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DIAGNOSTIC AND THERAPEUTIC MODALITIES IN THE MANAGEMENT OF A PATIENT WITH OCULAR SURFACE SQUAMOUS NEOPLASIA (OSSN)-CASE REPORT AND REVIEW

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Abstract

Ocular surface squamous neoplasia (OSSN) is a clinical term that includes epithelial dysplasia of various degrees, carcinoma *in situ* to invasive squamous cell carcinoma of the conjunctiva. Several procedures are used today to diagnose these lesions: biopsy with pathohistological analysis, cytology, *in vivo* confocal microscopy, ultrasound biomicroscopy, AS-OCT (Optical Coherence Tomography of the Anterior Segment) and OCT-A (Optical Coherence Tomography-Angiography).

Aim: To present the possible diagnostic and therapeutic modalities that are used today in dealing with OSSN, as well as to optimize the management of these lesions in everyday clinical practice, in order for the patient to receive appropriate treatment.

Case report, methods and results: In this paper we present the case of a 71-year-old patient, presented for an ophthalmological examination last year at the Clinic for Eye Diseases in Skopje. The patient reported a foreign body sensation and irritation of the right eye due to a tumor formation in the temporal limb that was gradually increasing over the past two years. Biomicroscopic examination and AS-OCT established a clinical diagnosis of OSSN. The lesion was excised and sent to the Institute of Pathology in Skopje, pathohistologically confirmed for *in situ* carcinoma of the conjunctiva.

Conclusion: AS-OCT, surgical excision, and pathohistological examination are the "optimal triad" in the management of these lesions.

Keywords: ocular surface squamous neoplasia, OSSN, carcinoma *in situ*, pathohistology, Optical Coherence Tomography of the Anterior Segment.

Introduction

Ocular surface squamous neoplasia (OSSN) is a clinical term that encompasses several entities of tumor pathology of the corneal and conjunctival squamous epithelium. It is a spectrum of diseases under the same pathophysiological mechanism, ranging from mild dysplasia to invasive squamous cell carcinoma of the conjunctiva. OSSN as a term in science was introduced by Lee and Hirst in 1995, analogous to changes in the cervical epithelium [1].

The lesion is usually unilateral but cases of bilateral involvement have also been reported.

According to several studies, OSSN is the most common non-pigmented tumor on the surface of the eye in a large number of patients [2].

It is mostly found in males, while in Africa there is no gender predisposition. The mean age of onset is 56 years, and in parts of Asia and Africa it is found in younger people and is more aggressive [1,3].

The incidence of the disease varies in different regions of the world. There are 19 cases per million in Australia, 12 cases per million in Uganda, and 0.3-8.4 cases per million in the United States [4,5].

The etiology of OSSN is multifactorial, with a number of endogenous and exogenous factors involved in the pathogenesis of the disease.

UV-B exposure in several studies has been correlated with the occurrence of OSSN. Evidence of this is that these lesions are much more common in equatorial states and are more common in those parts of the conjunctiva, nasal and temporal, that are exposed to UV light [3,4].

The second significant risk factor is HIV immunodeficiency and seropositivity. Analyses have shown that OSSN can be used as a marker in diagnosing HIV in people under 50 years of age. The incidence of OSSN is much higher in HIV-infected people in Africa than in the general population [6,7,8].

The role of HPV in the development of OSSN lesions is still controversial; some papers have found a positive correlation but others have not [7,9]. Other possible risk factors for developing OSSN are: cigarette smoking, vitamin A deficiency (xerophthalmia), light skin color, exposure to petroleum products, as well as autoimmune diseases, xeroderma pigmentosum, atopic diseases, etc. [3,10,11].

The pathophysiological mechanism is probably triggered by UV radiation, leading to damage to basal cells and their DNA, resulting in the formation of pyrimidine dimers. These dimers affect p53 (tumor-suppressor gene), but UV with HPV is also thought to be responsible for a direct mutation in this gene. Thus, UV, immunosuppression and HPV are triggers for neoplastic growth. Another mechanism for the development of OSSN, according to some studies, is the mutation in the promoter in the gene for telomerase reverse transcription (TERT) [12,13].

These lesions are clinically presented as leukoplakia (nodular or diffuse), gelatinous or papillary tumors with a fleshy consistency and size of a few millimeters to a centimeter and more [15].

Neoplastic growths originate from limbic stem cells. Larger lesions also contain conjunctival blood vessels for their vascularization [12,14].

Most often, the superficial cells of the lesion are with a lost mucin coating and they are stained with Rose Bengal dye, which is used for their initial diagnosis. Other stains are also used in practice: Methylene blue, Toluidine blue, and lissamine green, but none of them is strictly specific for these lesions, because other conjunctival changes, such as pterygium and pinguecula, are stained in the same way [16,17]. Therefore, in practice OSSN can hardly be clinically differentiated from other pathologies on the surface of the eye, such as: pterygium, pinguecula, pannus, actinic keratosis, xerophthalmia, amelanotic melanoma, conjunctival cyst, etc. [14,15].

Case report

A 71-year-old patient presented to the PHI University Clinic for Eye Diseases in Skopje with data on irritation and foreign body sensation in the right eye as well as a superficial formation that gradually increased in the past two years. Anamnestically, the patient said he was a farmer, frequently exposed to the sun throughout his life, as well as smoking a few cigarettes a day.

Past illnesses and comorbidities include hypertension and benign prostatic hyperplasia, regularly monitored with tablet therapy. Two years ago, the patient had been diagnosed with squamous cell carcinoma of the lower lip and had been treated surgically without additional radiotherapy or chemotherapy. In 2017 and 2019, he underwent phacoemulsification of cataracts of the right and left eye, respectively, without noting the existence of the above-described formation.

The best-corrected visual acuity (BCVA) in the right eye was 0.9 and in the left 0.3 according to the Snellen Optotype. Posterior capsular opacifications were seen on the dilated pupil of the left eye, explaining the decrease in visual acuity in that eye. Tonometry values were within normal limits on both sides.

Biomicroscopic examination of the patient, in the temporal limb (between 7 and 9 h) of the right eye, showed an exophytic, wrinkled 1 cm x 0.8 cm formation, which covered the surrounding conjunctiva, limbus, and spread to the cornea.

The lesion was positive for staining with Rose Bengal (Figure 1). In the surrounding subconjunctival tissue, two tortoiseshell blood vessels extended to the lesion, vascularizing it. IOL was in the posterior chamber and fundoscopic finding was without any changes.

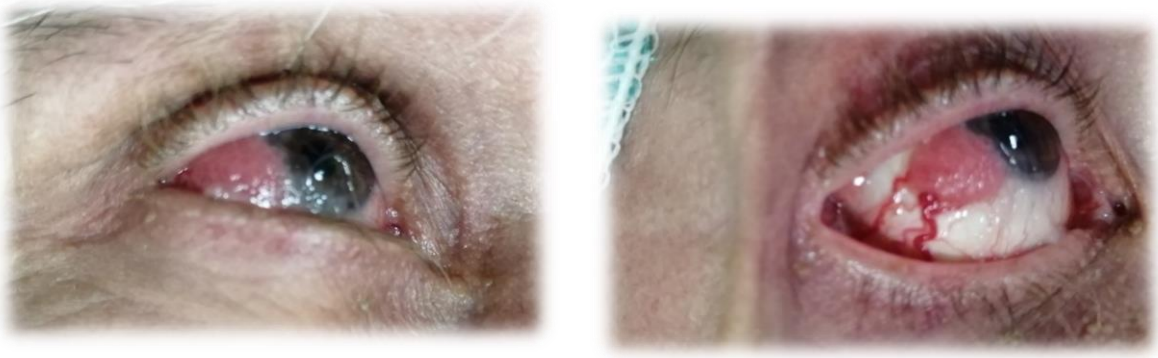
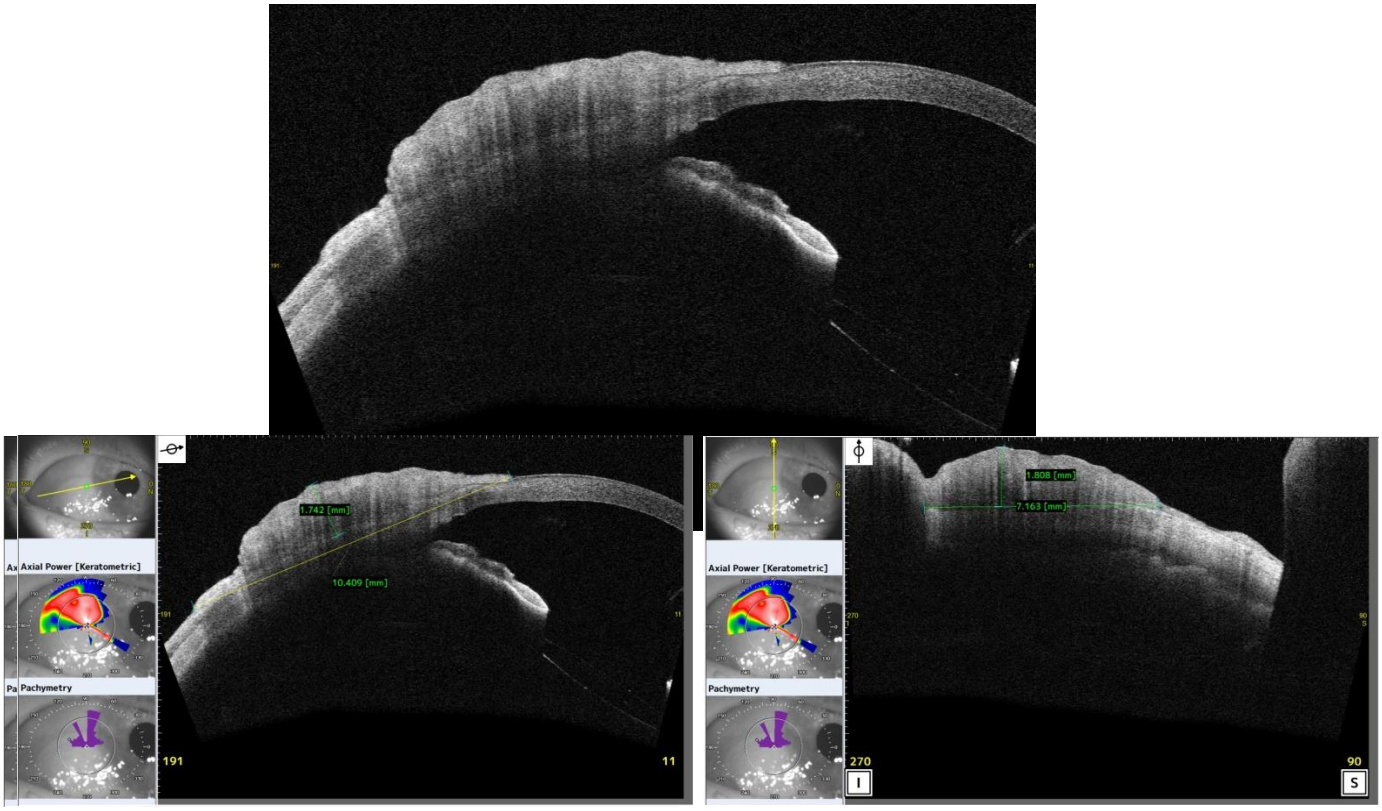


Figure 1. Tumor formation with superficial folds (Rose Bengal positive) in the temporal region of the limbus of the right eye. The picture on the right shows two blood vessels that vascularize the lesion.

AS-OCT with (Casia2: OCT - TOMEY) was performed for further evaluation, which showed a strong thickened lesion with hyperreflective characteristics. Tumor formation from the surrounding healthy corneal epithelium was delineated with a clear transition. Clear demarcation was also followed with the underlying tissues (Figure 2). According to the biomicroscopic findings and AS-OCT, a clinical diagnosis of ocular surface squamous neoplasia (OSSN) was made and surgery was indicated.



Fugure 2. AS-OCT finding. Exophytic lesion with hyperreflective features,dimensions of the lower images. It is separated from the surrounding corneal epithelium by a clear transition (white arrow).Welldrawn border between the lesion and the underlying tissues(blue arrows).

Intraoperative ligation of the two blood vessels that vascularized the tumor was performed under local anesthesia. It was removed 3 mm into healthy surrounding tissue and sent for pathohistological evaluation to the Institute of Pathology in Skopje. The excision edges were sutured with absorbable materials (Figure 3). The patient was postoperatively treated with topical antibiotic therapy and Vitamin A locally and systemically.

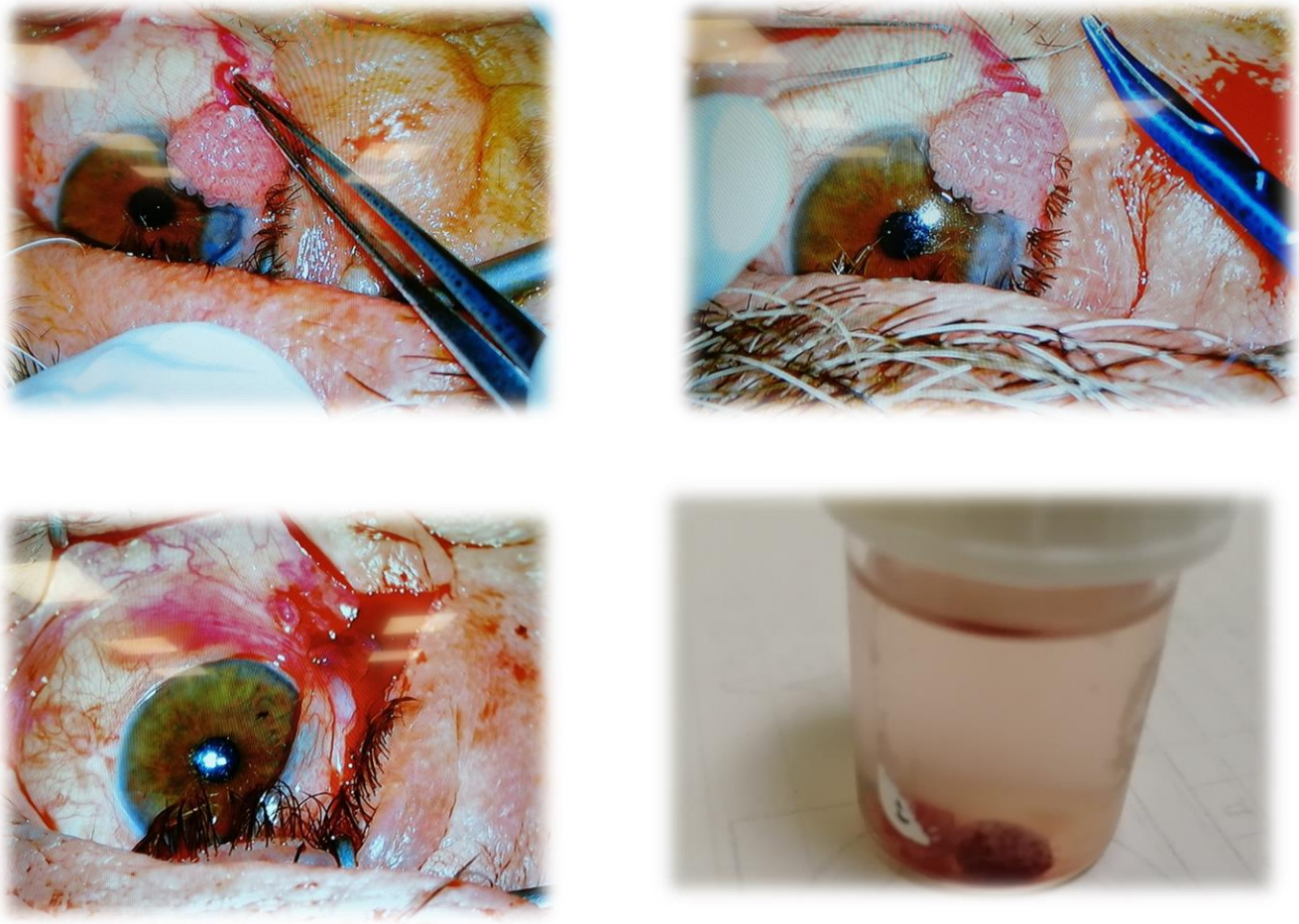


Figure 3. Intraoperative course. Images up - accession and ligation of the blood vessels that vascularize the tumor. Image below left - suturing of the excision edges of the conjunctiva. Image below - right postoperative material placed in 10% formalin, for pathohistological analysis.

At the Institute of Pathology in Skopje, the excised material was fixed in 10% formalin and processed by a paraffin fitting procedure, and then routinely stained with hematoxylin and eosin (H&E).

Microscopic analysis of the excision samples showed the presence of multilayered squamous epithelium, which in places was papillomatous proliferated, with marked acanthosis, parakeratosis, and the presence of superficial keratinization. In places the epithelium showed destratification of the nuclei throughout its thickness, with an increased nuclear-cytoplasm ratio, loss of cell polarity, and the presence of mitotic figures in the surface layers. Epithelial cells had a spindle morphology. Myxomatous stroma with a rich lymphocyte infiltrate was seen in the connective tissue. No penetration of the basement membrane and infiltration into the underlying connective tissue was visible (Figure 4).

According to the pathohistological characteristics, the diagnosis of severe epithelial dysplasia - carcinoma *in situ* (cCIS) according to the TNM classification of malignant tumors 8th edition UICC and WHO was made [18].

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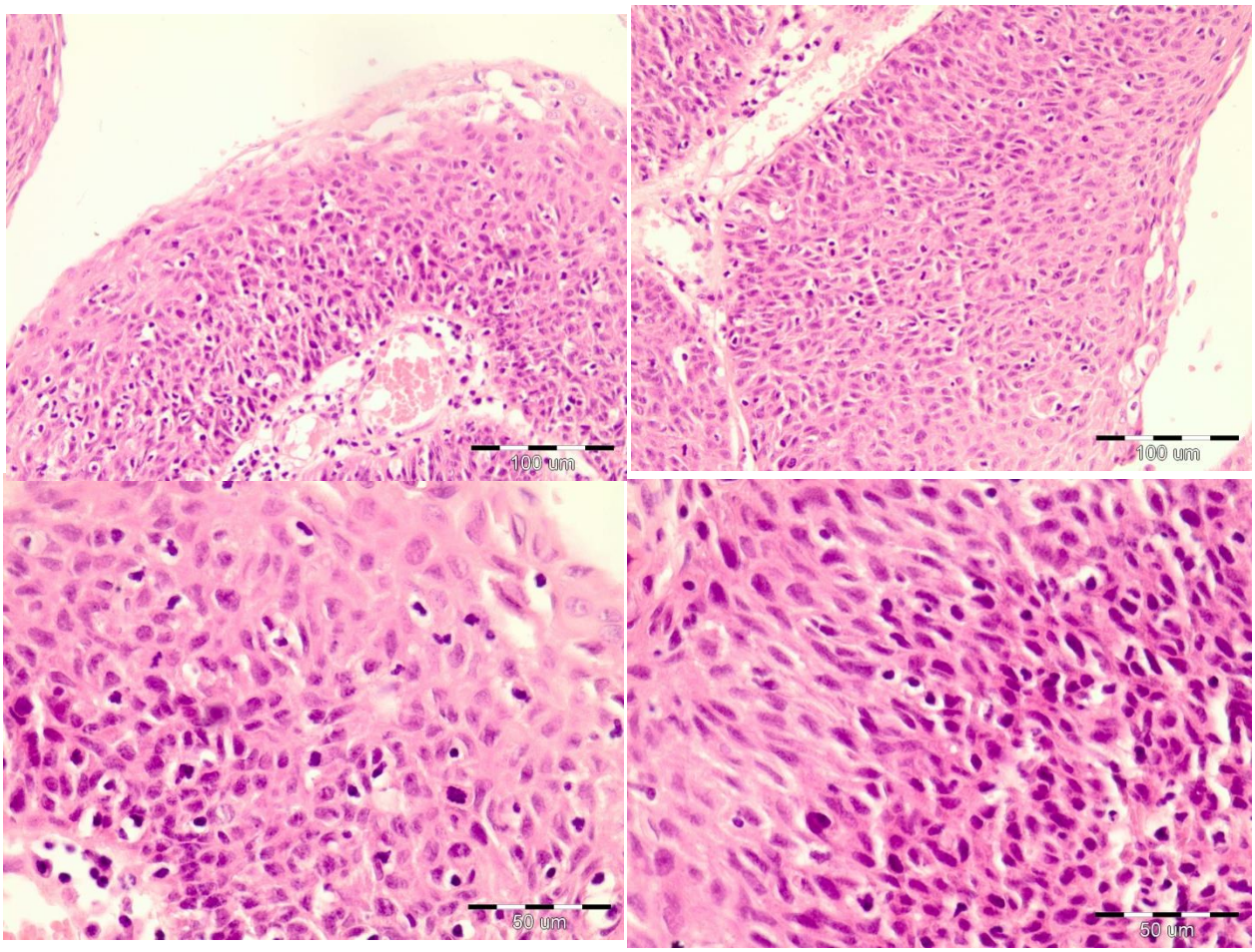

Figure 4. Pathohistological presentation of the lesion (H&E) The photos above show the process of dysplasia throughout the thickness of the conjunctiva, with superficial keratinization. The lower images show hyperchromia of the nuclei, pathological mitoses, loss of cell polarity and epithelial cells with spindle morphology

The patient comes for regular check-ups at the University Clinic for Eye Diseases in Skopje and he has been without recurrence for ten months (Figure 5).

Figure 5. Patient three months postoperatively at regular check-up. Visible conjunctival scar at the site of the lesion, with no signs of recurrence.

Discussion

The gold standard in the diagnosis of OSSN lesions is pathohistological analysis. It is based on certain morphological features of individuals or groups of epithelial cells (mucoepidermal or spindle cells): increased nuclear-cytoplasm ratio, cell pleomorphism, presence of mitotic figures, and loss of cell polarity.

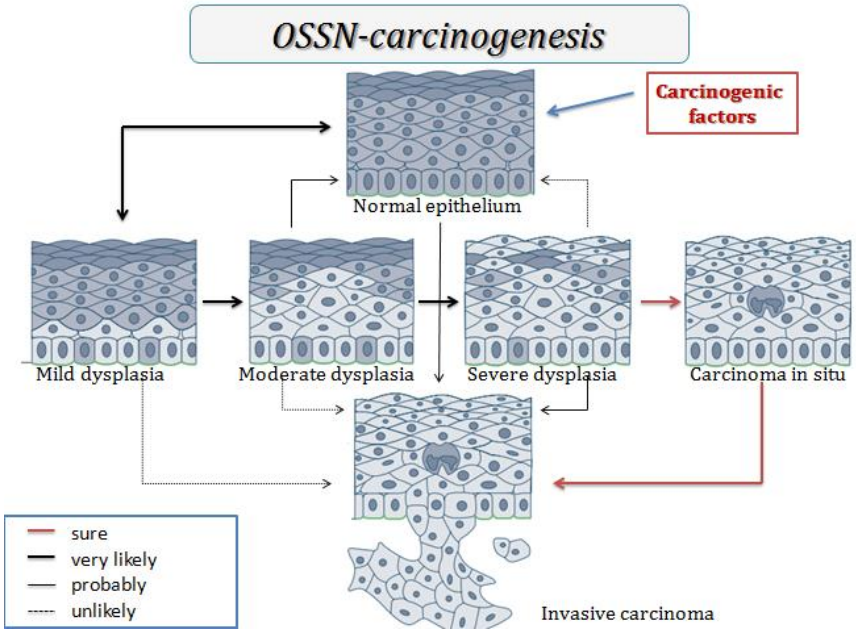

Figure 6. Occurrence of OSSN lesions, schematic representation

Initially, the pathological process of dysplasia begins in basal cells and this change is known as CIN I lesion (conjunctival intraepithelial neoplasia), a mild dysplasia. When this process affects the spinous layer of cells, it is CIN-2 or moderately severe dysplasia, and when almost the entire epithelium is dysplastically altered, then we say that it is severe dysplasia or CIN III. Later, in severe dysplasia, mitotic figures appear in different layers of the epithelium, its stratification is disturbed, the cell nuclei acquire

hyperchromic and pleomorphic characteristics, i.e., the cells have acquired neoplastic potential, so carcinoma *in situ* has occurred. When the malignant cells penetrate the basement membrane and infiltrate the underlying stroma, the process progresses to invasive squamous cell carcinoma of the conjunctiva (SCC). The cancer invades the surrounding orbital structures, rarely giving distant metastases (Figure 6). Typical sites for lymph node metastasis are the parotid, submandibular, and anterior cervical lymph nodes [15,18].

New potential immunohistochemical markers are currently being investigated as possible diagnostic tools for OSSN lesions. One of them is the tumor suppressor gene p16, which has so far been used as a marker for neoplastic pathologies of the cervix uteri, neck and head. Recently Carrilho *et al*. associated p16 as a possible marker for conjunctival SCC in HIV-positive patients. Another study classified IL-6 as a potential marker in the diagnosis of conjunctival dysplastic lesions [19,20].

The Staging system for conjunctival cancer according to the TNM classification of malignant tumors, 8th edition of the Union for International Cancer Control (UICC) and WHO, is applied in clinical practice (Table 1) [18].

Table 1. WHO classification of tumors of the eye,TNM classification of malignant tumors-8th edition.TNM classification of carcinoma of the conjuctiva

WHO classifiocation of tumors of the eye, TNM classification of malignant tumours-8th edition TNM classification of carcinoma of the conjunctiva, Carcinoma of Conjuctiva	
T Category	***T Criteria***
TX	*Primary tumor cannot be assessed*
T0	*No evidence of primary tumor*
Tis	*Carcinoma in situ*
T1	*Tumor (≤5mm in greatest dimension) invades through the conjuctival basement membrane without invasion of adjacent structures*
T2	*Tumor (>5mm in greatest dimension) invades through the conjuctival basement membrane without invasion of adjacent structures*
T3	*Tumor invades adjacent structures (excluding the orbit)*
T4	*Tumor invades the orbit with or without further extension*
T4a	*Tumor invades orbital soft tissues without bone invasion*
T4b	*Tumor invades bone*
T4c	*Tumor invades adjacent paranasal sinuses*
T4d	*Tumor invades brain*
N Category	***N Criteria***
NX	*Regional lymph nodes cannot be assessed*
N0	*No regional lymph node metastasis*
N1	*Regional lymph node metastasis*
M KCategory	***M Criteria***
cM0	*No distant metastasis*
cM1	*Distant metastasis*
pM1	*Distant metastasis, microscopically confirmed*
G (grade)	***G Definition***
GX	*Grade canot be assessed*
G1	*Well differentiated*
G2	*Moderately differentiated*
G3	*Poorly differentiated*
G4	*Undifferentiated*
Component of LVI Coding	***Lymphovascular Invasion (LVI)-Description***
0	*LVI not present (absent)/not identified*
1	*LVI present/identified, NOS*
2	*Lymphatic and small vessel invasion only (L)*
3	*Venous (large vessel) invasion only (V)*
4	*BOTH lymphatic and small vessel AND venous (large vessel) invasion*
9	*Presence of LVI unknown/indeterminate*
	Ki-67 growth fraction, reported as percentage of positive tumor cells by immunohistochemistry.

Cytology (aspiration - using an aspiration syringe or immersion - using filter paper) is another diagnostic modality that has been described in several studies as a possible tool in the diagnosis of OSSN lesions. Both types of cytological analysis are minimally invasive and several studies have shown that the results obtained in a large percentage (80-85%) correlate for the degree of dysplasia with pathohistological findings. However, the disadvantage of these is the need for an experienced cytopathologist, as well as the fact that the sample is taken from the superficial layers of the lesion, so cytology cannot provide an answer for a possible invasion of the tumor in the underlying stroma [21,22].

AS-OCT can help in the ophthalmic practice for good differentiation of lesions, whether it is OSSN or not. This non-invasive technique is now considered a clinical "optical biopsy" of conjunctival and corneal tissue. It exists as high resolution (5-10 μm) or ultra-high resolution (3-5 μm) optical coherence tomography.

Through this imaging technique, the thickness of the lesion can be assessed through its hyperreflective characteristics compared to the surrounding healthy tissue. The OCT clearly shows the boundary between the pathological change and the surrounding healthy epithelium, similar to the pathohistological section. And most importantly, in non-invasive changes, the OCT makes a clear distinction from the underlying tissue. However, in thicker and hyperkeratinized lesions, the hyperreflective nature of the tumor may cast a shadow and be difficult to assess whether it is an invasion or not [14,16,23].

In our case. the patient had all three AS-OCT features of the OSSN lesion: a clear border of the surrounding epithelium, a hyperreflecting thickened lesion, which was well demarcated from the underlying ocular tissue. Thus, AS-OCT helped in the correct clinical diagnosis of this not so common case.

OCT-A (OCT angiography of the anterior segment of the eye) is a relatively new modality that can help in locating the vascular network of the tumor and the blood vessel that vascularizes it [24].

Another clinical diagnostic modality is *in vivo* confocal microscopy (IVCM). It is a non-invasive technique that allows images from the depth of the cornea to be made parallel to its surface. The technique provides rapid information on the condition of the cornea at the cellular level. There is contact and non-contact confocal microscopy.

Studies on the application of IVCM in OSSN diagnostics have shown different results. Some studies indicate a good correlation of the changes seen through this technique with those in pathohistological examination, as well as determining the degree of dysplasia. However, other studies have shown that keratinization of the epithelium, hyperchromia of the cell nuclei, and necrotic areas in the tumor are factors that adversely affect imaging with this method, so IVCM cannot replace biopsy.

Also, for proper performance of this technique, a well-specialized staff is needed who will know how to operate the confocal microscope [16,25].

Ultrasound biomicroscopy is a tool used in the assessment of intraocular invasion and lesion infiltration. Tumors that are thick and nodular over 5 mm in size and have necrotic areas are at higher risk of possible intraocular invasion [14].

Surgical excision is still the gold standard for the treatment of this pathology today. It is important that the lesion is completely removed, 3-5 mm into the healthy surrounding tissue. Side effects of the surgical procedure include symblepharon, corneal stem cell deficiency, and conjunctival scarring. Cases of cryotherapy applied to the edges of the excised tissue have been reported to prevent possible residual neoplastic cells. Pathohistological analysis indicates more precisely whether the edges of the excision are clean [15,26].

Radiotherapy (brachytherapy and teletherapy) is used in cases of scleral invasion or when the lesion cannot be surgically removed. Satisfactory results are achieved in the local control of the tumor, but side effects are: cataract, neovascular glaucoma, dry eye syndrome, eyelash loss, eyelid dermatitis and others [14,27].

Today, chemical agents are used as a possible primary (in small lesions) or adjuvant therapy in this pathology (in cases with positive excision edges or in recurrent cases). The most commonly used drugs are: IFNα-2b (interferon α-2b), 5-FU (5-fluorouracil), MMC (mitomycin C), Vitamin A, anti-VEGF (anti-endothelial growth factor) and Cidofovir.

IFNα-2b-protein leukocyte derivative that increases phagocytic, cytotoxic activity reduces vasoproliferation and protein synthesis, stimulates apoptotic processes and inactivates viral RNA. Several studies have shown that it has an effect on OSSN spectrum lesions when used for several months as a topical agent or subconjunctival application. Side effects are cold-like symptoms. This product still has a high price for mass usage [5,14].

5-FU and MMC are chemotherapeutics, the first pyrimidine analogue, and the second alkylating agent, which inhibit DNA synthesis and promote apoptosis. Compared to IFNα-2b, having a lower cost, studies have shown a positive effect on lesion control, whether as primary or adjuvant therapy. Their irritating effect on the ocular surface (redness, chemosis, burning in the eyes), up to corneal epitheliopathy and superficial corneal melt makes them more toxic agents, especially MMC, compared to IFNα-2b [5,14,28,29].

The positive effect of the use of retinoids as stand-alone and combination therapy in the treatment of OSSN has been shown clinically. The mechanism of action of retinoids is thought to be regulation of cell growth and differentiation, with antineoplastic and apoptotic modulating effects [30].

Recent studies have demonstrated a modest effect on OSSN, with subconjunctival administration of anti-VEGF drugs [31]. Cidofovir is a monophosphate nucleotide analogue that is a potent *in vitro* antiviral agent, and has been shown in a small number of studies to have a positive effect on OSSN refractory compared to other therapies [32].

In our case, the clinical diagnosis was based on biomicroscopic examination and staining of the lesion with Rose Bengal.

Examination was complemented by AS-OCT through the characteristic, pathognomonic OSSN changes seen on the tomographic scan described above. Finally, pathohistological analysis confirmed the final diagnosis - *in situ* conjunctival SCC. From a therapeutic point of view, surgical excision with clean margins, supplemented with Vitamin A as adjuvant therapy has shown a good effect on maintaining remission in the patient for 10 months.

Accordingly, we can emphasize that AS-OCT together with careful surgical excision with clean margins, and pathohistological verification are the optimal strategy in managing these lesions in everyday practice.

OSSN lesions generally have a good prognosis, with a low rate of metastasis and mortality. However, untreated, they can lead to functional-aesthetic problems in the orbital region, and even to a fatal outcome. Relapses are possible after removal.

They mainly occur in the first six months and are often associated with positive edges from surgical resection, HIV infection, the presence of a visible blood vessel supplying the lesion, or a higher pathohistological degree. The conjunctival SCC, similar to that of the skin, has a greater potential for invasion of surrounding tissues than distant metastasis. However, recent studies have shown that conjunctival SCC is much more aggressive tumor than previously thought, with a higher potential for metastasis and fatal outcome [3,14,15].

Conclusion

We have presented a case report and review of possible diagnostic and therapeutic modalities used today in the management of OSSN - a not very common pathology in ophthalmology.

We emphasized the importance of AS-OCT, clean margin surgical excision, and pathohistological examination as the "optimal triad" in the diagnosis and treatment of these lesions in everyday clinical practice.

Finally, by presenting this study we wanted to point out the importance of cooperation between the ophthalmologist and the pathologist in the management of ophthalmic neoplasms.

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