# Is There Association between Ocular Surface Squamous Neoplasia and Hepatitis C Virus Infection?

Reham Refaat Shabana, MSc, Aiman Abdel Tawab Hashish, MD, Amr Mahmoud Awara, MD, Osama El Saied Shalaby, MD.

Ophthalmology Department, Faculty of Medicine, Tanta University, Egypt.
dr_rehamshabana@yahoo.com

**Abstract:** Background: Ocular surface squamous neoplasia (OSSN) is a term used to describe neoplastic epithelial changes of the conjunctiva, the cornea and the limbus ranging from squamous dysplasia to invasive squamous cell carcinoma. In recent times, OSSN is not uncommon and seems to be on the rise in Egypt. Aim: To detect if there is association between OSSN and HCV infection. Design: Prospective interventional case series. Patients and methods: This study included 58 eyes of 54 patients presented to the outpatient clinic of Tanta University Eye Hospital who were suspected clinically to have OSSN over a period of two years from January 2016 to January 2018. Results: The age of the studied patients ranged from 8 years to 74 years with the mean 52.9 years. Males were predominantly affected accounting for 88.9 %. 57.4% of the patients were HCV positive and 16.1% of the HCV positive patients were first discovered to have the viral infection. Conclusion: OSSN was observed more in older males and with outdoor occupations. Papillomatous lesion was the most common variety. HCV positive individuals had an increased incidence of OSSN. OSSN may be the first manifestation of underlying HCV infection.
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## 1. Introduction

The Ocular Surface Squamous Neoplasia (OSSN) is a broad term including conjunctival intraepithelial neoplastic lesions (CIN) and invasive squamous cell carcinoma (SCC) of conjunctiva, limbus and cornea. CIN includes varying grades of dysplasia, ranging from mild, moderate, severe dysplasia to carcinoma in situ (CIS). The term OSSN was first described in 1995 by Lee and Hirst. **(1)**

A number of risk factors, including ultraviolet exposure, genetic predisposition, immunosuppression, old age, human papilloma virus (HPV) infection, human immunodeficiency virus (HIV) seropositivity and smoking, have been associated with the appearance of OSSN. **(2)**

The clinical symptoms are generally non-specific; vary from asymptomatic to chronic irritation, redness, and varying degrees of visual involvement determined by the extension of lesions to the visual axis. Clinical patterns may be papilliform, as well as velvety, gelatinous, leukoplakic, nodular or even diffuse fashion. The lesions most commonly arise in the interpalpebral area of perilimbal conjunctiva. **(3)**

## 2. Patients and Methods

This study was prospective interventional case series; it included:

58 eyes of 54 patients presented to the outpatient clinic of Tanta University Eye Hospital who were suspected clinically to have OSSN over a period of two years from January 2016 to January2018.

**Inclusion criteria**: patients with:

- Any suspicious ocular surface lesion that met the criteria of OSSN e.g: gelatinous mass, leukoplakic, papilliform or diffuse lesions.

**Exclusion criteria:** patients with:

- Allergic conjunctival lesions.
- Degenerative conjunctival or corneal lesions eg: pterygium, pingecula or corneal degenerations.
- Other ocular tumors e.g: tumors of the iris or the ciliary body.

**Complete ophthalmological evaluation was done for all patients including:**

1. Detailed history taking.
2. Clinical examination.
3. Investigations.

**Detailed history taking:**

Proper history was taken from all patients including: Age, sex.

Symptoms of ocular surface lesion e.g: swelling, disfigurement, FB sensation, redness and visual impairment.

Past history of Hepatitis C Virus (HCV) infection or surgical excision of previous ocular surface neoplastic lesions.

**2. Clinical examination:**

❖ **General:**

General examination was done to all patients

including testing the visual acuity, ocular motility and slit-lamp examination of the lids, conjunctiva, cornea, sclera, anterior chamber, iris, pupil and the lens of both eyes.

❖ **Specific:**

- **Slit lamp evaluation of the OSSN lesion**:

All patients underwent detailed slit lamp examination of OSSN lesion including:

**Laterality:** unilateral and bilateral.

**Site:** conjunctival, perilimbal, corneoconjunctival and purely corneal.

**Size:** length, width and thickness. Shape: papillomatous, leukoplakic, gelatinous, nodular and diffuse.

**Surface:** leukoplakic patches and pigmentations. Feeder vessels.

**Dilated fundus examination**:

It was done with the indirect ophthalmoscope to assess the intraocular invasion of the tumor and exclude other tumors e.g: choroidal melanoma.

**3. Investigations:**

- **B-scan ultrasonography**: it was done only in cases with media opacity, to exclude intraocular lesions.

**-UBM (Ultrasound Bio Microscopy):** to detect angle invasion and exclude tumors of the iris and ciliary body.

**-Laboratory investigation:**

Serum anti- HCV antibodies were done to all cases.

HCV PCR (Polymerase Chain Reaction) was done for patients with positive anti-HCV Abs only.

**Internal medicine consultation for certain cases:**

It was done for HCV positive patients to receive their adequate treatment.

**Treatment:**

- All patients underwent combined surgical and medical treatment as following:

Complete surgical excision of the lesion was done with the following **4 Golden Rules**:

1-Wide safety margin (4mm). 2- No touch of the lesion.

3- No wash. (Dry method).

4- Double freeze-slow thaw cryotherapy.

Histopathological examination: The surgical biopsies were sent for histopathological laboratory for the definitive diagnosis of OSSN and accurate detection of its grade and were obtained after one week.

Medical treatment was given one week after surgery in the form of 5-fluorouracil (5-FU) 1% eye drop prepared from ampule (250mg/5ml) we took 1ml with 5ml syringe and added 4ml of tears natural eye drop so that the concentration became 10mg/ml and was put in a bottle for topical application as eye drop 4 times per day for one week and stopped for the next 3 weeks as a cycle (1week on – 3weeks off) for3cycles.

## 3. Results

This study included 58 eyes of 54 patients the age of the studied patients ranged from 8 years to 74 years with the mean 52.9 ± 15.57 years. They were 48 males (88.9%) and 6 females (11.1%). The results revealed that 50 patients (92.6%) had unilateral OSSN, while 4 patients (7.4%) had bilateral lesions; one of them (25%) was HCV positive.

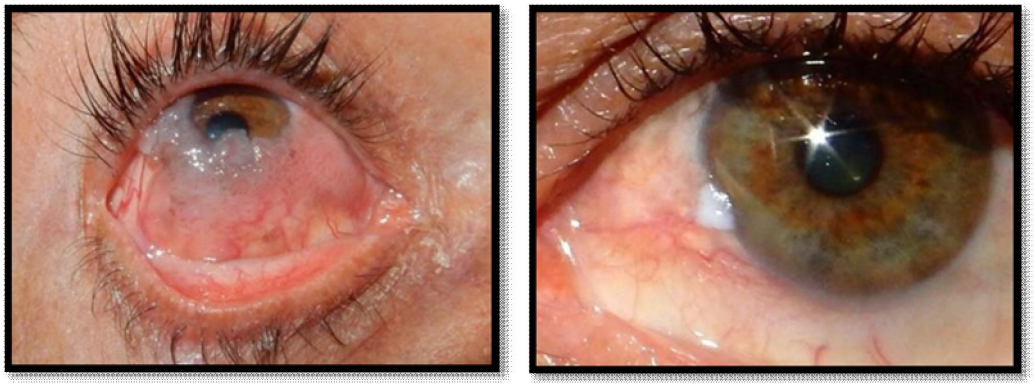

**Figure (1):** 49 years old HCV positive patient with bilateral OSSN lesions. Right eye showing large diffuse corneoconjunctival lesion, left eye showing small perilimbal gelatinous lesion.

There were 25 eyes with conjunctival & perilimbal lesions, 25 eyes with corneo-conjunctival lesions and 8 eyes with pure corneal lesions. 81% of the lesions were nasal and 19% were temporal.

There were 33 eyes with OSSN lesions less than or equal to 5 clock hours (or 10mm basal diameter) and 25 eyes with lesions greater than 5 clock hours (or greater than 10mm basal diameter). There were 32 eyes with papillomatous lesions, 17 eyes with gelatinous lesions and 9 eyes with leukoplakic lesion.

The results revealed that 45 eyes had primary OSSN lesions while 13 eyes had recurrent OSSN lesions.

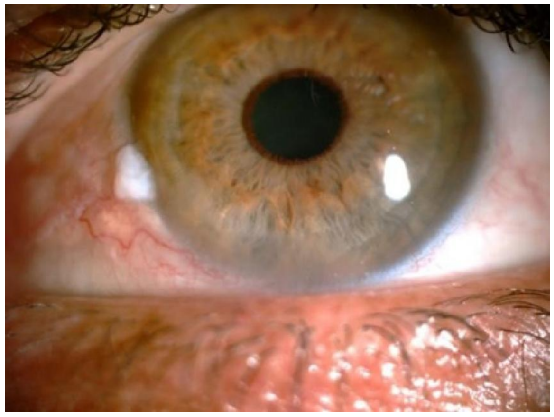

**Figure (2):** Nasal perilimbal OSSN lesion.

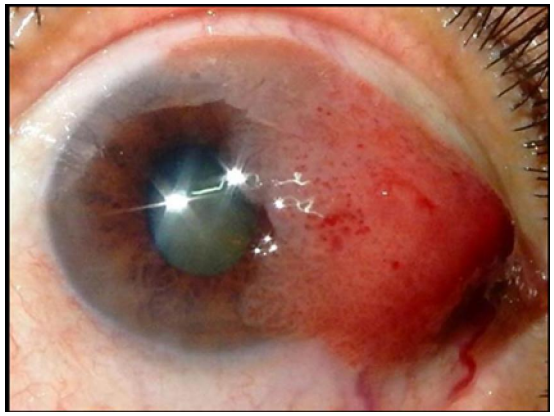

**Figure (3):** Temporal corneoconjunctival OSSN lesion.

**Figure (4):** Large papillomatous OSSN lesion.

Serum anti- HCV antibodies were done to all cases. It was positive in 31patients (57.4%), and negative in 23 patients (42.6%). HCV PCR (Polymerase Chain Reaction) was done for patients with positive anti- HCV Abs only that confirmed the diagnosis and detected the accurate measurement of the virus titer in the patient serum. 16.1% of the hepatitis C positive patients were first discovered to have the viral infection after performing this investigation.

**Table (1):** HCV seropositivity among the study population.

| HCV | frequency | percent |
|---|---|---|
| **Positive** | 31 | 57.4% |
| **Negative** | 23 | 42.6% |
| **Total** | 54 | 100% |

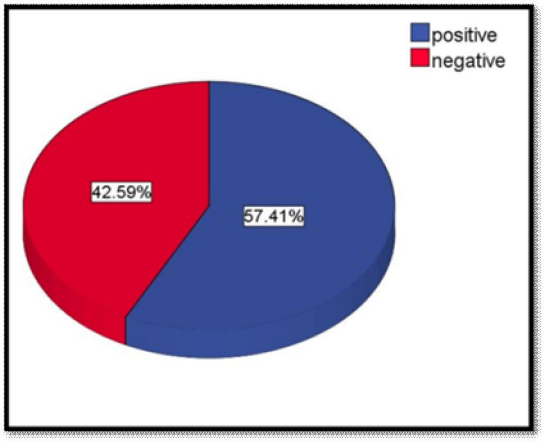


**Figure (5):** Pie chart showing HCV seropositivity among the study population.

Results revealed that there was statistically significant correlation between HCV seropositivity and the tumor size **(P-value <0.001**)** so that larger tumors were detected in 68.75% of HCV positive patients.

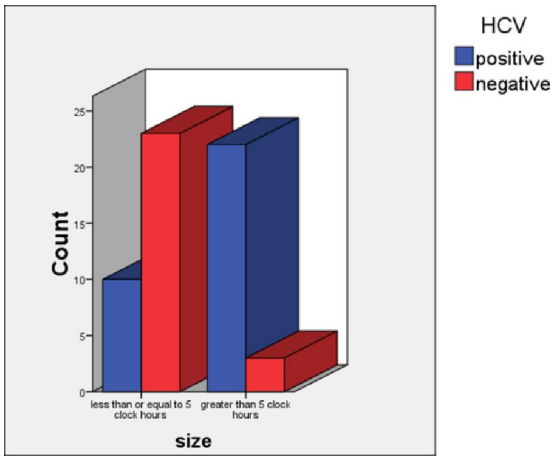


**Figure (6):** Bar chart showing correlation between HCV seropositivity and OSSN size.

**Table (2):** Correlation between HCV seropositivity and OSSN size.

| Size of OSSN | HCV | | Total |
|---|---|---|---|
| | positive | negative | |
| less than or equal to 5 clock hours (or 10mm basal diameter) | 10 | 23 | 33 |
| greater than 5 clock hours (or 10mm basal diameter) | 22 | 3 | 25 |
| Total | 32 | 26 | 58 |
| **Chi-Square** | **X2** | 19.145 | |
| | **P-value** | <0.001** | |

There was no statistically significant correlation between HCV seropositivity and OSSN shape **(P-value 0.292).**

**Table (3):** Correlation between HCV seropositivity and OSSN shape.

| Shape of OSSN | HCV | | Total |
|---|---|---|---|
| | positive | negative | |
| Papillomatous | 20 | 12 | 32 |
| Gelatinous | 9 | 8 | 17 |
| Leukoplakic | 3 | 6 | 9 |
| Total | 32 | 26 | 58 |
| **Chi-Square** | **X2** | 2.465 | |
| | **P-value** | 0.292 | |

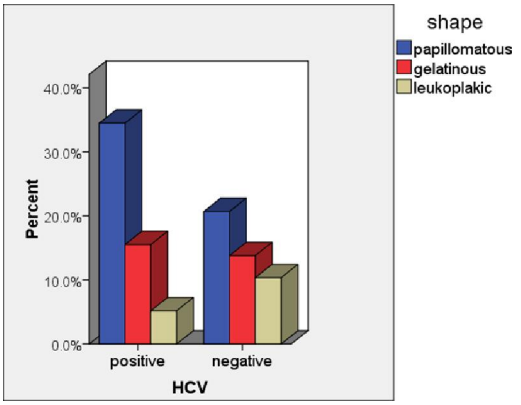


**Figure (7):** Correlation between HCV seropositivity and OSSN shape.

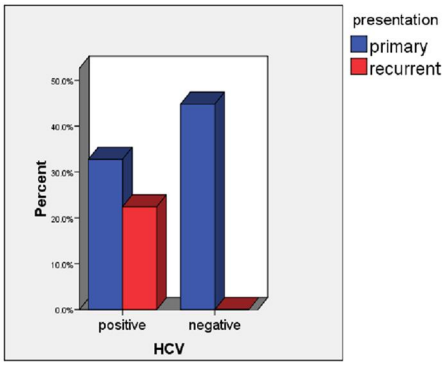


**Figure (8):** Correlation between HCV seropositivity and the presentation of OSSN lesions whether primary or recurrent.

There was also statistically significant correlation between HCV seropositivity and the presentation of OSSN lesions whether primary or recurrent. **(P-value 0.001**).** So that, all patients presented with recurrent OSSN lesions were HCV positive.

**Table (4):** Correlation between HCV seropositivity and the presentation of OSSN lesions whether primary or recurrent.

| Presentation | HCV | | Total |
|---|---|---|---|
| | positive | negative | |
| primary | 19 | 26 | 45 |
| recurrent | 13 | 0 | 13 |
| Total | 32 | 26 | 58 |
| **Chi-Square** | **X2** | 13.614 | |
| | **P-value** | 0.001** | |

## 4. Discussion

OSSN is a term used to describe pre-cancerous and cancerous epithelial lesions of the conjunctiva, the limbus and the cornea. It includes the spectrum of dysplasia, carcinoma in-situ (CIS) and invasive SCC. **(1)**

In a retrospective study that was done on 113 patients in India from February 2012 to January 2015, the age of the cases ranged from 18 to 78 years with mean 45.20 years. 65.48% of those affected were males**. (4)**

Our results revealed that 50 patients (92.6%) had unilateral OSSN, while 4 patients (7.4%) had bilateral lesions; one of them (25%) was HCV positive.

Documented cases of bilateral ocular surface squamous neoplasia (OSSN) are rare. [(5)]A case report was published in 2003. It was about 86 years old white woman who was referred to the Doheny Eye Institute for evaluation of conjunctival lesions in both eyes and surgical biopsies were obtained and revealed bilateral carcinoma insitu. [(6)]

Our results revealed that (57.4%) of the patients were HCV positive, 16.1% of the hepatitis C positive patients were first discovered to have the viral infection during this study. There was statistically significant correlation between HCV seropositivity and the tumor size so that larger tumors were detected in 68.75% of HCV positive patients. There was no statistically significant correlation between HCV seropositivity and OSSN shape but there was statistically significant correlation between HCV seropositivity and the presentation of OSSN lesions whether primary or recurrent because all patients presented with recurrent OSSN lesions were HCV positive.

Most of the studies of OSSN in the review of literature have proved that there is association between OSSN and HPV and HIV infections. These studies have considered that HPV and HIV infections are risk factors for OSSN. [(2,7,8)].

In 2009, there was a study about prevalence and epidemiology of HCV in patients with squamous cell carcinoma of the head and neck. It was retrospective study on patients diagnosed with squamous cell carcinoma of the head and neck who were analyzed to determine whether they were infected with HCV or not. In this study, 21% of these patients were infected with HCV. [(9)]

Another study published in October 2017, revealed that there may be a potentially new association between OSSN and HCV. It was a case report of a woman in her 80s with a history of chronic HCV infection presented with 2-weeks history of conjunctival mass in her right eye, surgical excision was done and it was SCC. [(10)]

**Conclusions**

OSSN is a common ocular surface lesion. It is mostly unilateral and observed more in older males. Papillomatous lesion is the commonest variety. HCV positive individuals have an increased incidence of OSSN. OSSN may be the first manifestation of underlying HCV infection.

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