DOI: 10.7860/JCDR/2022/55597.16439

Case Report

Ophthalmology Section

A Rare Case of Conjunctival Squamous Cell Carcinoma in a Patient on Long-term Azathioprine Therapy: Cause or Coincidence

STEPHEN SUDHAKAR[1], GAYATRI SUNDARESHWARAN[2], NEHA ARORA[3], LAWRENCE DCRUZE[4]

ABSTRACT

Autoimmune Polyglandular Syndrome (APS) is a cluster of endocrine abnormalities that occur in discreet patterns in subjects with immune dysregulation and that permit treatment and anticipation of associated systemic or other hormonal deficiencies. It is classified into four subtypes based on the extent of autoimmune manifestations. APS type 3 is characterised by the presence of an autoimmune thyroid disease and another autoimmune illness, excluding Addison's disease. Ocular manifestations of APS include keratoconjunctivitis, dry eye, corneal scarring, cataract, retinopathy and optic atrophy. Here, a case of a 23-year-old male patient with APS has been presented with a growth in the left eye for four months, with no other associated symptoms. The patient was a known case of APS type 3 with Autoimmune Haemolytic Anaemia (AIHA) since the age of five years. The patient was treated with long-term oral steroids and Azathioprine for 18 years. His visual acuity was 6/6; N6 in both eyes. A gelatinous lesion measuring 8×4 mm was located on the nasal bulbar conjunctiva of left eye, extending 3 mm onto the cornea. The lesion demonstrated intrinsic vascularity, feeder vessels and pigmentation, clinically suggestive of Ocular Surface Squamous Neoplasia (OSSN). Ultrasonography defined the extension of the lesion to involve the episclera, sclera and posterior cornea. Incisional biopsy established the diagnosis of conjunctival squamous cell carcinoma in-situ. Surgical excision was deferred in view of good visual acuity and deep scleral and corneal involvement. The patient was treated with topical Mitomycin C 0.04%, and remained on close follow-up for six months. A possible contribution of long-term intake of systemic azathioprine to the occurrence of conjunctival neoplasia can be considered.

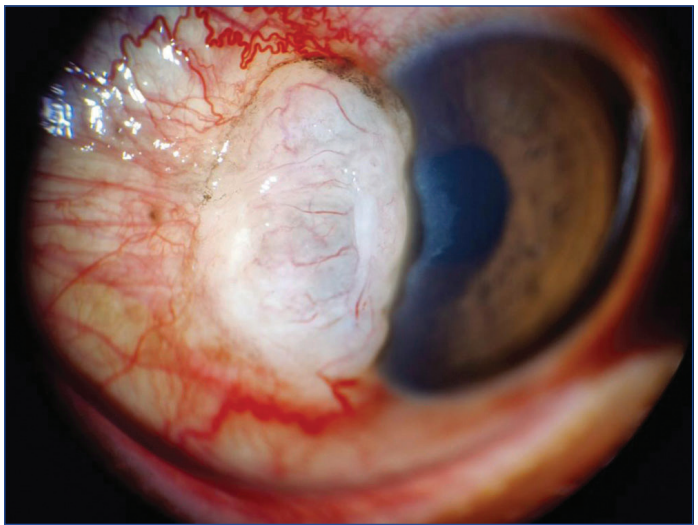
Keywords: Autoimmune haemolytic anaemia, Conjuctiva, Ocular surface squamous neoplasia

CASE REPORT

A 23-year-old male patient presented to the Ophthalmology Department with a growth in the left eye for four months. It was insidious in onset and gradually increasing in size. There was no watering, pain, redness, discharge, diplopia, decrease in vision or difficulty in closing eyelids. He had no prior history of ocular trauma or surgery. The patient was diagnosed with APS type 3 at five years of age which included primary hypothyroidism, primary hypogonadism, and probable growth hormone deficiency. The patient was on appropriate supplements for the same. The patient was born out of a non consanguineous marriage, and had no family history of endocrine dysfunction or malignancy and was also diagnosed with AIHA, at the age of five years, for which was on regular medications, oral prednisolone 10 mg and oral azathioprine 50 mg.

On examination, the patient was noted to have a short stature (height 139 cm and weight 44 kg). General examination revealed icterus and mild splenomegaly. There was no evidence of primary lesion or enlarged lymph nodes on systemic examination. Chest x-ray and abdominal ultrasound were normal and confirmed the same.

Both eyes possessed a Best Corrected Visual Acuity (BCVA) of 6/6 for distant and N6 for near and a normal colour vision. Ocular examination of the right eye was unremarkable. Left eye examination revealed an elevated, gelatinous, non ulcerative lesion in the nasal interpalpebral area measuring 8×4 mm, which was firmly attached to the underlying conjunctiva [Table/Fig-1]. The lesion had a sessile morphology, with intrinsic vascularity and brown pigmentation at the superior border. Telangiectatic vessels were seen over and around the lesion. The lesion was encroaching 3 mm onto the cornea, with corneal scarring at the leading edge. There was no leukoplakia or surface keratinisation. Fluorescein staining was negative. Corneal sensations were intact. The lesion spared the pupillary axis, and light reflexes were brisk. Anterior chamber showed no signs of inflammation. Fundus was normal. Intraocular pressure measured by Goldmann's



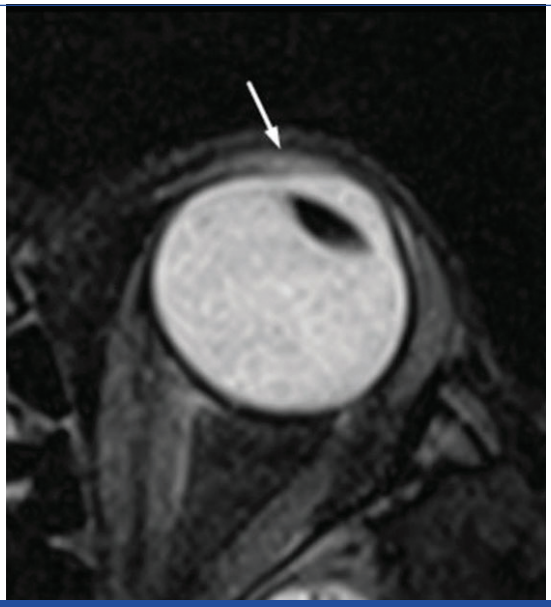
[Table/Fig-1]: Slit lamp examination of left eye with a raised, gelatinous-like lesion measuring 8 mm in height and 4 mm in breadth, in the nasal interpalpebral area with feeder vessels and brown pigmentation.

Applanation Tonometry was 15 mmHg and 13 mmHg in right and left eye respectively. The crystalline lens showed the presence of a posterior subcapsular cataract in both eyes, a probable consequence of long-term steroid intake. The eyes were orthophoric in primary gaze and there was no restriction of extraocular movements.

Laboratory investigations disclosed a low Red Blood Cell (RBC) count, with predominantly macrocytic RBCs and few tear drop cells. In view of AIHA flare, as per the physician's recommendations, the dose of steroids was stepped up to 20 mg per day.

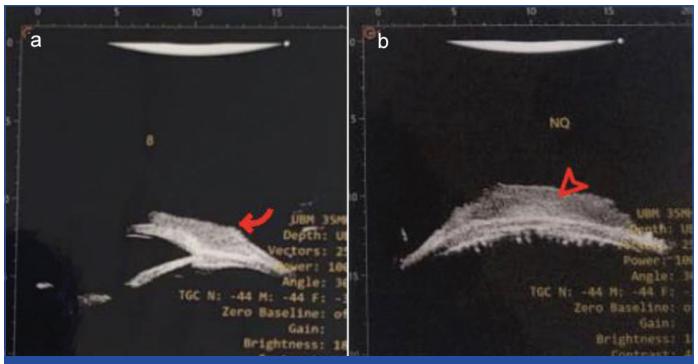
Contrast enhanced Magnetic Resonance Imaging (MRI) of orbit demonstrated thickening and hyper-intense signal on the surface of sclera and cornea at the nasal limbus of the left eye [Table/Fig-2]. There was no mass projecting into the anterior chamber. Mild

proptosis of both eyes was also noted, a probable consequence of hypothyroidism. The optic nerve and extraocular muscles in both eyes were normal.



[Table/Fig-2]: MRI of left orbit revealed hyperintense signal (arrow) on the nasal sclera, limbus and cornea.

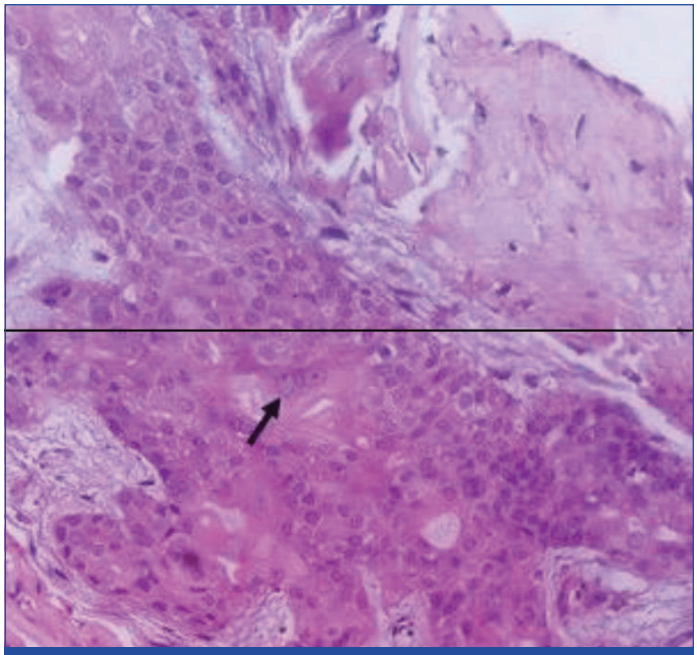
Anterior segment imaging with Ultrasound Biomicroscopy (UBM) showed a hyper-reflective mass lesion, measuring 8.09×2.09 mm and extending from 6 to 10 o'clock position [Table/Fig-3]. The lesion involved the episclera, sclera and cornea with posterior corneal invasion. The ciliary body and angle structures were spared.



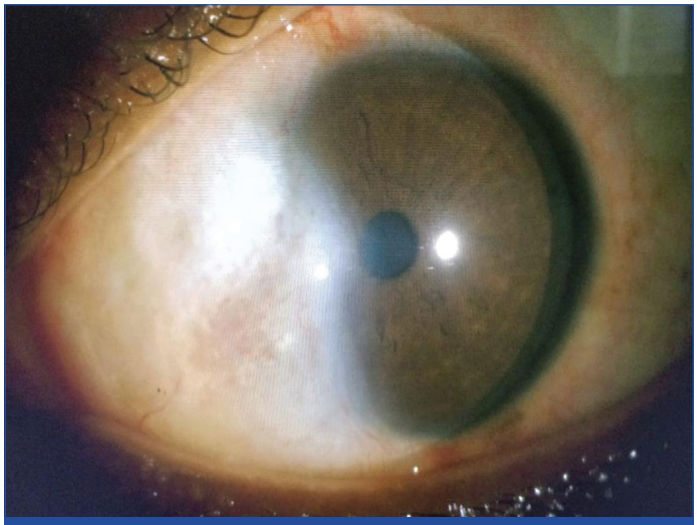
[Table/Fig-3]: (a) Ultrasound Biomicroscopy of left eye showing a hyper reflective mass (arrow) extending from 6 o clock to 10 o clock position, involving episclera, sclera and cornea. (b) Extent and depth of lesion (arrow head) in the nasal quadrant.

The patient underwent an incisional biopsy along with tumour debulking. Histopathological examination of the lesion unveiled nests and cords of atypical squamoid cells with surrounding myxoid stroma, suggestive of a conjunctival in-situ squamous cell carcinoma [Table/Fig-4]. No other dysplastic features were noted. A confirmation of OSSN was established, however the extent of invasion could not be determined by the incisional biopsy. Surgical removal was deferred in view of involvement of deeper structures at the limbus and the presence of an excellent visual acuity. Topical chemotherapy was initiated. Eye drop Mitomycin C (MMC) 0.04% was administered as one drop in left eye four times a day for one week, every alternate week for three cycles. Two such sessions were given. Lubricants were initiated and existing treatment with oral steroids and hormonal therapy was maintained.

At the end of three cycles, the surface appeared flat, with resorption of vascularity and pigmentation, suggestive of regression [Table/Fig-5]. The BCVA in the left eye was 6/6 for distant vision and N6 for near vision with an astigmatism of -1.0 dioptre cylinder. Patient has been on regular follow-up for six months after topical chemotherapy treatment, under a vigilant watch for signs of recurrence. Azathioprine therapy was halted after discussion with prescribing oncologist.



[Table/Fig-4]: Conjunctival squamous cell carcinoma in-situ, moderately differentiated. Nests and cords of atypical squamoid cells (arrow) with surrounding myxoid stroma, and with focal infiltration (Haematoxylin and Eosin, 400x magnification).



[Table/Fig-5]: Slit lamp photograph of left eye post chemotherapy showing features of regression.

DISCUSSION

The OSSN comprises of a spectrum of dysplasia ranging from mild epithelial dysplasia in Conjunctival Intraepithelial Neoplasia (CIN) to invasive Squamous Cell Carcinoma (SCC) that penetrates the basement membrane [1-3]. The above described patient had a unilateral, gelatinous like lesion with feeder vessels and pigmentation with nasal interpalpebral involvement, clinically suggestive of OSSN. Histopathological examination supported the same [4]. Several predisposing factors for OSSN, both environmental and host-related have been identified. While Ultraviolet B exposure and Human Papilloma Virus (HPV) have been postulated as the most significant risk factors, the status of the host immune system can also be attributed [4,5]. Patients with immune deficiency secondary to Human Immunodeficiency Virus (HIV) infection, or a consequence of immunosuppressive therapy, have been shown to be at a higher risk of development of OSSN. These patients generally have poorer outcomes with more aggressive spread and higher risk of recurrence [6].

This patient had a unique association of OSSN and autoimmune polyendocrinopathy. Various ocular manifestations of APS such as dry eye, corneal scarring, iridocyclitis, cataract and retinopathy have been reported [2]. Surgical management of OSSN comprises of resection of lesion with wide margins via no touch technique

to prevent tumour seeding, along with adjunct application of antimetabolites or cryotherapy. Medical management includes topical chemotherapy (MMC, 5-Fluorouracil), immunotherapy (Interferon α-2b), antiviral (Cidofovir) or Photodynamic Therapy (PDT) [4]. Surgery carries a high rate of tumour recurrence; hence adjuvant therapies are increasingly being used as alternatives [7,8]. The MMC is an antimetabolite which causes Deoxyribose Nucleic Acid (DNA) alkylation in all phases of the cell cycle [9]. Chemotherapy with MMC has been shown to have good efficacy and low risk of recurrence [7,10]. Shields CL et al., reported that treatment with 0.04% MMC eye drops applied four times a day for one week, followed by one week without medication for an average of three cycles, showed complete tumour regression and no recurrences for a mean follow-up interval of 22 months [11]. This was the treatment algorithm followed in the patient, which demonstrated tumour regression over initial four week period.

Immunosuppression has been identified as a mutagenic factor for the development of OSSN. In previous reports, OSSN was observed to have occurred in immunosuppressed organ transplant patients treated with long-term systemic calcineurin inhibitors cyclosporine and tacrolimus [12,13]. In a report by Shelil AE et al., a patient developed an aggressive conjunctival SCC following a liver transplantation which was attributed to severe immunosuppression with azathioprine and tacrolimus. It was undetermined as to which of the two drugs was causative [14]. This patient was also immunosuppressed as result of chronic use of azathioprine and steroids. In both scenarios, azathioprine seemed to play a role in immunosuppression and tumour development. In view of his young age with no additional risk factors such as prolonged sun exposure or viral infections, systemic immunosuppressive drugs could have contributed to the occurrence of OSSN in the above patient. To the best of our knowledge, this is the second reported case of SCC with Azathioprine as a probable etiological agent [14].

CONCLUSION(S)

The present case report was a rare presentation of a conjunctival SCC in a 23-year-old man with APS and autoimmune haemolytic anaemia on long-term immunosuppressive therapy with azathioprine. Immunosuppression is a well established risk factor for conjunctival neoplasia. In the absence of other risk factors, conjunctival SCC could have been a probable consequence of the chronic use of systemic azathioprine.

REFERENCES

[1] Betterle C, Garelli S, Coco G, Burra P. A rare combination of type 3 autoimmune polyendocrine syndrome (APS-3) or multiple autoimmune syndrome (MAS-3). Auto Immun Highlights. 2014;5(1):27-31.
[2] Chang B, Brosnahan D, McCreery K, Dominguez M, Costigan C. Ocular complications of autoimmune polyendocrinopathy syndrome type 1. J AAPOS. 2006;10(6):515-20.
[3] Shields JA, Shields CL. Eyelid, Conjunctival, and Orbital Tumors: An Atlas and Textbook. Lippincott Williams & Wilkins; 2008. 870 p.
[4] Shields CL, Chien JL, Surakiatchanukul T, Sioufi K, Lally SE, Shields JA. Conjunctival Tumors: Review of Clinical Features, Risks, Biomarkers, and Outcomes-The 2017 J. Donald M. Gass Lecture. Asia-Pac J Ophthalmol Phila Pa. 2017;6(2):109-20.
[5] Gupta S, Sinha R, Sharma N, Titiyal JS. Ocular Surface Squamous Neoplasia. DJO. 2012;23:89-96.
[6] Shields CL, Ramasubramanian A, Mellen PL, Shields JA. Conjunctival squamous cell carcinoma arising in immunosuppressed patients (organ transplant, human immunodeficiency virus infection). Ophthalmology. 2011;118(11):2133-37.e1.
[7] Blasi MA, Maceroni M, Sammarco MG, Pagliara MM. Mitomycin C or interferon as adjuvant therapy to surgery for ocular surface squamous neoplasia: Comparative study. Eur J Ophthalmol. 2018;28(2):204-09.
[8] Alvarez OP, Zein M, Galor A, Karp CL. Management of ocular surface squamous neoplasia: Bowman Club Lecture 2021. BMJ Open Ophthalmol. 2021;6(1):e000842.
[9] Nanji AA, Sayyad FE, Karp CL. Topical chemotherapy for ocular surface squamous neoplasia. Curr Opin Ophthalmol. 2013;24(4):336-42.
[10] Daniell M, Maini R, Tole D. Use of mitomycin C in the treatment of corneal conjunctival intraepithelial neoplasia. Clin Experiment Ophthalmol. 2002;30(2):94-98.
[11] Shields CL, Naseripour M, Shields JA. Topical mitomycin C for extensive, recurrent conjunctival-corneal squamous cell carcinoma. Am J Ophthalmol. 2002;133(5):601-06.
[12] Flynn TH, Manzouri B, Tuft SJ. Ocular surface squamous neoplasia in an immunosuppressed patient with atopic keratoconjunctivitis. Int Ophthalmol. 2012;32(5):471-73.
[13] Macarez R, Bossis S, Robinet A, Le Callonnec A, Charlin JF, Colin J. Conjunctival epithelial neoplasias in organ transplant patients receiving cyclosporine therapy. Cornea. 1999;18(4):495-97.
[14] Shelil AE, Shields CL, Shields JA, Eagle RC. Aggressive conjunctival squamous cell carcinoma in a patient following liver transplantation. Arch Ophthalmol Chic Ill 1960. 2003;121(2):280-82.

PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Ophthalmology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
2. Senior Resident, Department of Ophthalmology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
3. Postgraduate, Department of Ophthalmology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.
4. Senior Resident, Department of Pathology, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Gayatri Sundar Eswaran,
9/15, Masilamani Road, Balaji Nagar, Royappetah, Chennai-600014, Tamil Nadu, India.
E-mail: s.gayatri@sriramachandra.edu.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 14, 2022
- Manual Googling: Mar 22, 2022
- iThenticate Software: Apr 19, 2022 (6%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Feb 12, 2022**
Date of Peer Review: **Mar 26, 2022**
Date of Acceptance: **Apr 25, 2022**
Date of Publishing: **Jun 01, 2022**