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Displacement of submacular hemorrhage with intravitreal tissue plasminogen activator following 27 gauge transvitreal fine needle aspiration biopsy for choroidal melanoma

Ramsudha Narala [a], Zachary Bodnar [b], Prithvi Mruthyunjaya [c,*]

[a] Retina Vitreous Associates-Los Angeles, 1245 Wilshire Blvd Ste 380, Los Angeles, CA, 90017, USA
[b] Meadows Eye Physicians and Surgeons, 2749 Sunridge Heights Pkwy, Henderson, NV, 89052, USA
[c] Byers Eye Institute, Department of Ophthalmology, Stanford University Medical Center, 2452 Watson Ct, Palo Alto, CA, 94303, USA

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ABSTRACT

Purpose: To describe the management of submacular hemorrhage (SMH), a vision threatening complication following transvitreal choroidal biopsy, with intravitreal tissue plasminogen activator (tPA) and pure perfluoropropane (C_3F_8) gas bubble injection.

Observations: A 53 year old female with choroidal melanoma of the left eye underwent iodine-125 plaque brachytherapy placement and 27 gauge transvitreal fine needle aspiration choroidal biopsy for gene expression profiling. On postoperative day 2, large SMH was identified on dilated fundus examination. At the time of plaque brachytherapy removal, intravitreal tPA and pure C_3F_8 gas bubble injection with post operative positioning was also performed to attempt displacement of SMH. At postoperative month 1 following tPA and gas bubble displacement, the SMH was completely displaced inferotemporally outside of the macula and visual acuity improved from 20/70 at postoperative week 1 to 20/25 at postoperative month 1.

Conclusions and importance: Subretinal hemorrhage can be a complication of transvitreal choroidal tumor biopsy but early detection and prompt treatment can result in good visual outcomes.

1. Introduction

Biopsy of choroidal melanoma (CM) for cytogenetic testing provides the patient and physician with important prognostic information and thus, is being performed more frequently.[1–5] Choroidal biopsy is most commonly performed through an internal approach, either transvitreal fine needle aspiration biopsy (FNAB) or vitrectomy-assisted biopsy using a vitreous cutter.[1,6] We describe a patient with CM who underwent an uncomplicated transvitreal choroidal FNAB for gene expression profiling who developed delayed subretinal hemorrhage (SRH) following biopsy. We report our experience with tissue plasminogen activator (tPA) assisted pneumatic displacement of SRH in this rare complication of transvitreal choroidal biopsy.[1,7,8]

2. Case report

A 53 year female was referred to the Stanford University Byers Eye Institute Ocular Oncology clinic with an asymptomatic choroidal lesion in the left eye. Her vision was 20/20 in both eyes and intraocular pressure was 16 mmHg and 15 mmHg in her right and left eye, respectively. Dilated fundus examination of the right eye was normal. In the left eye, there was an elevated pigmented choroidal lesion with overlying orange pigment located 3 mm from the optic nerve and 1 mm from the fovea in the superior macula (Fig. 1). There was trace subretinal fluid (SRF) overlying the lesion and at the base of the inferior margin of the lesion with no SRF involving the fovea. On B scan ultrasound, the size of the lesion measured 7.0 mm × 6.4 mm x 2.19 mm, and A scan revealed low to medium internal reflectivity. Fundus autofluorescence showed patchy hypoautofluorescence with hyperautofluorescent foci consistent with lipofuscin on the surface of the tumor. With close serial monitoring, there was documented growth of the lesion. Based on clinical findings consistent with CM, treatment with plaque brachytherapy with transvitreal choroidal biopsy was discussed. The patient was otherwise healthy and not on anticoagulant medications. Risks, benefits, and alternatives of transvitreal choroidal biopsy were discussed in extensive detail with the patient. The benefit of biopsy

* Corresponding author. Department of Ophthalmology, Byers Eye Institute, Stanford University Medical Center, 2452 Watson Ct, Palo Alto, CA, 94303, USA.
E-mail address: prithvi9@stanford.edu (P. Mruthyunjaya).

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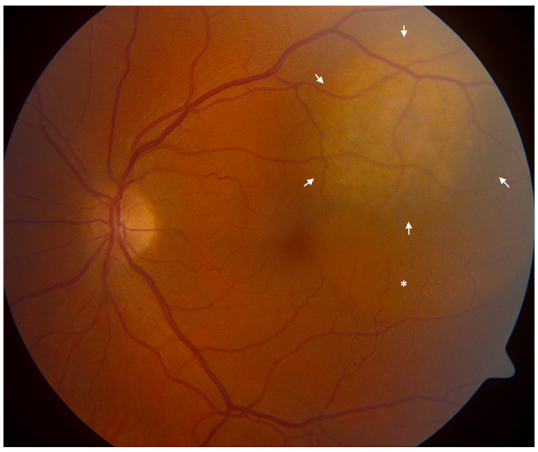

Fig. 1. Color fundus photograph (Zeiss, Germany) of the left eye showing pigmented choroidal lesion (white arrows) in the superior macula approximately 1 mm from the fovea and 3 mm from the optic nerve. There is orange pigment overlying the lesion and subretinal fluid (white asterisk) at the inferior margin of the lesion. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

for gene expression profiling to provide prognostic information, guidance for frequency of postoperative metastatic screening, and to provide molecular information that may serve as targets of emerging therapies was discussed. The risk of intraocular hemorrhage with biopsy and rare risk of retinal detachment, endophthalmitis, loss of vision, and extraocular seeding were also discussed. The patient was also informed of risk of inadequate tissue sampling especially in the setting of smaller tumors. The patient agreed to proceed and was scheduled for plaque brachytherapy with transvitreal fine needle aspiration choroidal biopsy.

Under retrobulbar block anesthesia, a dummy plaque was positioned and confirmed by intraoperative ultrasound to cover the macular tumor. Next, a transvitreal 27 gauge FNAB tumor biopsy to obtain material for prognostic genetic testing was performed. Two 27 gauge transscleral cannulas were placed in the superotemporal and superonasal quadrants. Using the wide-field viewing system and an endo-illuminating light pipe, a 1.5" 27 gauge needle, attached to short extension tubing and a 10 mL syringe, was bent slightly to provide access parallel to the retinal surface and then was introduced. The needle was advanced into the substance of the choroidal tumor and multiple suction maneuvers were engaged while the needle was within the tumor. During the biopsy, once the needle was withdrawn from the tumor, minimal bleeding was identified on the tumor surface with a small plume just over the entry site; bleeding was quickly stabilized with elevation of the intraocular pressure by manual compression of the globe. Next the cannulas were removed and the sclerotomies were sutured with 7-0 absorbable suture and freeze-thaw cryotherapy was applied to the wounds to prevent inadvertent tracking of tumor cells to the ocular surface. The active iodine-125 brachytherapy plaque applicator was brought onto the surgical field and secured with 5-0 nonabsorbable sutures. Ultrasound was again used to confirm accurate placement and no progressive retinal detachment or subretinal collection was noted.

Following surgery, the patient was admitted to the inpatient ward at Stanford University Medical Center for daily monitoring. On postoperative day 1, visual acuity (VA) was hand motion likely from postoperative inflammation. Dilated fundus examination only showed mild localized preretinal hemorrhage at the biopsy site. On postoperative day 2, the patient was noted to have count fingers VA and fundus examination revealed a thick submacular hemorrhage (SMH) (Fig. 2). No valsalva maneuvers were noted but the patient did report moderate postoperative discomfort.

Four days later, the plaque brachytherapy applicator was removed during a second surgical procedure. Indirect ophthalmoscopy confirmed

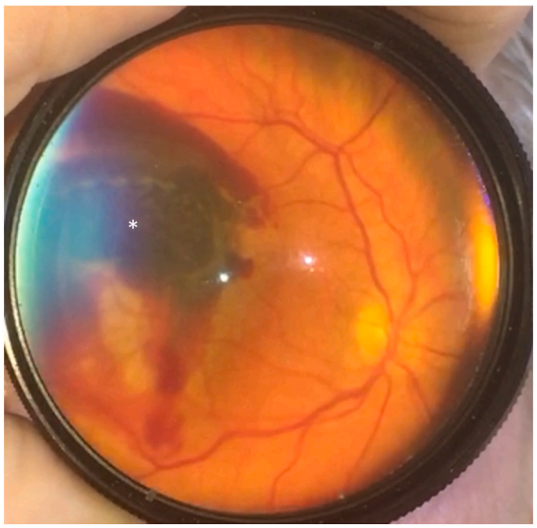

Fig. 2. Cell phone color image taken at the bedside with head mounted indirect ophthalmoscope and 20 diopter lens showing presence of submacular hemorrhage involving the fovea (white asterisk). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

stability of the thick SMH and small preretinal hemorrhage at the biopsy site with no vitreous hemorrhage (VH). Next an intravitreal injection of 25 μg in 0.1 mL tPA was delivered through the pars plana followed by 0.25 mL of undiluted pure perfluoropropane gas via a 30 gauge needle on a 1 mL syringe and aqueous paracentesis. Face down positioning was instructed for 3 days.

At postoperative week 1, VA improved to 20/70 and the SMH was noted to be mostly displaced inferotemporally although some residual SRH persisted adjacent to the fovea (Fig. 3A and B). By post-operative month 1, the VA in the left eye improved to 20/25 and there was complete displacement of the dehemoglobinized SRH inferotemporally outside of the macula (Fig. 4A and B). Gene expression profiling from choroidal biopsy revealed Class 1A, PRAME positive (Castle Biosciences, Phoenix, AZ), and the choroidal lesion was monitored every four months following treatment.

3. Discussion

Choroidal tumor biopsy is being performed with increasing frequency for CM to obtain tissue samples, for confirmatory cytology and prognostic testing via chromosomal analysis or gene expression profiling, with high yield.[1–5] Choroidal biopsy can be performed via an external transscleral approach or more commonly an internal transvitreal approach for post equatorial tumors.[1,6,7,9] Transvitreal choroidal biopsy, either via fine needle aspiration or using a vitreous cutter,[1] results in a high rate of adequate sample yield for diagnostic and prognostic purposes.[7,9] There are many advantages of choroidal biopsy but risks of transvitreal biopsy with either method include SRH, VH, retinal detachment, or extraocular extension.[1,8]

Localized intraocular hemorrhage at the biopsy entry site is the most common, though typically self-limiting, complication of transvitreal choroidal biopsy.[1] In the setting of concurrent SRF or exudative retinal detachment overlying a choroidal tumor, needle entry through the retina and into the choroid is likely to rupture delicate vessels releasing a small amount of blood into the subretinal space around the biopsy site.[1] As the needle is withdrawn from the tissue, most of the hemorrhage can be seen as a localized plume of blood emanating from the biopsy site. Occasionally, this VH can disperse and lead to visual obscuration, which typically resolves with observation.[1] We find the localized SRH and VH to be potentially beneficial, inducing platelet aggregation which leads to

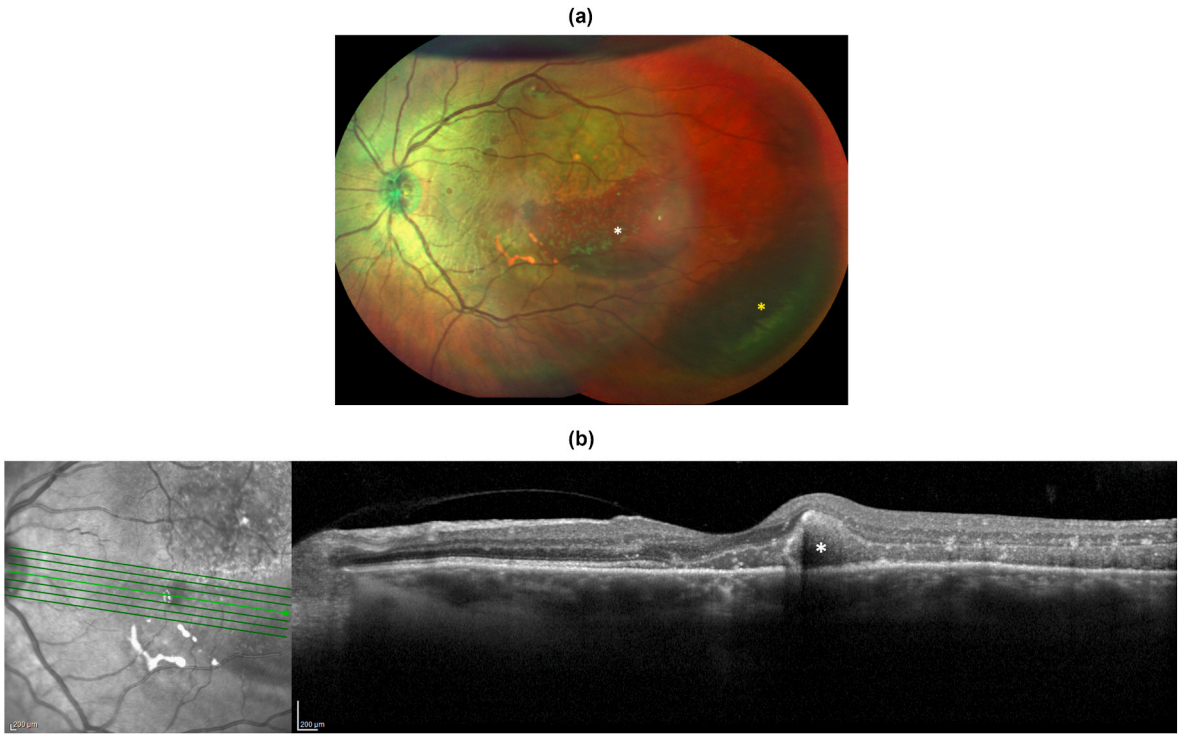

Fig. 3. A. At postoperative week 1 following intravitreal tissue plasminogen activator and perfluoropropane gas for submacular hemorrhage, there is inferotemporal displacement of most of the subretinal hemorrhage away from the fovea (yellow asterisk) with some persistent submacular hemorrhage (white asterisk) adjacent to the fovea. B. Enhanced depth imaging optical coherence tomography (EDI-OCT) (Spectralis, Heidelberg, Germany) shows subretinal hyperreflectivity (white asterisk) temporal to the fovea consistent with subretinal hemorrhage. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

fibrosis, acting as a form of retinopexy to the biopsy site obviating the need for adjunctive laser photocoagulation or cryotherapy to the area of biopsy.[1] In addition, the underlying choroidal tumor provides a make-shift scleral buckle effect helping to bring the retinal pigment epithelium in proximity to the biopsy site.[1]

Grewal et al. described 18 eyes that underwent 27 gauge vitreous cutter choroidal biopsy for CM.[9] Of the 18 eyes, 13 eyes (72.2%) developed a VH after biopsy, with 6 eyes requiring vitrectomy at the time of biopsy.[9] Bagger et al. found that the rate of significant VH requiring repeat vitrectomy following 25 gauge vitrectomy assisted choroidal biopsy is low at 5.9%.[10] FNAB is associated with even lower rates of hemorrhage compared to biopsy with a vitreous cutter.[1] In a study by Shields et al., only 3 of 56 patients developed VH following FNAB.[11] Singh et al. noted that FNAB via a transvitreal approach resulted in high diagnostic yield (84%) while only 1% of patients that underwent FNAB via a transvitreal, transcleral, or transcorneal approach developed visually significant VH or SRH.[7]

Though preretinal hemorrhage is more common,[1] our patient developed a fovea involving SRH following an uncomplicated 27 gauge transvitreal choroidal FNAB. Postoperatively following biopsy, serial indirect ophthalmoscopic examinations were performed, allowing early detection of the SRH and timely treatment. Although some studies have supported improvement of vision with observation alone, in many cases,[12,13] delayed treatment of SRH can result in poor visual outcomes especially when the hemorrhage is thicker or when a choroidal neovascular membrane is present.[14–16] In animal models, Glatt et al.[15] found photoreceptor loss and Toth et al.[16] found significant loss of outer retinal structures 7 days after onset of SRH. Treatment methods for SRH include subretinal surgery with or without subretinal tPA, gas bubble injection only, and combined intravitreal tPA and gas bubble injection.[14] Subretinal surgery, although reported to be efficacious in some studies, has higher risk of complications compared to more conservative therapies and limited visual acuity outcomes due to damage to photoreceptors and retinal pigment epithelial cells.[14] Ohji et al. studied outcomes of patients with gas bubble injection only and showed dramatic displacement of SRH away from the macula in 3 of 5 eyes with mild displacement and reduction in subfoveal thickness in 2 of 5 eyes.[17] Gopalakrishan et al. published a prospective case series of 20 patients with SMH treated with intravitreal perfluoropropane gas only followed by prone positioning with complete or partial displacement of hemorrhage away from the fovea in 16 of 20 eyes.[18] Of note, large comparative studies have not been performed to compare the various treatment methods.

We performed combined intravitreal tPA and gas bubble injection in our patient within 4 days of recognizing the thick SMH in attempts to avoid vitrectomy assisted displacement techniques. We suspect delayed hemorrhage was due to postoperative valsalva maneuver resulting in rupture of an injured vessel from the biopsy. tPA is a 70 kDa molecule that activates plasminogen into plasmin and dissolves fibrin clots, allowing easier displacement of hemorrhage.[17,19,20] In a series by Krepler et al., 11 patients with SRH from exudative age-related macular degeneration underwent intravitreal tPA and sulfur hexafluoride gas injection, and 10 had displacement of SRH with 8 patients showing improvement in VA.[20] Hassan et al. described 15 patients with SRH treated with intravitreal tPA (25–100 µg/0.1–0.2 mL) and gas tamponade with either perfluoropropane or sulfur hexafluoride gas with face down positioning for 1–5 days afterwards. In all patients, there was complete displacement of hemorrhage outside of the fovea.[21] In our patient, combined intravitreal injection of tPA with subsequent perfluoropropane gas bubble injection resulted in successful displacement of SRH outside of the fovea and improved VA to 20/25.

Intraoperatively, steps can be taken to minimize the risk of hemorrhage from choroidal tumor biopsy.[1] Increasing the intraocular pressure by either applying digital pressure or raising the infusion pressure enables tamponade, decreasing bleeding. The pressure is then gradually reduced once hemostasis is achieved.[1] Closure of sclerotomy sites can

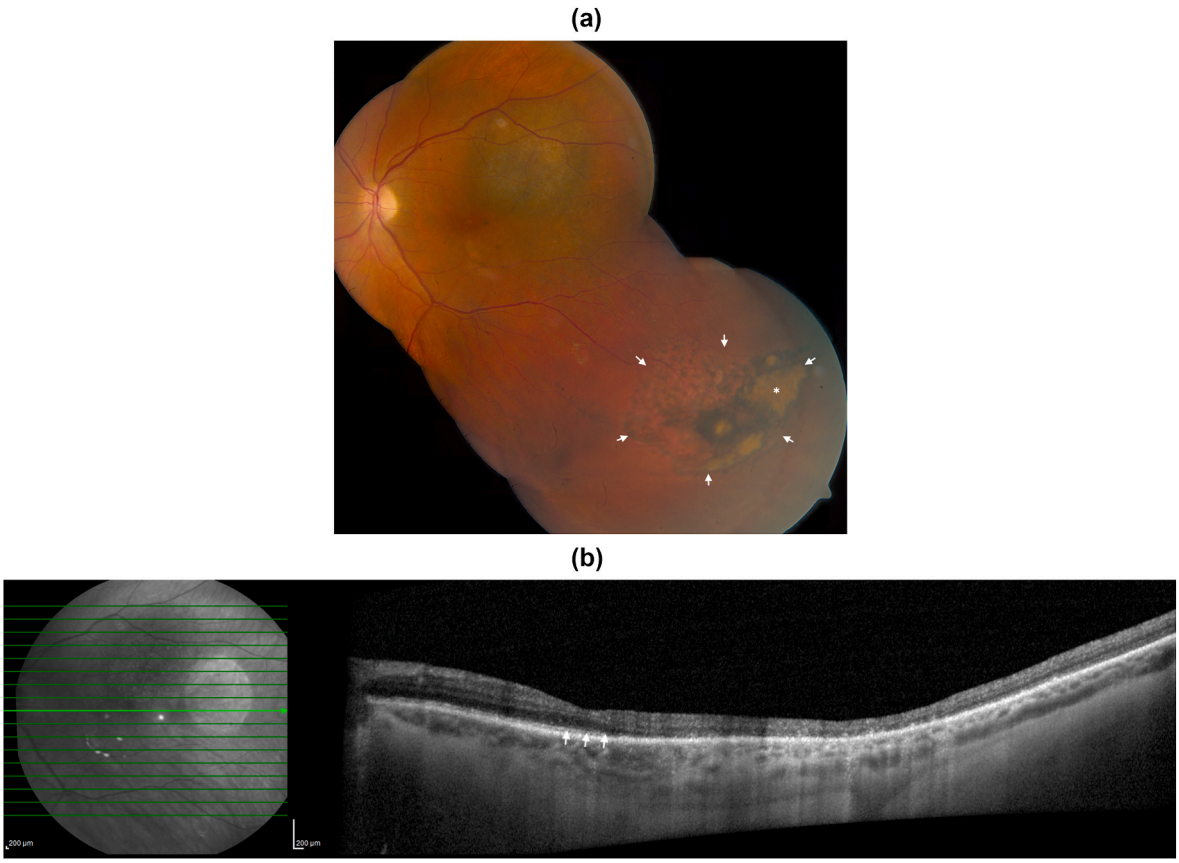

Fig. 4. A. Color fundus photograph (Zeiss, Germany) of the left eye at postoperative month 1 visit showing inferotemporal displacement of the submacular hemorrhage outside of the macula (white arrows). The submacular hemorrhage is dehemoglobinized (white asterisk). B. EDI-OCT (Spectralis, Heidelberg, Germany) at postoperative month 1 visit demonstrates intact foveal contour with resolution of the previous subretinal hyperreflective material corresponding to subretinal hemorrhage. The ellipsoid zone subfoveally is intact (white arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

decrease the chance of postoperative hypotony.[1] Also, the choice of biopsy location is important to decrease the chance of vision threatening VH or SRH.[1] Avoidance of retinal blood vessels and biopsy of the non-foveal edge of the tumor decreases the risk of sub-foveal SRH and VH over the fovea.[1]

4. Conclusion

Transvitreal choroidal biopsy provides many benefits including providing prognostic information through cytogenetic testing for CM and allowing diagnosis of indeterminate lesions. Visually significant complications are uncommon but can result in permanent vision loss without early detection and treatment. Intraoperatively, it is important to take precautions that decrease the risk of hemorrhage from biopsy. Postoperatively, close follow up with serial indirect ophthalmoscopic examination is important to allow early detection and treatment of vision threatening complications. If SRH develops, combined tPA and gas bubble injection may be an effective treatment and can result in good visual outcomes if performed early.

Patient informed consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images. Risks, benefits, and alternatives of transvitreal choroidal biopsy were discussed in extensive detail with the patient. Biopsy can be important for diagnosis as well as for gene expression profiling. Gene expression profiling provides prognostic information that guides frequency of postoperative metastatic screening. Based on the results of gene expression profiling, adjuvant therapies may be available. Gene expression profiling also provides molecular information that may serve as targets for emerging therapies. The risks of biopsy include intraocular hemorrhage, inability to obtain enough sample for analysis especially with small tumors, retinal detachment, endophthalmitis, loss of vision, and extraocular seeding.

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Declaration of competing interest

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