Resident Perspectives: Subclinical ocular inflammation in patients with recurrent aphthous stomatitis

Recurrent aphthous stomatitis is the most common oral mucosal ulcerative disease, primarily affecting the buccal mucosa and tongue.1 This condition has been linked to several systemic, inflammatory, genetic, nutritional, and microbial factors.1 Most notably, recurrent aphthous stomatitis (RAS) has been noted to be one of the most common signs of Behcet’s disease, present in 97% to 100% of all patients diagnosed with Behcet’s disease.2 Given that RAS often presents as the initial sign of Behcet’s disease, which can have significant ophthalmic manifestations, it would be beneficial to understand possible ophthalmic features associated with RAS. Gaining a better understanding of potential ophthalmic features associated with RAS may help achieve earlier diagnosis and improved patient outcomes in those who go on to develop signs meeting diagnostic criteria for Behcet’s disease.

In this issue, Sereficican and colleagues report on their investigation of ocular findings in patients with RAS.3 This cross-sectional case control study included 34 patients diagnosed with RAS and 34 healthy controls who were matched by age, sex, and smoking status. Corneal thickness, retinal nerve fiber layer thickness, foveal thickness, and nasal, temporal, and subfoveal choroidal thicknesses were examined in all study participants. The multivariate logistic regression analysis of these values revealed foveal choroidal thickness as the only statistically significant association with RAS. Specifically, increased foveal choroidal thickness was found to be associated with the presence of RAS, with an odds ratio of 1.922 and 95% confidence interval of 0.820 to 3.915.

This is the first study investigating ocular coherence tomography (OCT) evaluation of choroidal thickness in patients with RAS. The authors suggest that the increased subfoveal choroidal thickness in patients with RAS may be due to changes in choroidal vascularity, with greater increase in subfoveal thickness as compared to nasal and temporal thickness due to the higher vascular density of the subfoveal choroid. This study also suggests that choroidal thickness may be increased earlier on in the disease course, prior to progression to true Behcet’s disease. This finding is in contrast to another study that found choroidal thickness was negatively correlated with panuveitis due to Behcet’s disease.4 This difference in findings suggests that choroidal thickness may decrease as disease progresses from subclinical ophthalmic manifestations of RAS to true ophthalmic involvement in Behcet’s disease.

There are, however, a few limitations of the current study that should be taken into consideration. As the authors acknowledge, this was a single center case-control study with small sample size. Prospective studies of larger cohorts of RAS patients will help add to our current understanding of systemic and ophthalmic inflammatory changes associated with RAS.

In summary, Sereficican and colleagues have eloquently described the changes in ophthalmic clinical findings in patients with recurrent aphthous stomatitis. Studies such as this are important to facilitate our understanding of the pathogenesis of this interesting entity and the potential utility of screening examinations in patients with RAS, potentially allowing for earlier diagnosis and even more effective treatment of patients with Behcet’s disease in the future.

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Resident Perspective: The many faces of ocular syphilis

In the past 2 decades, there has been resurgence of syphilis in Canada and the United States. Although syphilis was historically seen primarily in men who have sex with men, it is increasingly being seen in patients across all sexes and sexual orientations. Patients with ocular syphilis may not fit the classic demographic group or disclose important risk factors until after diagnosis, which is often challenging. For instance, syphilis is sometimes referred to as the “Great Imitator” for its wide variety of presentations, which include rash, neurologic symptoms, and generalized lymphadenopathy. Its ocular manifestations can vary significantly as well, often leading to misdiagnoses. In this issue of the CJO, Schulz and colleagues present a case series and review the diagnosis and treatment of ocular syphilis.\(^1\)

The cases were identified from individual databases of specialists in posterior uveitis, retina, neuro-ophthalmology, and infectious disease from 2010 to 2020. Each chart was reviewed for age, sex, risk factors, HIV status, ocular manifestations, syphilis serology, and treatment. Of 26 cases, 5 were presented in illustrative details.

To summarize, all 5 cases were middle-aged heterosexual men and women without the typical risk factors that would alert the examiner to suspect syphilis. The first case was a 44-year-old male with optic neuritis, anterior uveitis, rash, and vasculitis. He was initially treated for an autoimmune disease with high-dose prednisone. The second case was a 52-year-old male with hypertensive uveitis, serous retinal detachment, optic neuritis, and vitritis, initially diagnosed as Purtscher’s retinopathy. The third case was a 56-year-old male with hypopyon, corneal edema, vitritis and retinitis, initially suspected and treated as acute retinal necrosis. The fourth case was a 53-year-old male with iris and ciliary body granuloma, initially suspected to be leprosy. The last case was a 49-year-old male with acute syphilitic posterior placoid choriotretinitis, with initial working diagnosis as acute zonal occult outer retinopathy. All cases were appropriately treated with Penicillin G once diagnosis of syphilis was confirmed. The case presentation was followed by comprehensive review of each ocular finding—anterior/intermediate/posterior/pan-uveitis, iris granuloma, and optic neuritis—present in the patients, along with detailed description of management with intravenous Penicillin G.

This paper highlights the diagnostically challenging nature of syphilis. The study demonstrates that the typical risk factors for syphilis are often absent or not disclosed at consultation, contributing to misdiagnoses that in turn leads to inappropriate—for example, immunosuppressive or antiviral—treatment. Inappropriate or delayed treatment can potentially lead to poor visual prognoses or permanent visual loss. Hence, this study advocates for syphilis screening, which is especially important in this era of syphilis resurgence. Readers will be better equipped to consider syphilis as an important differential diagnosis for non-straightforward cases of uveitis, vasculitis, and optic neuritis. Furthermore, by presenting a comprehensive review of varying presentations of ocular syphilis and relevant clinical pearls, this paper will also benefit its readers by allowing them to develop a good understanding of ocular syphilis and its treatment strategies.

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Resident Perspective:
Incremental effect of topical and oral moxifloxacin with surgical intracameral prophylaxis

Post-operative endophthalmitis (POE) after is a rare but devastating complication after cataract surgery. Among other factors, aseptic technique and various antibiotic protocols are used to reduce the risk of POE. However, there is no universally accepted prophylactic antibiotic regimen. Debate exists as to the optimal route of administration.
(intracameral, topical, and/or oral), antibiotic choice, and duration and frequency of use.

In this issue, Lukewich and colleagues use a mathematical model to investigate the theoretical efficacy of topical and oral antibiotic supplementation to intracameral antibiotics during cataract surgery. Moxifloxacin was used as the antibiotic of choice given its confirmed efficacy intracameral and preferred use topically. The model integrated data from previous studies measuring anterior chamber (AC) moxifloxacin concentrations after topical or oral administration with a mathematical model estimating AC moxifloxacin concentration abatement after intracameral administration. Concentrations were studied in relation to threshold values, which included the minimum inhibitory concentration of 90% (MIC90) of the most common POE pathogen (methicillin-sensitive Staphylococcus aureus [MSSA]) and of the most resistant POE-causing bacteria (coagulase negative Staphylococci [CoNS] and methicillin-resistant Staphylococcus aureus [MRSA]). Concentrations were also compared to the mutant prevention concentration (MPC), the concentration above which reduces the chance of mutant survival.

AC concentrations of intracameral moxifloxacin (600 μg in 0.4 mL) alone decrease rapidly in the first hour postoperatively, after which it decreases linearly by logarithmic dilution. It provided coverage above the MIC90 of the most resistant bacterial strains for 7.5 hours, above the MIC90 of MSSA for about 37 hours, and above the MPC of MSSA for about 24 hours. Topical moxifloxacin alone achieved AC concentrations above the MIC90 of MSSA after the first drop. Q4h and q6h topical dosing achieved AC concentrations near or above the MPC of MSSA, and q8h dosing produced levels just below the MPC. However, topical drops didn’t provide coverage for resistant strains of MRSA and CoNS. Adding topical moxifloxacin at these dosing schedules to IC use didn’t provide enhanced AC levels until about 17 to 19 hours postoperatively. This suggests topical antibiotic supplementation does not provide much benefit in normal circumstances with a well-sealed surgical incision. However, they can be useful if a wound leak develops postoperatively.

Oral moxifloxacin alone (12 hours preoperatively and immediately postoperatively) achieved an AC concentration above the MPC of MSSA within 1 hour of surgery and sustained this level for 24 hours. It prolonged the AC concentration above the MIC90 of MSSA to >50 hours postoperatively. But its use alone, like the topical drops, did not provide coverage for CoNS and MRSA. Its supplemental use with IC moxifloxacin increased the AC concentration after about 16 hours postoperatively and maintained levels above the MPC of MSSA for an additional 5 hours. Again, under normal postoperative conditions, this additional oral supplementation does not offer much added benefit. The exception being in patients with systemic bacteremia, where oral antibiotics could potentially prevent endogenous spread.

A study by Creuzot-Garcher and colleagues suggested an association between intraoperative intracameral antibiotic use and decreased rates of POE, though controversy remains as to whether other factors such as improved surgical techniques and new topical antibiotic regimens may also be factors. Topical antibiotic drops still remain the most commonly used POE prophylaxis approach but as demonstrated in this study, they do not provide coverage for the most resistant bacterial strains when used alone and offer benefits only in specific postoperative circumstances when combined with IC use. The clinical utility of oral antibiotics in preventing POE has not been thoroughly established and this theoretical model also demonstrated limited intraocular benefits for oral antibiotic supplementation. The model presented by Lukewich and colleagues can inform approaches of prophylactic POE prevention, however future studies are needed to confirm the accuracy of the model clinically.

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Resident Perspective: Applications of iodine-125 plaque radiotherapy for residual or recurrent retinoblastoma

In the present issue of CJO, Soliman and colleagues present a case series of patients who were given iodine-125 plaque radiotherapy as treatment for residual or recurrent retinoblastoma (RB) following primary focal therapy with or without systemic and/or regional chemotherapy.1

From a trainee perspective, this article is worth reading for multiple reasons. First, the authors concisely summarize the treatment options available for RB including recent historical developments. This is a complex area, which many of us may have little direct experience with. As reflected in the International Classification of Retinoblastoma, management decisions must consider tumour size and laterality, proximity of the tumor to the macula and optic nerve, presence of vitreous or subretinal seeds, and evidence of invasion into surrounding tissues.2 Options for small, localized tumours include laser photocoagulation, cryotherapy, thermotherapy and plaque radiotherapy. Whereas, for more extensive disease, enucleation, intravenous chemoreduction, and intra-arterial chemotherapy may be used. Though historically the first line for extensive disease, external beam radiation therapy is now considered a last alternative because it significantly increases the risk of secondary malignancies in children with germline RB mutations. The present study demonstrates a promising role for plaque brachytherapy in the treatment of recurrent and residual RB. Figure 1 is a particularly helpful summary of the guidelines for this treatment.

Second, the study highlights the various types of RB tumour regression and their salience for risk of recurrence after plaque radiotherapy. These patterns were initially described following external beam radiation therapy. Briefly, type 0 describes complete tumour disappearance without scar; type 1 refers to complete calcification, appearing like cottage cheese; type 2 is a completely non-calcified mass, also described as fish flesh; type 3 is a partially calcified mass; and type 4 is a flat atrophic scar.3 In the current study, type 2 (fish flesh) regression was associated with higher risk of local recurrence than the other patterns observed (types 1 and 4). This could possibly be explained by a previous study which found that, after systemic chemotherapy, fish flesh appearing tumours could still contain large quantities of actively dividing retinoblastoma cells, which tended not to be present in the other types of regressed tumours.4

Finally, the study evidences an interesting issue relevant to research study design in ocular oncology. That is, deciding on the appropriate unit of analysis, be it person, eye, or tumour. One must be aware that when analyzing data on pairs of eyes, or multiple tumours in a single patient, it may be necessary to use statistical methods that account for this source of correlation in the data.5

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