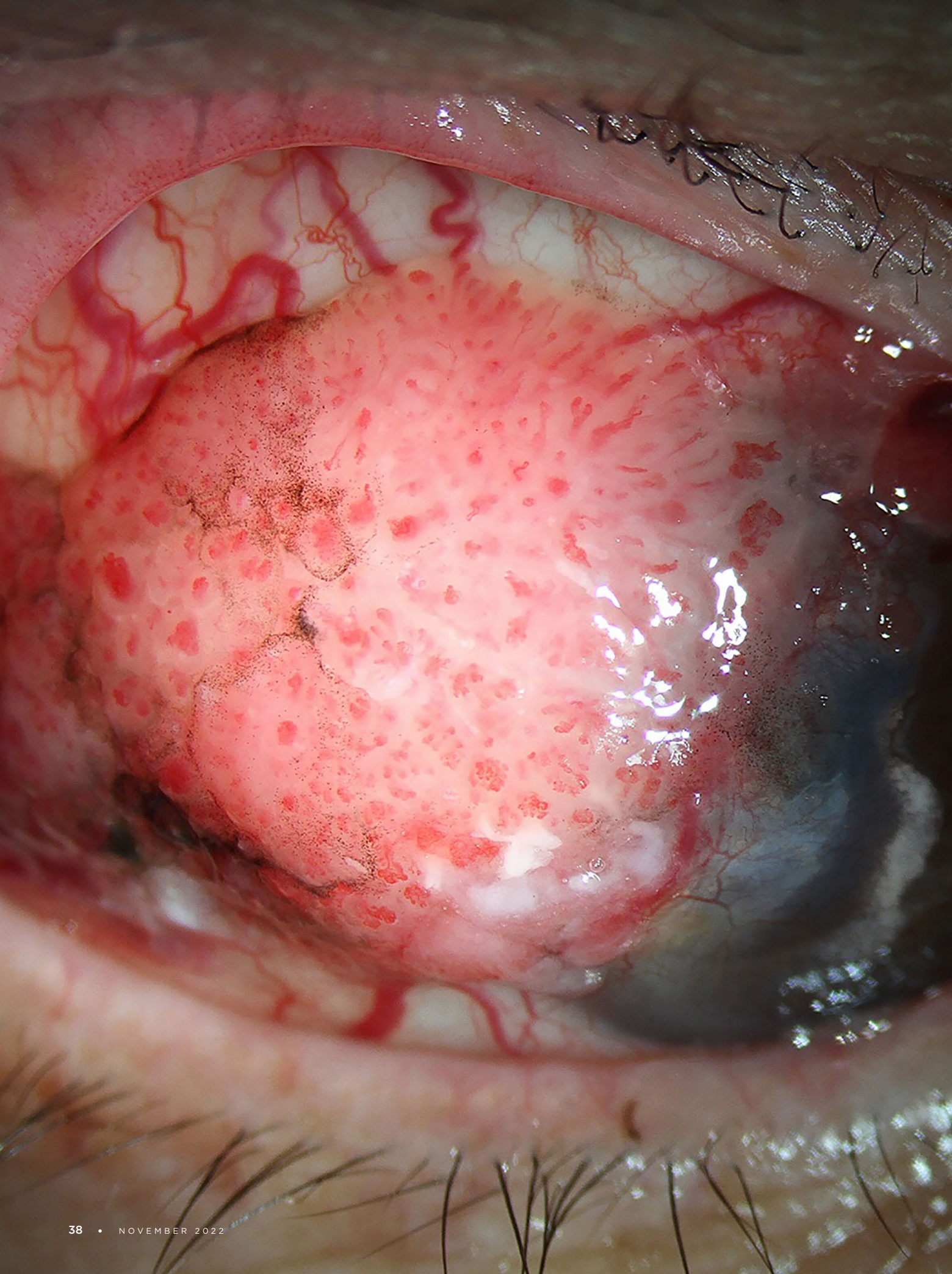


New Approaches With OSSN

While surgical excision has traditionally been the gold standard for diagnosing and treating ocular surface squamous neoplasia, high-resolution imaging and topical therapies are increasingly popular as valuable and effective strategies.

By Mike Mott, Contributing Writer

OCULAR SURFACE SQUAMOUS NEOplasia (OSSN) is the most common ocular surface malignancy of the cornea and conjunctiva. It encompasses a wide spectrum of disease, ranging in severity from mild epithelial dysplasia to invasive squamous cell carcinoma (SCC). And while OSSN typically presents as a localized, slow-growing tumor with a good prognosis, in rare cases, it can invade the globe, sinuses, or orbit.

Early detection is key to decrease the risk of locally aggressive disease. Although surgical excision has been the gold standard for decades, more recent advances in imaging and pharmacotherapy have revolutionized the diagnosis and treatment of OSSN.

Who's at Risk?

The risk of developing OSSN is determined by both environmental and host factors. It typically presents in older white men, and sun exposure is the most significant risk factor, said Anat Galor, MD, MSPH, at Bascom Palmer Eye Institute in Miami. Other risk factors more weakly associated with OSSN include cigarette smoking and vitamin A deficiency.

Patients with immune dysregulation also are at higher risk of developing OSSN, Dr. Galor said. For instance, HIV and human papilloma virus (HPV) have been associated with OSSN, perhaps due to the inhibition of immune cells' tumor recognition or impaired effector function. This risk profile also extends to patients on immunosuppressive medication following an organ transplant, said Dr. Galor, as well as to those with lymphoma and autoimmune disorders such as atopy. In addition, adolescent patients with xeroderma pigmentosum —a rare genetic disorder associated with defective DNA repair—often develop the most difficult cases of OSSN.

Presentation and Differential Diagnosis

On examination, OSSN can appear as a flat or elevated lesion, but it typically presents as a vascularized mass in the interpalpebral limbal area. While corneal involvement is typically opalescent, conjunctival features often include papillary, gelatinous, and nodular epithelial changes, said Carol L. Karp, MD, also at the Bascom Palmer Eye Institute. As OSSN also can be bilateral or multifocal in nature, she said, "it is very important to examine both eyes and to evert the eyelids."

And because of the shared risk factor of ultraviolet (UV) light exposure, OSSN can resemble other ocular surface lesions such as pterygia and pinguecula, said Carol L. Shields, MD, at Wills Eye Hospital in Philadelphia. "Papilloma is another lesion that can look very similar to squamous

Jason S. Calhoun, COA

neoplasia due to the small hairpin feeder vessels they have in common," said Dr. Shields. "When considering a differential diagnosis, you also don't want to forget other masqueraders like amelanotic melanoma, conjunctival lymphoma, sebaceous cell carcinoma, and amelanotic nevus."

Diagnosis: Biopsy Versus Imaging

The case for biopsy. Incisional and excisional biopsies alongside histopathologic analysis allow for the definitive OSSN diagnosis, said Jasmine H. Francis, MD, at Memorial Sloan Kettering Cancer Center in New York City.

"A biopsy not only confirms the diagnosis and distinguishes it from other entities in the differential diagnosis—most importantly, corneal/conjunctival intraepithelial neoplasia versus SCC—but also provides histopathological information that's helpful for prognostication," Dr. Francis said. This includes the lesion size, mitotic index, extent of disease, depth and degree of invasion, and any perineural involvement.

A biopsy is also important when the presentation is not characteristic, said Dr. Galor. "Especially with small lesions, or with lesions that coexist with other ocular surface diseases, like atopy or pterygium, it can be very difficult to definitively diagnose OSSN. If I am unsure, I have a low threshold for biopsy."

The case for imaging. However, biopsies are associated with some adverse sequelae, said Dr. Francis. Surgical risks include conjunctival scarring, symblepharon, and conjunctival hyperemia as well as limbal stem cell deficiency (see under "Treatment: Surgery or Medication?," on page 45).

As a result, a growing number of ophthalmologists are including noninvasive imaging modalities in their armamentarium. These include high-resolution (HR) anterior segment OCT, in vivo confocal microscopy, and ultrasound biomicroscopy.

Diagnosis: Imaging Options

HR-OCT. "The gold standard for the diagnosis of OSSN is getting tissue," said Dr. Karp. "That's plain and simple, but the pendulum has swung toward imaging, and we're finding that a very large number of ophthalmologists are now employing HR-OCT alongside clinical documentation."

Dr. Karp and her group at Bascom Palmer have pioneered the use of HR-OCT for noninvasively diagnosing OSSN. They've found the imaging to be both highly sensitive and specific and capable of distinguishing OSSN in the setting of other coexisting ocular surface diseases.[1-4]

"With a nice cross-section view of the cornea and conjunctiva, we've discovered that OSSN has very characteristic features on HR-OCT," said Dr. Galor. "The typical finding is an abrupt 90-degree transition from normal epithelium to an abnormal epithelium that is thickened and hyperreflective."

HR-OCT also can be used to guide manage-

Potential Link Between Vaping and Ocular Cancer

Electronic cigarettes have been touted as a safer alternative to standard cigarettes, but that is far from true. Cases of vaping-related lung disease such as acute respiratory distress requiring intensive care are appearing more frequently in the medical literature, said Dr. Shields. And physicians are growing increasingly concerned about what other types of disease will result from chronic exposure to vapors from e-cigarettes.

In the first study to connect vaping and ocular cancer, Dr. Shields and her colleagues at Wills Eye Hospital reported on conjunctival intraepithelial neoplasia (CIN) in a 22-year-old male with a five-year history of e-cigarette use.[1] The young man noted painless blurred vision in his right eye due to mild corneal opacification that was unresponsive to antiviral therapy. A year later, a keratectomy revealed high-grade CIN, and he was treated with IFNα-2b.

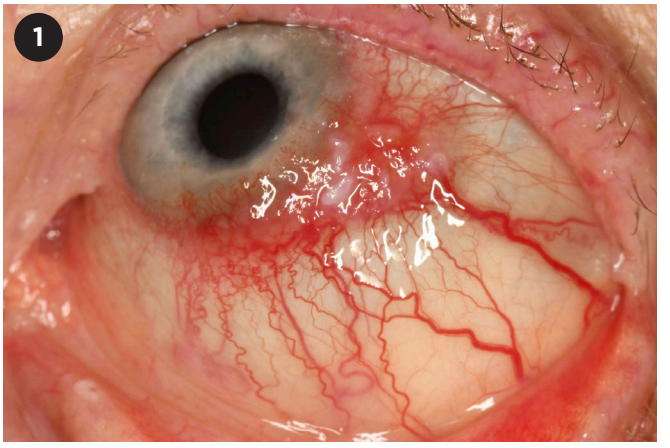
"Because the patient denied any immune suppression, HIV, organ transplantation, or xeroderma pigmentosum, we associated the squamous neoplasia with chronic vapor exposure," said Dr. Shields. And that wasn't exactly a surprise, she said. "We see this all the time in traditional cigarette smokers. The carcinogens blown out of the mouth settle on the mucous membranes of both eyes, and patients tend to get a more aggressive variant of OSSN that occurs in the inferior fornix rather than the limbus."

What is a surprise, said Dr. Shields, is the continued perception that e-cigarettes are somehow safe. "The public seems to think, 'Oh, it's just kids vaping. They're not going to have any problems.' Wrong. If we've already seen carcinoma in the eye, you can bet we're going to see it in the lungs."

1 Shields CL et al. *Indian J Ophthalmol.* 2020;68(8):1699-1701.

ment of lesions that appear to have resolved clinically but continue to show subclinical disease by HR-OCT. "This is important because it prevents us from prematurely terminating treatment," said Dr. Karp. "At the same time, because we can continue to monitor for complete resolution, we can prevent the overuse of topical therapies and the associated potential for ocular toxicity and increased cost to the patient."

Although no sensitivity or specificity will ever be exactly 100%, HR-OCT has revolutionized her practice, said Dr. Karp. "Tissue is always the issue, and if you ever have any doubts with your imaging results, a histological biopsy will give you the final answer," she said. "But I call HR-OCT my 'optical biopsy,' because, in my hands, it helps me tremendously to 'see' morphological features of the tumor to guide diagnosis in the vast majority of patients with extremely high success."



SQUAMOUS CELL CARCINOMA. *An 88-year-old man with a red gelatinous mass at the limbus in his left eye. The prominent dilated feeder vessels are consistent with conjunctival squamous cell carcinoma.*

Courtesy of Carol L. Shields, MD

A caution regarding noncancerous metaplasia. However, HR-OCT is not without its limitations, said Dr. Galor. New evidence suggests that HR-OCT is less than ideal at distinguishing between noncancerous squamous metaplasia and OSSN.[5] As a result, many patients with metaplasia may be incorrectly diagnosed with OSSN based on OCT imaging and undergo unnecessary treatment. "Like OSSN, metaplasia displays a thickened, hyperreflective epithelium on OCT," said Dr. Galor. "However, a deeper look at the cellular level of metaplasia doesn't reveal any dysplasia."

This is a good example of when you can't use OCT in isolation, Dr. Galor said. "Metaplasia tends to occur in more pigmented individuals, and clinically, the borders of the lesion appear smoother than OSSN lesions, so you need to look at the entire clinical picture. Ultimately, OCT has revolutionized our practice because it's allowed us to see at a level that we couldn't see before—but it's still not a cellular level."

In vivo confocal microscopy. Although it's a less-accessible and more time-consuming means of imaging ocular surface tumors, in vivo confocal microscopy does allow for distinguishing abnormalities at the cellular level, providing insight into nuclear-to-cytoplasmic ratios, pleomorphism, and hyperreflective and indistinctly bordered cytoplasm, said Dr. Francis.

It can also be useful for determining the extent of subclinical disease, given its ability to view cytologic details from a microscopic perspective. However, the quality of the imaging relies on the illumination of the object and its reflected light, Dr. Francis said. "Ocular surface tumors have less than ideal optical properties due to keratinization, hypoxia, and nontransparent proliferation, and therefore interpretation of confocal microscopy images is challenging, particularly when there is leukoplakia." As a result, said Dr. Francis, it's not common for confocal microscopy on its own to markedly influence the clinical management of OSSN.

Ultrasound biomicroscopy. Although it's not able to provide the epithelial details seen with HR-OCT or confocal microscopy, ultrasound biomicroscopy (UBM) does offer higher optical penetration and better resolution of a lesion's posterior margins, said Dr. Karp. As such, it can be a helpful tool for distinguishing the posterior extent of the disease and thus can help direct management.

"UBM is something that I utilize whenever a lesion appears stuck on the eye," Dr. Karp said. "So if I can slide the lesion back and forth with my cotton swab, it's superficial. When it's fixed to the eyeball, I worry that there's penetration into the globe itself." In this event, confirmation with UBM is important, she said, to help guide the management plan.

Moreover, Dr. Karp said, in such cases, surgical treatment is needed. Topical therapy may be used in a neoadjuvant manner to "chemo-reduce" the tumor, but the patient is likely to need eventual surgical excision of the residual tumor.

Treatment: Surgery or Medication?

The case for surgical excision. The gold-standard treatment for OSSN has been surgical excision with wide margins using the "no-touch" technique, said Dr. Shields. Adjuvant cryotherapy is also commonly applied to the conjunctival margins. Cautery and absolute alcohol "cleanup" are used on the bare

scleral bed to eradicate any remaining dysplastic or neoplastic cells.

"We prefer surgery as our first approach," said Dr. Shields. "We tend to perform surgical excision when first meeting a patient." From her perspective, surgical excision has four advantages: "One, it's fast and definite—within 20 minutes, the lesion is off and we know it's off; two, insurance covers it; three, pathology can give us detailed results; and four, we can assure the patient, 'Don't worry. It was only squamous cell carcinoma, not melanoma.'"

Surgical challenges to consider. There is a challenge to surgical intervention, said Dr. Francis, and that's the balance between taking enough tissue to remove the cancerous cells but not so much that you affect the patient's vision.

"A surgical excision is very well suited for smaller, well-circumscribed lesions," Dr. Francis said. "But if you have a tumor that is more than 180 degrees around the limbus, you'll want to avoid removing all of that tissue because those limbal stem cells are so necessary for patients to retain their vision."

A majority of patients will not have that degree of limbal involvement, but for those who do, a careful debulking or incisional biopsy is the first step, said Dr. Francis. "The challenge is that, if you don't treat the cancer at the limbus, the cancer is going to destroy the stem cells. However, treatment can have the same effect—although medical management does this to a lesser degree."

Thus, even when the disease is adequately treated, limbal stem cell deficiency can remain or even be accentuated, Dr. Francis said. This can lead to corneal opacification and visual decline that is difficult to reverse. In some scenarios, limbal stem cell transplantation from the fellow eye may be an option to mitigate this, she added.

The case for medical management. Overall, there is no question that excisional biopsy is an effective treatment for OSSN, said Dr. Shields. "In our hands, recurrence is not that common following surgery. Despite what I see in the literature, in experienced hands, recurrent OSSN is less than 5%." But because of the negative sequelae associated with excisional surgery—and the fact that many patients prefer to avoid surgical intervention—a number of pharmacotherapies have emerged to provide ophthalmologists with valuable alternatives, said Dr. Karp.

"The pendulum for treating OSSN has definitely swung toward medical therapy," Dr. Karp said. An increasing number of surgeons are opting for topical therapy as a first-line treatment or an adjuvant alongside surgery, especially for recurrent cases and lesions that are diffuse with

Gene Targeting and the Future of OSSN Treatment

Gene targeting as it relates to OSSN is something that will evolve in the future, said Dr. Francis. At the moment, researchers are trying to discover the larger genetic picture behind the disease before developing genetically informed therapies.

Many recent studies have revealed a significant range and variety of genetic alterations present in OSSN. For example, the Bascom Palmer team has identified alterations in DNA repair and cell cycle genes (*TP53, MSH6, BRCA1,* and *BRCA2*) as well as those genes guiding cellular development and growth (*HGF* and *APC*).[1] In addition, the team found that mutations in the titin (TTN) gene not only were among the most common genetic aberrations in OSSN cases but also conveyed resistance to topical IFNα-2b.[2]

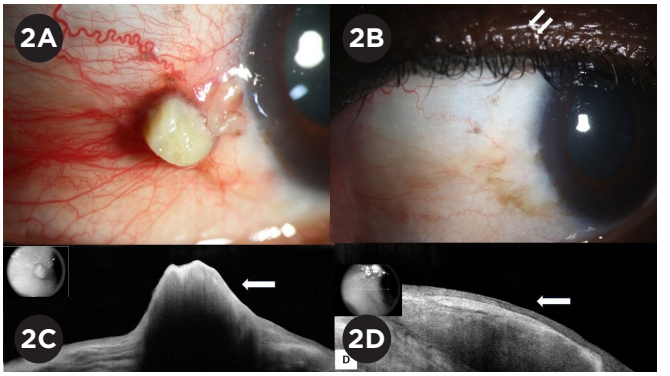
Other studies have hinted that *TP53*-associated SCC is more frequent in African than in European populations, said Dr. Francis. In addition, UV signature mutations such as TERT have been reported in SCC,[3,4] along with upregulation of matrix metalloproteinases and downregulation of clusterin.[5] And in other types of cutaneous and oral SCC, expression of these matrix metalloproteinases have correlated with higher-risk pathological features and lymph node invasion.[6]

Nonetheless, it remains largely unclear how genetic alterations drive OSSN pathogenesis and resistance to treatment, Dr. Francis noted. Thus, even though many of these genes might have actionable drug targets that could set the foundation for testing new therapeutics, the current genetic landscape is not close to influencing the primary management of OSSN.

1 Ramos-Betancourt N et al. *Ocul Surf.* 2020;18(4):627-632.
2 Djulbegovic MB et al. *Int J Biol Macromol.* 2022;195:93-101.
3 Jayaraj P et al. *Indian J Ophthalmol.* 2022;70(3):971-975.
4 Scholz S et al. *Invest Ophthalmol Vis Sci.* 2015;56(10):5854-5861.
5 Mahale A et al. *Mod Pathol.* 2016;29(5):452-460.
6 Patil R et al. *J Oral Maxillofac Pathol.* 2021;25(2):239-246.

indistinct margins, she noted. "I have been a big proponent [of this shift] since the 1990s because it really has the advantages of covering the entire ocular surface and reaching subclinical disease that, if left on the ocular surface with surgery, can cause significantly higher chances of recurrence."

Although clinicians need to take side effect profiles and costs into consideration, medical therapies are easy to use, Dr. Karp said. And this approach "can save stem cells. It can help avoid surgical procedures, which can lead to limbal stem cell deficiency and scarring. Topical therapy also can be used postoperatively to augment the success of surgery; it can reduce the chance of recurrence down to that of having negative margins."



BEFORE AND AFTER. *This 47-year-old Hispanic female had a limbal conjunctival lesion in her right eye. She was treated with four one-week cycles of 5-FU eyedrops. (2A) Note leukoplakic appearance of the lesion prior to treatment. (2B) Eye after treatment. (2C) Before treatment, HR-OCT shows thickened hyper-reflective epithelium (arrow). Note shadowing of posterior border due to highly thickened lesion. (2D) After treatment, note normalized thin epithelium (arrow).*

Treatment: Drug Options

Interferon. Interferon alpha 2b (IFNα-2b) is an immunomodulatory cytokine produced by immune cells to protect against viruses and microbes. Injected subconjunctivally or used as an eyedrop, the protein has antiproliferative, cytotoxic, and antigenic properties that help in identifying and targeting neoplastic cells.

As IFNα-2b is well tolerated and has an efficacy rate of up to 100%, it has been an ideal choice for many ophthalmologists, said Dr. Karp. "We pioneered the use of interferon in the 1990s when Steven L. Maskin, MD, published the first case of topical drops for treating limbal epithelial dysplasia," she said. "We then designed studies to evaluate it. I absolutely love it because it's so gentle."

However, IFNα-2b has a few drawbacks, said Dr. Galor. It requires refrigeration, and patients need to apply the drops four times a day until resolution, which can hinder compliance. And because it's an immunomodulator, patients with immune dysregulation often don't receive the same efficacy. IFNα-2b eyedrops must also be compounded, so it can be a more expensive option that's not always covered by insurance.

And there is an even bigger drawback: IFNα-2b is no longer being produced by the manufacturer, and U.S. institutions are seeing their stockpiles dwindle. "It was put to sleep during the COVID-19 pandemic for reasons that are unclear," said Dr. Galor. "It was close to an ideal treatment, but it's now gone."

Without a direct substitute, ophthalmologists find themselves in a transitional period, Dr. Francis noted. "There is some literature outside the United States on using IFNα-2a as a replacement, but it hasn't yet been well established as an agent for this particular indication."

5-FU. As a result of the IFNα-2b shortage, many ophthalmologists are now opting for 5-fluorouracil (5-FU) drops. "5-FU is now my favorite drug because it's extremely effective and extremely cost effective at roughly $50 a month for most patients," said Dr. Karp. The drop is a topical chemotherapy that blocks DNA formation and interrupts cell growth. "My regimen is four times a day for a week with three weeks off," so the treatment is relatively easy on patients, she said. Usually, four to six cycles are needed, she added.

However, 5-FU is associated with more unfavorable side effects than interferon. These can include mild ocular irritation, conjunctival congestion, filamentary keratitis, and superficial stromal melting. The latter is a relatively rare adverse event.

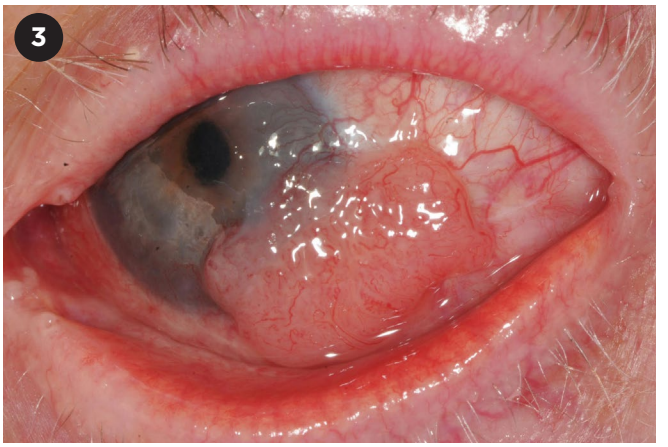
MMC. Mitomycin C (MMC) is an antimetabolite with antineoplastic and antibiotic properties that alkylates DNA and disrupts the production of RNA. Treatment with MMC is also cycled similar to 5-FU, said Dr. Shields, and it can be an effective drug under the right circumstances when all else fails. However, the side effect profile is much more severe and frequent than that of 5-FU. In addition to allergic conjunctivitis, hyperemia, and ectropion, MMC can induce punctal stenosis. As such, many ophthalmologists opt for punctal plug occlusion prior to initiating topical MMC.

Because of this toxicity, ophthalmologists consider MMC the drug of last resort, said Dr. Karp. "When I communicate treatment options to patients, I describe interferon as my 'angel

Courtesy of Carol L. Karp, MD

drop' and 5-FU as my 'baby devil drop.' MMC, however, is 'el Diablo,' because it definitely does not play nice with the ocular surface."

On the horizon. "Many of us would like to get away from using 5-FU and MMC and return to a nicer drug like IFNα-2b," said Dr. Shields. "Our patients had almost no complications, and they were very happy with the results. But if interferon is no longer a possibility, I do think there are other medications and treatments in the pipeline that could prove beneficial."



FUTURE THERAPIES. *Therapeutic options under investigation include HPV vaccines and nanoparticle conjugates.*

HPV vaccines. Drs. Karp and Galor are currently exploring novel immunomodulatory therapies for the treatment of OSSN.[6] While Dr. Galor noted that they don't know where this will lead, "We were recently able to resolve a case of conjunctival papilloma using two injections of an HPV vaccine as an off-label treatment in a patient who did not tolerate topical 5-FU," said Dr. Karp. "We are still exploring how this intervention may help our patients."

These results also call into question exactly what role HPV plays in OSSN, Dr. Galor said. At Bascom Palmer, for example, up to 70% of OSSN specimens harbor HPV—but in India, that percentage is close to zero. So although HPV is not necessary for OSSN to develop, said Dr. Galor, there is a potential contributive effect that might aid in the development of new therapeutics.

Photodynamic therapy. Another emerging option for the treatment of ocular cancer is photodynamic therapy, said Dr. Shields. For example, light-activated belzupacap sarotalocan (AU-011; Aura Biosciences) comprises viral nanoparticle conjugates that target and selectively destroy cancer cells in primary uveal melanoma. Having already been fast-tracked by the FDA for the treatment of bladder cancer, AU-011 holds promise for its ability to rapidly disrupt malignant cells and activate long-term antitumor immunity, said Dr. Shields.

As such, this technology could result in a much more precise, nonsurgical way to target ocular cancers—especially those invasive cases requiring adjunctive brachytherapy—all while preserving healthy surface cells, said Dr. Shields. "And because it can be performed with equipment commonly found in an ophthalmologist's office, this therapeutic drug looks to be very promising."

1 Kieval JZ et al. *Ophthalmology*. 2012;119(3):481-486.
2 Shousha MA et al. *Ophthalmology*. 2013:120(5):883-891.
3 Nanji AA et al. *Ocul Surf*. 2015;13(3):226-235.
4 Atallah M et al. *Ocul Surf*. 2017;15(4):688-695.
5 Stevens SM et al. *Cornea*. 2022. Published online April 9, 2022.
6 Sripawadkul W et al. *JAMA Ophthalmol*. 2022;140(4):434-435.

Meet the Experts

Jasmine H. Francis, MD Ophthalmic oncologist at Memorial Sloan Kettering Cancer Center in New York City. *Relevant financial disclosures: None.*

Anat Galor, MD, MSPH Staff physician at the Miami Veterans Affairs Medical Center and professor of ophthalmology at Bascom Palmer Eye Institute in Miami. *Relevant financial disclosures: None.*

Carol L. Karp, MD Professor of ophthalmology, Richard K. Forster Chair in Ophthalmology, and Dr. Ronald and Alicia Lepke Endowed Professor in Corneal and External Diseases at Bascom Palmer Eye Institute in Miami. *Relevant financial disclosures: None.*

Carol L. Shields, MD Chief of Ocular Oncology Service at Wills Eye Hospital and professor of ophthalmology at Thomas Jefferson University in Philadelphia. *Relevant financial disclosures: Aura Biosciences: C.*

See disclosure key, page 8.

For full disclosures, see this article at aao.org/eyenet.

Courtesy of Jasmine H. Francis, MD