

CASE REPORT

Conjunctival invasive poorly differentiated squamous cell carcinoma in a 91-year-old female patient

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Abstract

The invasive conjunctival squamous cell carcinoma (SCC) of the eyeball is a malignant tumor that invades only the conjunctiva and rarely the eyeball and the tissue of the orbit. We presented the clinical case of a 91-year-old patient, hospitalized at the 2nd Ophthalmology Clinic of the "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital of Iași, Romania, due to a solid tumor mass of approximately 1×2 cm, which was noticed under the bulbar conjunctiva of the right eye in the nasal sector. The magnetic resonance imaging (MRI) examination showed an adherent tumor of the right eye sclera, presenting invasion into the tissue of the orbit. The right eyeball was enucleated en bloc with the adherent tumor and the partial exenteration of the nearby orbital tissue was carried out as well. The pathological examination revealed that the immunohistochemical (IHC) reactions turned positive for the anti-cytokeratin AE1/AE3 antibody and showed a relatively high Ki67 labeling index, but it did not show immunoreactivity for human melanoma black-45 (HMB-45) marker and S100 protein. The histopathological (HP) diagnosis was poorly differentiated SCC of the right ocular conjunctiva with infiltration of cornea, sclera and orbital connective and adipose tissues (pT4N0M0). The invasive conjunctival SCC requires an early diagnosis for elderly patients in order to prevent the ocular and orbital invasion and the appearance of metastases. This tumor rarely occurs during the ninth life decade, the literature reporting only three cases. HP examination of the lesion is the gold standard for diagnosis, especially when IHC stainings are added.

Keywords: conjunctiva, invasive squamous cell carcinoma, immunohistochemistry.

Introduction

Conjunctival invasive squamous cell carcinoma (CISCC) is a malignant tumor of the conjunctival epithelium, exhibiting varying degrees of squamous differentiation and invading the depth of the conjunctiva [1].

The incidence of CISCC is 0.1 per 100 000 people per year, but in Africa it is 1.3 per 100 000 people per year, being the highest in the world [2]. This neoplasia is considered to be twice more common in men than in women [3–5].

Its etiology is represented by exposure to solar UV radiation, human immunodeficiency virus (HIV), human papillomavirus (HPV) and allergic conjunctivitis. The limbal epithelial cells appear to be the progenitor of this disease [2]. Epidemiological studies show that UV radiation (290–320 nm) may be important in its pathophysiology [6, 7] as it induces point mutation in the p53 tumor suppressor protein. CISCC occurs in immunocompromised patients or individuals with albinism or *xeroderma pigmentosum* [3]. It develops at the level of the limbus on a preexisting carcinoma *in situ*, solar keratosis or epithelial dysplasia [3, 4, 8].

Patients with CISCC come to the ophthalmologist because of a conjunctival foreign body sensation, conjunctival congestion, and the appearance of a tumor on the surface of the eyeball [1]. The tumor mass is initially mobile on the conjunctiva, but in the advanced stages it adheres to the eyeball showing scleral infiltration [9].

Clinical exam could reveal a lesion with a smaller size than it really is, especially when it invades the eyeball structures and the tissues of the orbit [2]. CISCC has a macroscopic appearance similar to other conjunctival tumoral or non-tumoral lesions, including: squamous papilloma, actinic keratosis, keratoacanthoma, pterygium, pinguecula [10], carcinoma of the sebaceous gland, malignant melanoma, and mucosa-associated lymphoid tissue (MALT) lymphoma [1].

Researchers have shown that only 40% of the diagnoses of ocular surface squamous neoplasia (OSSN) are correct [11]. Moreover, only histopathological (HP) exam could differentiate between corneo-conjunctival intraepithelial neoplasia (CIN) and a CISCC.

In this paper, we present the third case of an invasive conjunctival poorly differentiated squamous cell carcinoma (SCC), with corneal, scleral and orbital extension, which developed in a female patient older than 90 years. Also, we review the literature on this issue.

Case presentation

A female patient (OE), aged 91, was admitted to the 2nd Ophthalmology Clinic of "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital of Iași, Romania (medical file N.O. 20 425/22.10.2013), because of a solid tumor that slowly developed in the right eye, under its bulbar conjunctiva, in the nasal sector. It was painless, but it grew in dimensions, moving the right eye towards the

temporal side. The magnetic resonance imaging (MRI) examination revealed an internal, solid, round, orbital tumor adherent the sclera of the right eye. The patient was hospitalized for investigation and surgery. Patient's medical history revealed a recurrent conjunctiva tumor for which she was two-times operated, but with no known pathological report, an age-related cataract in both eyes, previous surgical intervention for acute appendicitis, atherosclerotic hypertension, aortic and mitral atheromatosis, and gastroduodenitis. Ophthalmologic examination revealed that visual acuity in the right eye was the perception of light, and best-corrected visual acuity at left eye was 0.2. Following the examination of the ocular annexes, a solid nodular tumor of approximately 1×2 cm in diameters was found at the level of the palpebral fissure in the internal sector, located under the bulbar conjunctiva of the right eye (Figure 1). Slit lamp examination revealed that the cornea had a central vascularized leukoma; the anterior chamber had normal depth and no other details could be detected. Adduction limitation was found in the right eye. Intraocular pressure in both eyes was within normal limits. Ophthalmoscopic examination at right eye could not be done due to corneal leukoma, but in the left eye optic disc was normally colored, cup/disc ratio was 0.4, and stage I retinal angiosclerosis was found. Clinical examination did not reveal any preauricular or cervical lymphadenopathy. The patient written consent for surgery was obtained. An enucleation of the right eyeball and together with the adherent tumor and partial exenteration of the orbital fat adjacent to the tumor was done. The specimen was sent to the Laboratory of Pathology for HP examination.

The pathologist cut the eyeball and the adherent tumor along their antero-posterior axis and noted a solid tumor of 1.5×2.5 cm, adherent to the eyeball, but without any apparent infiltration of its structures (Figure 2).

Then, the specimens were fixed in 10% neutral buffered formalin, processed routinely and embedded in paraffin

wax. Histological sections of 5-μm thickness were stained with Hematoxylin and Eosin (HE), according to the standard procedure. Then, serial sections (5-μm thick) were cut, deparaffinized, and processed according to the manufacturer's instructions, using the monoclonal mouse anti-human cytokeratin (CK) AE1/AE3 antibody (clone AE1/AE3, 1:400 dilution; DAKO, Carpinteria, CA, USA), and the monoclonal mouse anti-human Ki67 antibody (clone MIB-1, 1:75 dilution; DAKO, Glostrup, Denmark). An EnVision detection system (DAKO, Denmark), 3,3'-Diaminobenzidine as chromogen and Mayer's Hematoxylin for nuclear counterstaining were applied. Relevant immunostaining with anti-CK AE1/AE3 antibody was taken as positive when a brown cytoplasmic coloration appeared in the tumoral cells. The proliferative index was calculated as the average percentage of tumor Ki67 labeled nuclei counted in 10 high-power fields (HPFs, ×400) that were located in the most active parts of the tumor.



Figure 1 – Clinical image: elevated, nodular gelatinous tumor with prominent vascularity located at the level of the bulbar nasal conjunctiva of the right eye, adherent to the sclera and with orbital invasion.



Figure 2 – Gross examination: white-grayish (after formalin fixation), solid tumor of 1.5×2.5 cm, adherent to the eyeball, apparently without infiltration of the cornea or sclera on cut-section.

The HP exam showed large nests made up of tumoral epithelial cells with ovoid shape, indistinct cells borders, high nuclear to cytoplasmic ratio, markedly atypical nuclei, and minimal keratinization (Figures 3 and 4).

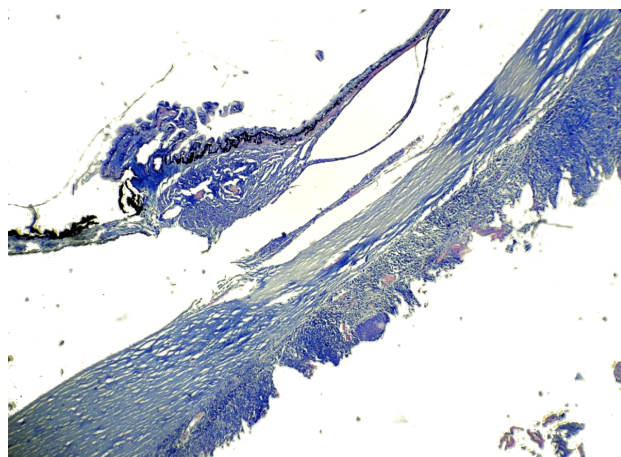


Figure 3 – Epithelial tumor proliferation having a conjunctival starting point covered the eyeball, infiltrating corneal stroma and sclera in their outer, superficial areas (HE staining, ×50).

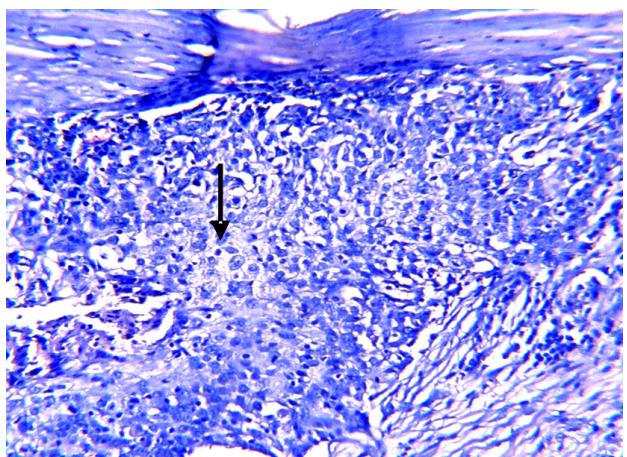


Figure 4 – The tumor was made up of epithelial cells with atypical nuclei that exhibited mitotic figures (black arrow). Tumor cells were arranged in nests separated by prominent stroma infiltrated with lymphocytes (HE staining, ×200).

The tumoral nests showing sometimes central necrosis were separated by vascular-connective stroma (Figure 5). This neoplasia embraced the eyeball in its medial part

and showed microscopic invasion into the adjacent cornea and sclera (Figure 5) and massive invasion into connective and adipose tissues of the orbit. Tumor cells

exhibited intense immunopositivity for anti-CK AE1/AE3 antibody (Figures 6 and 7), but no immunoreactivity for anti-human melanoma black-45 (HMB-45) antibody and S100 protein, thus revealing their epithelial origin. Fourteen percents of tumor cells were positive for Ki67 immunomarker (clone MIB-1), being consistent with a highly proliferative activity of this neoplasia (Figure 8).

The final diagnosis was poorly differentiated SCC of the right ocular conjunctiva with infiltration of cornea,

sclera and orbital connective and adipose tissues (pT₄N₀M₀).

After surgical intervention, patient's evolution was favorable under antibiotic and anti-inflammatory treatment, but she refused the referral to the Department of Oncology for further evaluation and preferred the follow-up. After six months, the patient did not show any recurrent tumor or metastases.

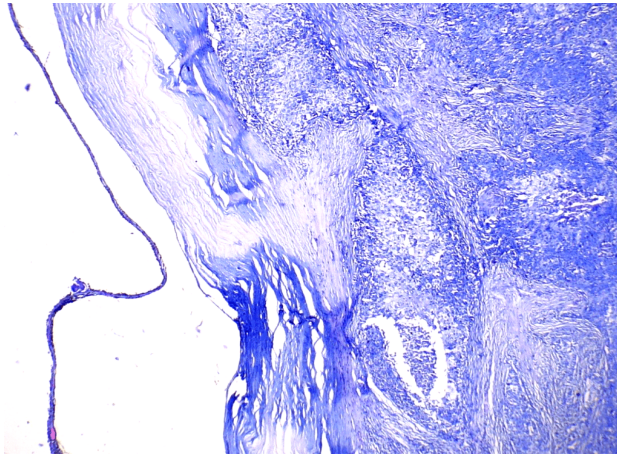


Figure 5 – In some other fields, tumor nests showed central necrosis (HE staining, $\times 100$).

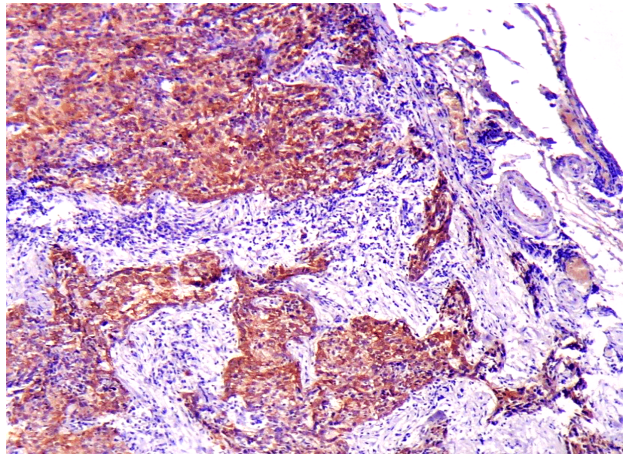


Figure 6 – Cytoplasmic positive immunostaining of tumor cells with anti-CK AE1/AE3 antibody ($\times 200$).

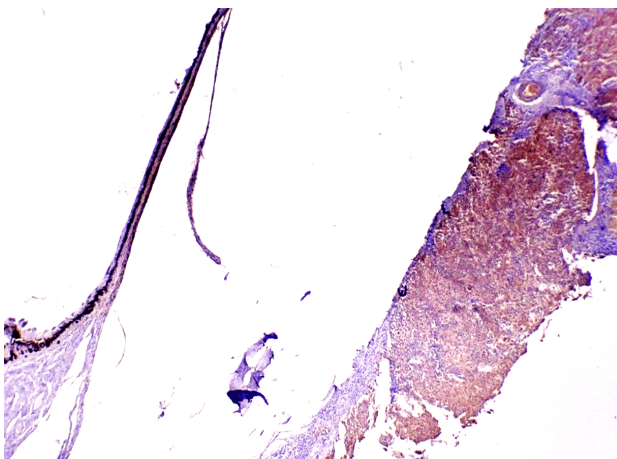


Figure 7 – Immunostaining with anti-CK AE1/AE3 antibody revealed the invasion of sclera in almost all its thickness ($\times 50$).

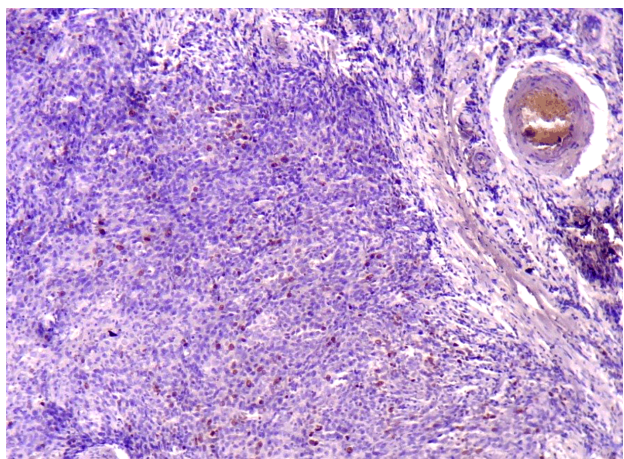


Figure 8 – The tumor cells were arranged in large nests that infiltrated the orbital connective and adipose tissue and exhibited nuclear immunostaining for anti-human Ki67 antibody, clone MIB-1 (average Ki67 labeling index: 14%) ($\times 100$).

Discussions

Ocular surface squamous neoplasia (OSSN) is a term that includes a wide spectrum of disease involving the epithelium of the conjunctiva or cornea. From a clinical point of view, OSSN presents itself as a tumor that develops at the level of the interpalpebral fissure in the nasal part [12].

In Africa, and especially in sub-Saharan Africa, where acquired immunodeficiency syndrome (AIDS) became epidemic, OSSN is more often diagnosed in younger women [13], but in Western European countries and in United States of America, this neoplasia remains a disease of elderly men, being in their seventh or eighth decades of life [14].

However, there are only two cases published from what we know so far describing patients aged more than 90 years [15, 16], making our case the third in literature with this disease at this advanced age.

Some researchers described OSSN as a tumor that could be gelatinous and papillomatous, being accompanied by inflammation and markedly dilated blood vessels; some pigmentation of the lesion is common in African population groups [2]. Confronting with such a lesion, the ophthalmologist should carry out the differential diagnosis with the conjunctival nevus and the malignant melanoma [17, 18]. In the case of extensive orbital tumors, unilateral exophthalmia may occur, and differential diagnosis with other systemic diseases with ocular involvement or with palpebral tumors accompanied by

orbital invasion and other orbital tumors, is vital [19–21]. However, it is also important to distinguish OSSN from sebaceous carcinoma [22], but using immunohistochemical (IHC) staining, a proper diagnosis could be established.

OSSN encompasses the spectrum of conjunctival and corneal intraepithelial neoplasia (CIN) and SCC [23, 24].

Relying on the degree of tumor invasion into the conjunctival submucosa, CISCC can be classified into two entities: (i) with superficial invasion, characterized by atypical squamous epithelial cells penetrating the epithelial basal membrane and invading into the superficial conjunctival *substantia propria*; (ii) with deep invasion, when malignant epithelial squamous cells penetrate the epithelial basal membrane and migrate into the deep conjunctival *substantia propria* or into the adjacent structures [25, 26].

Our patient presented a poorly differentiated SCC of the conjunctiva, with deep invasion into ocular structures like cornea and sclera, but also infiltrated the orbital adipose tissue.

From HP point of view, CISCC consists of nests of squamous epithelial cell originating in the conjunctival epithelium and invading conjunctiva on varying depths. Tumor cells have eosinophilic cytoplasm and vesicular nuclei, preserving more or less the intercellular bridges. The tumor nests can contain keratin in varying degrees, from focal to extensive presence, depending on the degree of tumor differentiation. So, CISCCs can be classified in well-differentiated, moderately differentiated or poorly differentiated tumors.

There are also several other subtypes of CISCCs and their differential diagnosis could be made only by HP exam completed with histochemical and IHC stainings. They are all rare and most of them are much more aggressive than the classical variant. SCC with clear cells is characterized by hydropic cytoplasmic changes that determine a “clear” appearance of the cytoplasm in HE staining, while the histochemical stainings for glycogen, mucin and lipids are negative [27]. Adenoid SCC is characterized by a pseudoglandular appearance due to the acanthosis of neoplastic squamous cells in the center of the tumor nests [28]. Spindle cell SCC, a poorly differentiated variant of squamous carcinoma, is considered to be a more aggressive subtype and with a much worse prognosis than the classic variant due to its metastases [29]. Positive immunostaining with CK AE1/AE3, epithelial membrane antigen (EMA), melanoma marker HMB-45 and S100 protein are useful to differentiate SCC with spindle cells from other tumors, such as amelanotic melanoma, malignant schwannoma, fibrosarcoma, leiomyoma and malignant fibrous histiocytoma [30]. Mucoepidermoid SCC is a rare tumor that develops in the caruncular area. It is very aggressive and has the tendency to invade the orbit [1]. Histologically, it has a mixed appearance, consisting of cells with squamous differentiation and cells with mucous secretion, in varying proportions [25].

Some authors considered that surgical treatment of CISCC should be the wide excision of the tumor mass (with safety margins of 4 mm), with/without sclerectomy and cryotherapy at the edges of the conjunctival excision

[1, 4, 31, 32]. The prognosis of CISCC is favorable for small lesions that are treated with excisional biopsy combined with adjuvant topical chemotherapy. CISCC invading the sclera and orbital tissues could be treated by enucleation or exenteration, depending on the tumor extension [9].

Johnson *et al.* (1997) [33] mentioned in their study that tumor recurrence can be predicted depending on its dimensions (>5 cm in diameter), histological diagnosis and stage of the tumor at the time of its examination. Our patient's tumor was smaller than 5 cm, and no lymphatic invasion or distant metastasis could be identified, but the microscopic exam revealed a poorly differentiated SCC with immunopositivity for anti-CK AE1/AE3 and a relative high Ki67 labeling index. Despite this worrisome histology, recurrences did not appear at six months after surgery, even in the absence of the oncological treatment.

Wide surgical excision of large conjunctival tumors should be completed with conjunctivoplasty or amniotic membrane patch [1, 34]. In some other cases, local excision may be combined with brachytherapy [35, 36]. Orbital invasion by CISCC requires orbital exenteration. The involvement of the regional lymph nodes requires their radical excision [4], as it is done also in another cases of ocular and periocular tumors with orbital invasion and regional lymphadenopathy [37]. Postoperatively, it is recommended to apply antibiotics and steroids for four weeks, as well as topical 5-Fluorouracil (5-FU) for four weeks. Radiotherapy is recommended after enucleation/exenteration in severe cases with extensive neoplasia [38, 39].

In their study, Gichuhi & Sagoo (2016) [2] found out that the recurrence rate for CISCC is between 3.2% and 67%, at an average period of 32 months. Our patient had a history of operated recurrent conjunctival lesion, but she could not mention the previous HP diagnosis. Thus, in our case, CISCC had a long evolution, with corneal, scleral, and orbital fat invasion. In this advanced condition of the disease, it was necessary to enucleate the eye and partially to exenterate the orbital content, but the eyelids remained unaffected by surgery.

According to a large retrospective study made by Tunc *et al.* (1999) [14] on 60 cases of intraepithelial and invasive SCC of the conjunctiva, the right eye was involved in 27 patients and the left eye in 31 cases. CISCC affected both eyes only in one case. The age of the patients ranged between 26 and 84 years old, with an average age of 64 years. The most common symptom was red eye in 41 (68%) cases and ocular irritation in 34 (57%) patients. From HP point of view, 22 cases were CIN and 38 were CISCC. The scleral invasion appeared in 14 (36%) patients, intraocular involvement in five (13%) cases and orbital invasion in four (11%) cases with CISCC.

Tabin *et al.* (1997) [40] highlighted the fact that in cases with 25% incomplete excision edges, recurrences were twice more frequent than in the cases with “clear” edges. In our case, as we made a comprising partial the eyeball and the orbital tissue in its vicinity and no recurrences appeared at six months of follow-up.

Our patient also had a residual corneal leukoma, which has led the ophthalmologist to make a differential

diagnosis with other lesions of the anterior segment of the eye: cataract, retinal detachment, intraocular metastasis, etc. [41]. However, in the cases of CISCC, misdiagnosis and confusion with other conjunctival or eyelid tumors could delay treatment and increase morbidity [3, 42, 43].

Conclusions

Patients with any kind of conjunctival lesion, especially with a recurrent lesion as it was in this case, should be educated to pay a visit to their ophthalmologist for the follow-up, because a neglected lesion can be the trigger of a cancer. This rare and uncommon type of tumor found at this 91-year-old patient, needed thorough investigations and radical approach. HP examination completed with histochemical and IHC staining was the gold standard for diagnosis. Enucleation and partial orbital exenteration was indicated in this case of invasive conjunctival SCC because of the extensive invasion. With the proper surgical excision, the CISCC had a good prognosis with no recurrences at six months after surgery, even in the absence of the oncological treatment.

Conflict of interests

The authors do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interests in the context of the subject of the manuscript.

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Received: October 29, 2017

Accepted: May 5, 2018