)

the paranasal cavities, in the case of determining metastases in the brain using CT or MRI examination).

DISCUSSION

The incidence of malignant melanoma of the uveal tract of the eye always means serious problems for both the patient and the doctor. With regard to the fact that MMU frequently develops unobserved (in a “deaf” zone or without symptoms of pain), mortality at the interval of 10 years after treatment for metastases of MMU is around 50-60% (15,16).

The clinical stage of development of malignant melanoma in the uveal tract of the eye in which the patient sought professional medical attention is linked to the localisation of development of the neoplasm in the uvea. The further the MMU is from the posterior pole, the lower the probability that the patient will have subjective complaints. In this, the matter of the clinical stage of development of the MMU in which the patient sought medical attention is of considerable significance after determination of the diagnosis, not only for the selection of therapeutic procedure, but especially for determination of the prognosis. At present, the applied diagnostic procedures enable determination of the correct diagnosis to almost 95% (15).

A fundamental change took place in the last quarter of the 20th century in the approach to the treatment of MMU

with regard to attitudes towards the use of ionising radiation (14). In the literature we see various stances regarding the problem of applying ionising radiation after enucleation of the eyeball. Some authors emphasise that preoperative local irradiation (for example in the application of two doses of 400 rad) devitalises approximately 90% of malignant cells and is a significant preventive measure against the possibility of chance iatrogenic dissemination of MMU cells (17, 18).

Upon localisation of MMU in the choroid, in the past enucleation was considered the only successful and possible therapy. It was also indicated in cases of eyes with still usable central visual acuity. Even despite early treatment, 75% of patients died from metastases within the course of 5 years (13). Modern microsurgical operations can remove the neoplasm by resection following opening of the fibrous enveloping of the eye. Regular checks of the patient, observation of suspicious pigment lesions and good photo documentation are the most important measures. When there is no longer any doubt concerning progressive growth of the tumour, a microsurgical operation is favoured. The process may often be hidden, and a previous injury or frequent inflammations of the eye may be in correlation with the incidence also of a malignant uveal melanoma (9, 20).

Mortality is linked to the fourth clinical stage of MMU – the stage of remote metastases. Metastases of tumours are an under-researched area of oncology (1). Although the ma-

majority of cases of metastases of MMU appear within the first 5 years after the end of treatment, they can appear at any stage of the disease. The incidence of metastases is most frequently connected with MMU localised in the choroidea, as demonstrated by Reese in the 1950s. There is an increased danger of metastasis of MMU following injuries to the eye, after diagnostic punctures, and also following subconjunctival injections (19). The scattering of tumour cells into the orbit is possible also after previous therapy with ionising radiation (10).

The prognosis of MMU is evidently linked to the type of cells in the tumour. On the basis of an analysis of a cohort of 3 852 cases of melanomas with large dimensions, which caused serious damage to the eye (retinal detachment, inflammation reaction, haemorrhage into the vitreous and secondary glaucoma connected with pain and loss of sight), the American authors McLean et al. expressed the opinion that the prognosis of MMU is dependent to a substantial degree on the size of the tumour (13). These symptoms make diagnosis easier. However, small tumours may be the cause of serious diagnostic problems, and as a result a waiting tactic is recommended until the tumour unequivocally increases in size (13). From an evaluation of 270 small melanomas (volume smaller than 1.4 cm³) they summarised 16 risk factors. Of these they consider 7 to be serious: type of cells, pigmentation, size (largest dimension), affliction of the sclera, mitotic activity, location of frontal boundary of tumour and affliction of the optic nerve. They determined the 4 most important of these by linear discrimination function: type of cells, size (largest dimension), affliction of the sclera and mitotic activity. They recognise the 4 highest risk factors analogously. The prognosis of MMU is relatively good if the diameter is less than 11 mm, and deteriorates when it exceeds 10 mm (16). Davidorf points to the controversial opinion that the incidence of metastases is rather the result of enucleation than a growth of a primary tumour (2). He emphasises that the fundamental oncological principle that the removal or destruction of a tumour reduces the possibility of the incidence of metastases and exit is thus not sufficiently appreciated. In particular, he points to the fact that biologically all melanomas have equal potential for the formation of metastases, and that the dimension of a tumour may be the most significant factor for prognosis. However, in his opinion small MMUs (up to 300 mm³) have a better prognosis, which is analogously comparable with a large melanoma on the skin. As against this, in the case of large MMUs he states a higher mortality rate than for analogously large melanomas of the skin.

From the perspective of prognosis, in particular the relationship between the diameter of the tumour and its lethality is emphasised (18, 21). In the case of an MMU localised in the iris, the hypothesis applies that the patient has a better prognosis upon timely determination of the tumour (14). Clinical cases repeatedly confirm the opinion that it is necessary to enucleate eyeballs without light sensitivity and with the presence of "pseudoglioma" with symptoms of inflammation reaction leading to further complications, subjective and objective complaints, and to submit them to a histological examination for the potential presence of malignant melanoma (4, 9).

It is necessary to resolve malignant melanomas in stage T4 radically, in which a large, mutilating defect in the region of the orbit shall ensue. After stabilisation of the patient's overall condition and healing of the defect a prosthesis is individually produced for, containing a replacement eyeball and the surrounding soft tissues, enabling patients to enjoy an active life and full application in both their private and professional life. In the final phase the affixing of the prosthesis is resolved. At present we use three methods of affixing. The first is everyday adhesion to the skin using a special glue. This option may be suitable for patients who are not interested in using eye glasses to affix the prosthesis. Whilst this first option may suit patients following exenteration, it may be unsuitable due to the content of substances in the glue in question. This could also cause acute contact or chronic dermatitis, not only due to the effect of the glue used upon everyday application, but also due to the influence of the prosthesis itself. Acute contact dermatitis is an inflammation reaction of the skin, which occurs after only single exposure to the harmful factors from the external environment, namely the effect of the glue or the prosthesis itself. Clinical manifestations may include increased temperature, pruritus, feeling of stinging to pain. However, these local symptoms are not necessary for patients following a serious surgical procedure, and the patient may test the glue beforehand on a small area of skin. Another form of use is a prosthesis affixed to the frame of eye glasses, which the patient affixes both together. Both options are practical for the patient, and provide the option of deciding which is more comfortable and suitable.

Patients with a prosthesis are in most cases at a disadvantage upon their incorporation into the process of employment. This leads to frequent fears of random loosening or detachment, or falling of glasses with the prosthesis at work or during regular activities. Over the course of time, patients may engage less in social activities, becoming increasingly isolated, and in a small number of cases this may lead to psychological problems. For precisely this reason we must ensure communication with patients, explain to them the nature and correct use of the prosthesis, that we have sufficient time to respond to patients' questions and in general ensure a positive psychological influence on patients. The third option is limited to patients who did not have a malignant tumour diagnosed before surgery. In this option titanium screws with a magnetic head are applied directly into the bone during the operation. The prosthesis can subsequently be anchored without the use of glue or eye glasses. For patients in whom the finding requires repeated MRI examination after exenteration of the orbit (paranasal cavities and surrounding structures), this form is limited with regard to the ensuing obstacles upon examination.

CONCLUSION

The treatment of malignant tumours in the region of the orbit and eye is demanding, in many cases surgical treatment is indicated with additional radiotherapy and chemotherapy. Malignant tumours in an advanced stage must be resolved radically

– surgically, in which a large defect ensues in the region of the orbit and this part of the face. Patients of active age following operations resulting in a facial defect are at a disadvantage upon inclusion in the process of employment, which leads to serious socio-economic problems. Following stabilisation of the overall condition and healing of the defect, patients are

provided with an individually produced prosthesis containing a replacement eyeball and the surrounding soft tissues, enabling them to lead an active life and full application in both their private and working life.

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