NOTES FROM THE 47TH ANNUAL ARDS MEETING

The doctors who attend the Aspen Retinal Detachment Society (ARDS) annual meeting are courageous, innovative, and committed to their field. They understand that taking on complex cases is part of their mission, and they are not afraid to wade into uncharted territory to treat a patient who presents with advanced disease. In this issue's digest of 2019 ARDS meeting presentations, lecture scribe Ru-Ik Chee, MD, summarizes my talk about the value of investigating tumors in a way that challenges our specialty's paradigms, asking doctors to tap into their most admirable characteristics as they further their field.

The ARDS prides itself on maintaining an international audience and speaker panel. This year, David H.W. Steel, MBBS, FRCOphth, joined us from the United Kingdom to discuss, among other topics, management of submacular hemorrhage. Dr. Chee breaks down Dr. Steel's lecture and shares his algorithm for treating this all-too-common presentation.

In 2020, the ARDS will meet February 29–March 4 in Snowmass, Colorado. Visit MedConfs.com to register—and be sure to check that last year's ski pants still fit.

—Timothy G. Murray, MD, MBA

VITREORETINAL SURGERY: WHEN YOU DO WHAT OTHERS WON'T

A new approach to surgical management of small ocular melanoma is reviewed.

By Ru-Ik Chee, MD

At the 2019 ARDS meeting, Timothy G. Murray, MD, MBA, delivered a presentation titled "Vitreoretinal Surgery: When You Do What Others Won't." This article presents a summary of portions of his presentation.

Dr. Murray focused the beginning of his talk on the evolution of clinical and surgical management of ocular melanomas and then described outcomes of a new approach to managing small ocular melanomas with microincisional vitrectomy surgery (MIVS), intraoperative laser ablation, tumor biopsy, and molecular analysis, with intravitreal administration of triamcinolone acetonide.

Recounting the history of management of ocular melanomas, Dr. Murray noted that, at the beginning of his career, routine treatment for ocular melanomas was enucleation, but management was transitioning toward brachytherapy related to the ongoing Collaborative Ocular Melanoma Study. Treatment of small ocular melanomas was still controversial, however, as historically all pigmented lesions were enucleated. Leading surgeons at Bascom Palmer Eye Institute proposed observation of small melanomas. Dr. Murray emphasized that, as with any malignancy, there was a need for discretion in management based on tumor size, as the 5-year mortality rate for small ocular melanomas was 1%, compared with 10% and 30% for medium and large ocular melanomas, respectively.

There was growing accuracy in the diagnostic classification of small tumors. In the medium tumor trial under the Collaborative Ocular Melanoma Study, half the eyes were enucleated and half underwent plaque brachytherapy. The misdiagnosis rate for treatment in these medium tumors was less than 1%. This study did not initially include smaller tumors, but, when the apical height limit for a medium tumor was reduced to 2.5 mm from 3 mm, no reduction in the diagnostic accuracy was noted, suggesting that even small ocular melanomas can be precisely diagnosed by clinical and imaging analysis.

TRANSPUPILLARY THERMOTHERAPY

Transpupillary thermotherapy (TTT) for small ocular melanomas was explored as a possible alternative treatment to enucleation or radiation. However, the failure rate for TTT was approximately 30%, compared with virtually zero for brachytherapy. This unfavorable result was compounded by the observation that the risk of mortality from metastatic disease increases when primary therapy fails. Dr. Murray noted, however, that results of intraoperative laser ablation may be different from those of TTT, based on observations of postoperative tumor shrinkage in eyes with small ocular melanomas that underwent surgery for other concurrent pathologies such as retinal detachment.

TUMOR BIOPSY DURING VITRECTOMY

Developments in genetic analysis led to the incorporation of tumor biopsy during MIVS. The molecular classification of tumors was found to be the single greatest predictor of survival. The 5-year survival rate of individuals with class 2 tumors was 25%, compared with 99% for those with class 1a tumors.

There was also a hypothesis that earlier intervention could alter the cascade of molecular alterations that leads to progression from a class 1 to a class 2 tumor. Furthermore, in other

fields of oncology, treatment was moving away from radiotherapy toward more focal therapy, sparing some of the morbidity related to treatment. In ocular melanomas, this morbidity included radiation maculopathy, optic neuropathy, and secondary neovascular glaucoma.

A NEW TECHNIQUE

Dr. Murray then switched gears, discussing a surgical MIVS approach to management of small ocular melanoma. In patients with melanoma, he said, in which the alternative to surgery is either enucleation or brachytherapy, a globe-conserving, radiation-sparing surgical approach can be an appealing option.

Dr. Murray shared surgical videos illustrating this technique in two patients. The key element of the technique is the removal of the tractional component of the tumor. Dr. Murray expressed his long-standing belief that all eyes with ocular melanomas have tractional alterations associated with the tumors, and they virtually all have focal subretinal fluid. This has now been demonstrated with intraoperative OCT imaging, he said.

In surgery, Dr. Murray ensures that the hyaloid is separated from the tumor, completes the vitrectomy, and ensures removal of the overlying epiretinal membrane and internal limiting membrane, which is stained with ICG. Subsequently, confluent laser is applied to ablate the tumor, and the tumor is biopsied with a 25-gauge needle using a multipass approach. Intravitreal triamcinolone acetonide is then instilled to suppress inflammatory alterations.

In the video cases, one patient had a class 1a tumor and one had a class 2 tumor. Both patients were still alive and doing well without metastatic disease at the time of the ARDS presentation. As part of his focus on reporting his findings to the wider community, Dr. Murray said, he has presented these cases at conferences and published them in peer-reviewed scientific journals. Dr. Murray discussed the importance of presenting novel techniques for discussion at meetings such as the ARDS, and then more formally submitting both techniques and results for peer-reviewed professional publication.

Translatability and reproducibility of results are essential for other professionals to understand and potentially implement a new treatment technique. To this point, Dr. Murray reported the outcomes of this surgical technique for small ocular melanoma, which he has performed in 200 patients with a follow-up duration of approximately 5 years. Starting VA was 20/100+, and mean tumor apical height was 1.9 mm. Postoperative tumor apical height decreased uniformly in all patients to an average of 1.4 mm. In patients with small tumors located in the macula (but sparing the fovea), VA was better than 20/50 in 98% of patients. Ten patients had class 2 tumors, and all are alive. Only three patients in this series had a nondiagnostic biopsy study.

Dr. Murray concluded by encouraging the audience not to be afraid to try new things, as long as they are being done for the good of the patient. Subsequent sharing of results with colleagues and at conferences allows the entire field to advance.

Eyetube Meeting Coverage: ARDS

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SUBMACULAR HEMORRHAGE IN AMD: HOW SHOULD WE MANAGE IT? TECHNIQUES AND DECISIONS

A review of the literature with clinical pointers.

At the 2019 ARDS meeting, David H.W. Steel, MBBS, FRCOphth, delivered a presentation titled "Submacular Hemorrhage in AMD: How Should We Manage It? Techniques and Decisions." Dr. Steel reviewed some of the literature and shared his experience managing submacular hemorrhages (SMH) in patients with age-related macular degeneration. This article presents a summary of portions of his presentation.

Untreated subfoveal hemorrhage can cause vision loss through several mechanisms, including shear stress from fibrin contraction, oxidative stress from iron toxicity, and recruitment of macrophages and fibrotic factors. Bopp et al found that about 12% of patients with age-related macular degeneration experience some degree of SMH,[1] although UK population studies have found the rate to be 5 to 20 per 1 million.[2,3]

Risk factors for hemorrhage include use of warfarin and antiplatelet agents; hypertension and smoking have not been shown to be risk factors. There have been no associations with neovascular lesion type, although high retinal pigment epithelium (RPE) detachments are a risk factor in some series. In 9% to 22% of cases, RPE rips may be observed after resolution of SMH.

Most of the pivotal clinical trials of anti-VEGF agents excluded patients

with large SMH, and therefore long-term prospective studies in this patient population are not available. Furthermore, some of the literature on SMH may include patients with polypoidal choroidal vasculopathy, which has a different and generally more favorable course. These factors should be taken into account when interpreting the literature.

Aside from observation, treatments for submacular hemorrhage can include intravitreal anti-VEGF injections alone, anti-VEGF injections combined with expansile gas displacement with or without intravitreal tissue plasminogen activator (tPA), or pars plana vitrectomy (PPV) with subretinal tPA and gas displacement.

Dr. Steel stated that it is best to administer treatment within 14 days of subretinal hemorrhage (SRH) diagnosis. If the SRH is changing to a yellow hue, this suggests chronicity, and it may be resistant to breakdown. He also noted the importance of distinguishing between SRH and sub-RPE hemorrhage, which has a darker red-brown tinge and can be readily seen on OCT. The presence of a sub-RPE hemorrhage typically does not change visual prognosis much, however.[4]

Dr. Steel showed a time-lapse set of photographs of an individual who was treated with anti-VEGF therapy alone, illustrating clinical improvement and resolution with time.

Many studies have shown benefit to patients of treatment with anti-VEGF therapy alone. One study using anti-VEGF monotherapy in 13 patients found that 60% of patients exhibited improved VA and 40% maintained stable VA; no patient worsened.[5] A study by Shin et al in Asia, using specific cutoff criteria for treating patients with anti-VEGF therapy only (central macular thickness < 550 µm and SRH < 300 µm), suggests that this may be a reasonable approach for smaller SRH.[6]

Does the removal or displacement of subfoveal blood make a difference to visual outcomes? If so, approaches such as pneumatic displacement with expansile gas and intravitreal tPA may be preferable. Dr. Steel said his approach includes injecting 0.3 cc of C_3F_8 and 50 µg of tPA in 0.05 cc, plus an anti-VEGF agent; he typically performs a 0.4 cc anterior chamber tap with globe compression immediately beforehand. This technique can work well, but it requires a patient who can maintain positioning, although complete prone positioning may not be necessary.

PPV with air or gas with subretinal tPA injection is another very effective management option. De Jong et al found no difference in amount of displacement between PPV displacement techniques and pneumatic displacement.[7] However, that study included only patients with relatively small hemorrhages, and high-contrast central vision was used to gauge success, which may have missed subtle effects from paracentrally nondisplaced hemorrhage.

Is subretinal tPA necessary? Intravitreal tPA may not penetrate into the subretinal space in normal eyes, but it seems to do so in eyes with SMH. One study found that subretinal tPA achieved better displacement than intravitreal tPA combined with PPV.[8]

The benefits of PPV and subretinal tPA include allowing a greater air or gas fill, requiring less need for posturing, and causing less shear stress due to immediate clot lysis and displacement.[9] Dr. Steel said his approach includes PPV, subretinal tPA injection (12.5 µg/0.01 cc, up to 0.3 cc for larger heme) mixed with subretinal bevacizumab (Avastin, Genentech) or ranibizumab (Lucentis, Genentech), and complete air-fluid exchange. He advised against using aflibercept (Eylea, Regeneron), as he said it is broken down by tPA.[10] Instruments for subretinal injection include several manufactured by Dutch Ophthalmic and MedOne Surgical.

Dr. Steel advised injecting slowly and as far from the fovea as possible.[11] Other pearls include making a bleb that surrounds the clot and avoiding areas of pigment epithelial detachment. A complete air-fluid exchange immediately follows this step. A drainage retinotomy is rarely necessary.

Displacement of SRH using this technique occurs within hours. Air is typically gone in a week with a full air

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Eyetube Meeting Coverage: ARDS

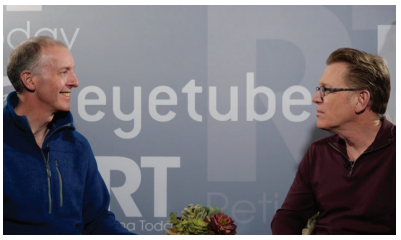

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TABLE. ALGORITHM FOR MANAGING SUBRETINAL HEMORRHAGE

Size of Subretinal Hemorrhage	Therapy
Small (< 15 mm², 250 µm thick)	Anti-VEGF injection alone
Medium (15-25 mm²) and patient can maintain position	Expansile gas with intravitreal tPA and anti-VEGF
Medium and unable to position or large (> 25-30 mm²)	PPV with subretinal tPA and anti-VEGF
Massive (> half of retina and bullous)	Preoperative intravitreal tPA, then PPV at least 12 hours later, external drainage, and displacement of residual hemorrhage

After therapy, treat what remains (eg, an RPE patch or macular relocation surgery may be warranted in some patients with huge submacular lesions despite displacement surgery, etc.).
Abbreviations: PPV, pars plana vitrectomy; RPE, retinal pigment epithelium; tPA, tissue plasminogen activator.

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fill, whereas displacement with expansile C_3F_8 may last for several weeks.[12,13] Martel and Mahmoud described a technique in which subretinal air is injected after tPA, requiring about a 50% air fill in the vitreous cavity.[14] The additional effectivity added by this technique is uncertain.

Although displacement of the hemorrhage occurs with pneumatic therapy, the displaced hemorrhage may cause a scotoma. VA results are difficult to compare directly among these treatments because patients who undergo vitrectomy typically have larger SRH than those who undergo pneumatic displacement. Rebleeding afterward is common (in 20%–30% of eyes), and close follow-up and vigilant treatment with anti-VEGF therapy are recommended to reduce the risk of rebleeding.

Dr. Steel ended his talk by noting that we do not yet know which patients will benefit from displacement surgery compared with anti-VEGF therapy alone. A randomized controlled trial is needed. He is involved in a pilot trial in the United Kingdom investigating four modalities of treatment for SMH (TAPAS) that recently finished recruiting, as well as a large pan-European trial funded by Euretina comparing anti-VEGF therapy alone to vitrectomy with subretinal tPA (TIGER) that will start soon.

Dr. Steel closed his talk by sharing his current algorithm for managing SRH (Table). ■

1. Bopp S. Subretinal hemorrhage. Natural course and staging [article in German]. *Ophthalmologe*. 2012;109(7):635-643.
2. McGowan A, Silvestri G, Moore E, et al. Retinal vascular caliber, iris color, and age-related macular degeneration in the Irish Nun Eye Study. *Invest Ophthalmol Vis Sci*. 2014;56(1):382-387.
3. Al-Hity A, Steel DH, Yorston D, et al. Incidence of submacular haemorrhage (SMH) in Scotland: a Scottish Ophthalmic Surveillance Unit (SOSU) study. *Eye (Lond)*. 2019;33(3):486-491.
4. Treumer F, Wienand S, Purtskhvanidze K, Roider J, Hillenkamp J. The role of pigment epithelial detachment in AMD with submacular hemorrhage treated with vitrectomy and subretinal co-application of rtPA and anti-VEGF. *Graefes Arch Clin Exp Ophthalmol*. 2017;255(6):1115-1123.
5. Shienbaum G, Garcia Filho CA, Flynn HW Jr, Nunes RP, Smiddy WE, Rosenfeld PJ. Management of submacular hemorrhage secondary to neovascular age-related macular degeneration with anti-vascular endothelial growth factor monotherapy. *Am J Ophthalmol*. 2013;155(6):1009-1013.
6. Shin JY, Choi HJ, Chung B, Choi M, Lee J, Byeon SH. Anti-vascular endothelial growth factor with gas for submacular hemorrhage. *Optom Vis Sci*. 2016;93(2):173-180.
7. de Jong JH, van Zeeburg EJ, Cereda MG, et al. Intravitreal versus subretinal administration of recombinant tissue plasminogen activator combined with gas for acute submacular hemorrhages due to age-related macular degeneration: an exploratory prospective study. *Retina*. 2016;36(5):914-925.
8. Hillenkamp J, Surguch V, Framme C, Gabel VP, Sachs HG. Management of submacular hemorrhage with intravitreal versus subretinal injection of recombinant tissue plasminogen activator. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(1):5-11.
9. Berger JW, Brucker AJ. The magnitude of the bubble buoyant pressure: implications for macular hole surgery. *Retina*. 1998;18(1):84-86; author reply 86-88.
10. Klettner A, Grotelüschen S, Treumer F, Roider J, Hillenkamp J. Compatibility of recombinant tissue plasminogen activator (rtPA) and aflibercept or ranibizumab coapplied for neovascular age-related macular degeneration with submacular haemorrhage. *Br J Ophthalmol*. 2015;99(6):864-869.
11. Xue K, Groppe M, Salvetti AP, MacLaren RE. Technique of retinal gene therapy: delivery of viral vector into the subretinal space. *Eye (Lond)*. 2017;31(9):1308-1316.
12. Sandhu SS, Manvikar S, Steel DH. Displ acement of submacular hemorrhage associated with age-related macular degeneration using vitrectomy and submacular tPA injection followed by intravitreal ranibizumab. *Clin Ophthalmol*. 2010;4:637-642.
13. Waizel M, Todorova MG, Rickmann A, Blanke BR, Szurman P. Efficacy of vitrectomy combined with subretinal rtPA injection with gas or air tamponade. *Klin Monbl Augenheilkd*. 2017;234(4):487-492.
14. Martel JN, Mahmoud TH. Subretinal pneumatic displacement of subretinal hemorrhage. *JAMA Ophthalmol*. 2013;131(12):1632-1635.

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