

CLINICAL UPDATE

JSEI Study Weighs Risk of Macular Edema from Cancer Drugs

Could drugs that are mainstays for treating certain cancers have a side effect that is more common than previously believed: an elevated risk of microcystic macular edema? David Sarraf, MD, associate clinical professor at the Jules Stein Eye Institute (JSEI) has launched the first prospective cohort study aiming to determine the incidence of this visually-compromising complication in association with certain chemotherapeutics.

Microtubule inhibitors, or taxane drugs — including paclitaxel (Taxol), albumin-bound paclitaxel (Abraxane), and docetaxel (Taxotere) — are important forms of chemotherapy used in the treatment of breast, lung, stomach, and prostate cancers. But a number of recent case reports

(including one of the original case reports co-authored by Dr. Sarraf) have discovered an association between the use of these drugs and the development of cystoid macular edema (CME). The advent of high-definition spectral-domain optical coherence tomography (SD-OCT), a state-of-the-art ocular imaging technique, increases the sensitivity of detection and this prospective study may reveal that the incidence of taxane- and tamoxifen-induced microcystic maculopathy may be more common than prior reports would indicate.

“These macular cysts are difficult to identify with traditional ophthalmoscopic examination,” says Dr. Sarraf. “Identifying macular cysts require the high-definition capability of SD-



OCT, which has a 5-micron resolution and that has only recently been introduced to the retinal clinical arena.”

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Noninvasive Imaging Method Could Help Detect, Monitor Limbal Stem Cell Deficiency

A noninvasive imaging technique has the potential to play a significant role in the detection of early-stage limbal stem cell deficiency (LSCD), as well as providing a tool for monitoring LSCD patients’ response to treatment, Jules Stein Eye Institute (JSEI) researchers have found.

A research group headed by Sophie X. Deng, MD, PhD, assistant professor of

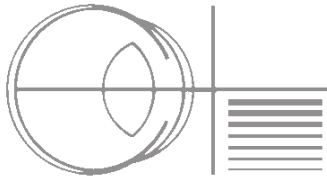
ophthalmology and director of JSEI’s Cornea Biology Laboratory, was able to use in vivo laser scanning confocal microscopy to analyze the cellular changes during various stages of the disease. Dr. Deng’s study, reported in *Archives of Ophthalmology*, was the first to use the confocal microscopy approach to describe the microstructural changes in LSCD.

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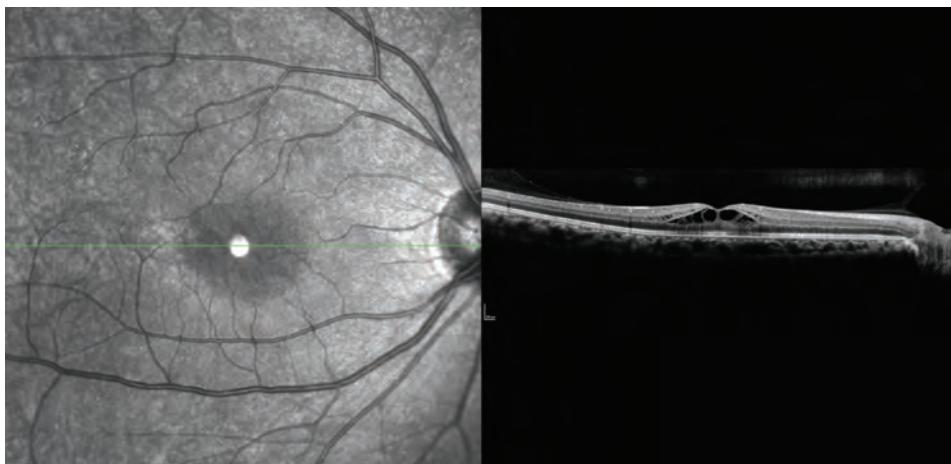
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Advances in Imaging Technology Enables More Accurate Assessment

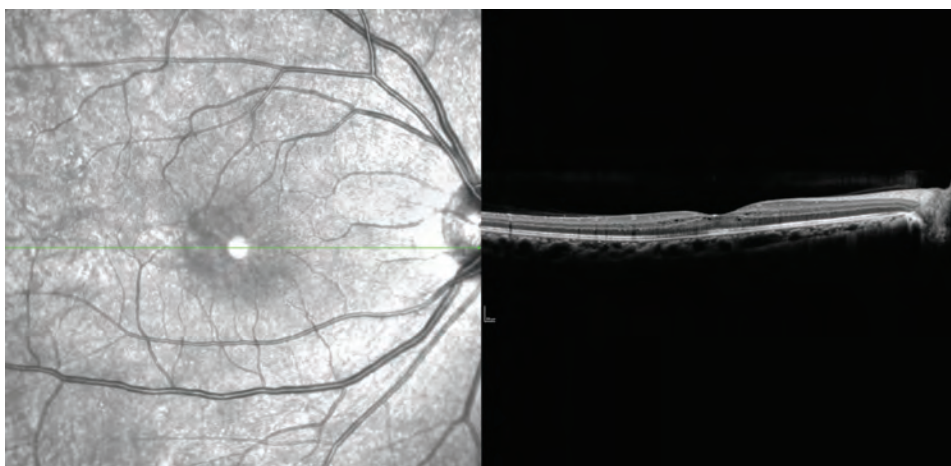
Optical coherence tomography has been used to image the macula for nearly two decades, but rapid advances in the technology, including the recent introduction of SD-OCT, have led to dramatic improvements in resolution and image quality. “With the advent of high-definition OCT imaging we are able to detect macular pathology previously not appreciated,” says Robert Beardsley, MD, a past JSEI resident who is a coauthor of the study protocol. “With the enhanced resolution of this imaging system, the fine details of the fovea are much more apparent, and the impact of these anti-cancer drugs can be more accurately assessed.”

The use of SD-OCT has resulted in several recent case reports of subclinical microcystic changes in the macula among patients on one of the taxane drugs. “The significance and etiology of the microcysts is not known, though patients can experience visual symptoms while on these medications significant enough to discontinue their use,” says Dr. Sarraf. “Importantly, the microcysts appear to be reversible with medication cessation and medical therapy.”

Dr. Sarraf recently identified their first patient with subjective and objective vision loss who demonstrated severe CME under SD-OCT imaging, although the CME was barely noted upon clinical ophthalmoscopic examination. The patient had been receiving weekly Abraxane therapy for nine months to treat metastatic breast cancer. The Abraxane was discontinued and replaced with a non-taxane chemotherapeutic; within three weeks, the CME had nearly resolved and the patient’s vision had improved. After six weeks the CME had completely resolved and vision had recovered to normal in each eye (20/15 OU). Only a handful of other such cases have been published in the world literature. “The case numbers are too low to make any definitive



▲ The first SD-OCT image shows significant CME OD while on Abraxane weekly for nine months.



▲ The Abraxane was stopped and three weeks later repeat SD-OCT shows nearly resolved CME OD. Similar outcome OS as well. VA improved from 20/40 to 20/25 OD.

conclusions,” says Dr. Beardsley. “Only by screening a large population of patients can the true incidence of the microcysts and the clinical course be better understood.”

Study Can Help to Inform Guidelines

In their study, “Taxanes and the Prospective Incidence of Cystoid Macular Edema Using Spectral Domain Optical Coherence Tomography,” Drs. Sarraf and Beardsley have set out to determine the incidence and characteristics of microcystic maculopathy in association with paclitaxel, albumin bound paclitaxel (Abraxane), and docetaxel therapy using high-resolution SD-OCT imaging. In collaboration with oncologists at UCLA’s Jonsson Comprehensive Cancer Center, breast

cancer patients receiving taxane (and tamoxifen) therapy are being referred for prospective screening with retinal examinations, as well as with SD-OCT imaging of the macula.

“Because they were isolated case reports, previous studies have failed to determine the incidence of microcystic maculopathy as determined by spectral domain OCT imaging in patients using these drugs,” explains Dr. Sarraf. “As a result, characterization of these cystic changes on a larger scale and a determination of the natural history and potential impact on vision are lacking. Such a determination is critical in order to establish guidelines for retinal screening examination and discontinuation of therapy.”

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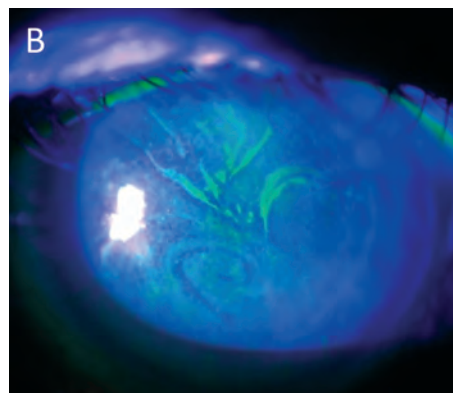
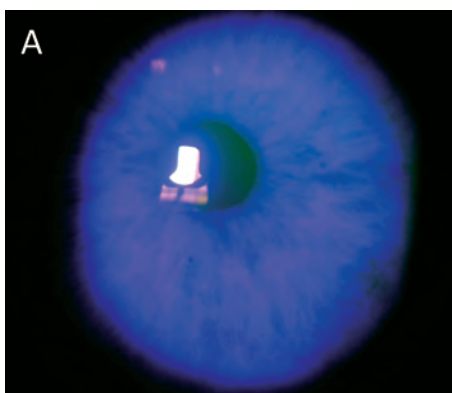
LCSD, in which the limbal stem cells are lost or become deficient, can cause unremitting pain along with significant visual impairment. It is most common as a result of chemical burns, but can also be found in patients who have had multiple intraocular surgeries, as well as those with Stevens-Johnson syndrome. Limbal stem cells are believed to play a role in maintaining the integrity of the corneal epithelial surface; when they become dysfunctional, the conjunctival epithelial cells move onto the cornea, reducing vision and causing pain.

Effective Test Needed to Quantify Limbal Stem Cell Damage

Diagnosing LSCD and monitoring patients' response to treatment have proved challenging. "The diagnosis of LSCD is mainly based on history and clinical presentation," Dr. Deng and colleagues wrote in the journal article. But, they noted, "At the time of presentation, patients with partial or sectoral LSCD often have very subtle changes that may be missed by clinical examination alone." Impression cytology, a diagnostic test for LSCD, has a high false-negative rate. There is no sensitive test to quantify limbal stem cell damage. "LSCD is a disease caused by the loss of limbal stem cells," says Dr. Deng. "It is important to investigate the cellular changes in the cornea and limbus where these cells are located to understand the pathogenesis of this disease."

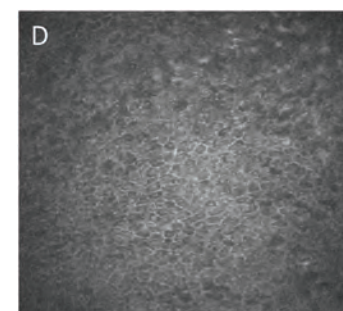
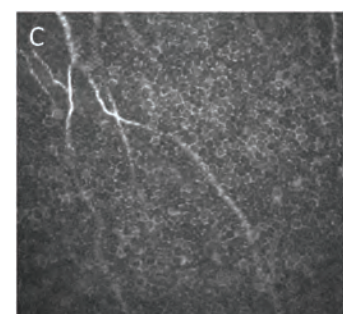
To do that, Dr. Deng's group turned to in vivo laser scanning confocal microscopy, an increasingly employed approach capable of producing high-resolution images of the ocular surface at the cellular level. In vivo laser scanning confocal microscopy is now commonly used to evaluate physiologic and pathologic changes in the cornea, conjunctiva, and limbus, but until Dr. Deng's study no one had used the imaging technique to elucidate and quantify the cellular changes in various stages of LSCD.

To evaluate the cellular changes occurring in the corneal epithelium and surrounding structures in LSCD, Dr. Deng and colleagues used in vivo laser scanning confocal microscopy for examinations of 27 eyes of 20 LSCD patients, along with 12 eyes of 10 healthy subjects used as controls. Following a slit-lamp exam, the LSCD patients were classified into three groups based on their disease stage. Through confocal imaging of the central cornea and four limbal locations, the researchers evaluated morphologic characteristics of the corneal epithelium, basal epithelial cell density, and sub-basal nerve density in the central cornea. In addition, they weighed a potential correlation between the decrease in basal epithelial density and sub-basal nerve density in LSCD.



A) Normal clear and smooth corneal epithelial surface without fluorescein staining. B) Pooling and stippling of fluorescein staining in a classic vortex pattern in sectoral limbal stem cell deficiency.

"Patients with partial or sectoral LSCD often have very subtle changes that may be missed by clinical examination alone."



▲ In vivo confocal image of basal epithelial cells in normal eyes (C) and in sectoral limbal stem cell deficiency (D).



AARP The Magazine ranks Jules Stein Eye Institute as No. 3 in the country for complex eye-care referrals.



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Finding Could Change Understanding of LSCD

The researchers found that patients with early and intermediate stages of the disease experienced a significant reduction in the density of the basal epithelial cells and the sub-basal nerve cells compared with the control group. In the patients with late-stage disease, normal basal epithelial-cell morphology was completely lost and sub-basal nerves were absent. The reduction in basal cell density correlated with the decrease in sub-basal nerve density in LSCD patients.

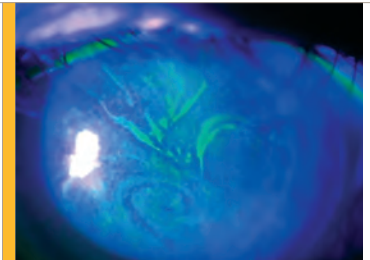
“As we had expected, the basal cells were affected as a result of the decreased limbal stem cells; however, we did not realize that there would be a reduction in the nerve density,” says Dr Deng. “This is a very interesting finding as it may change our current understanding of LSCD. Neurotrophic factors

might be important in the pathogenesis of limbal stem cell deficiency.”

Dr. Deng believes a better grasp of the significant cellular changes in early LSCD as revealed by in vivo laser scanning confocal microscopy could lead to an improved understanding of the underlying disease process. Moreover, the study points to the potential for an effective and noninvasive new approach to the diagnosis and management of LSCD. “We need to continue the study and further delineate the changes,” Dr Deng says. “However, these findings could be used to identify early LSCD and to classify the disease in a noninvasive manner. This method could also be used to monitor the treatment outcome in the future.”



Reference: F. Thomas (S. Deng), *Ophthalmology Times Europe*, 2012;8(2):45.



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