American Journal of Ophthalmology Case Reports 29 (2023) 101777

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Bilateral choroidal effusions and angle closure in the setting of systemic capillary leak syndrome from HLA-directed vaccine and pembrolizumab therapy for squamous cell carcinoma

A. Itzam Marin *, Galia A. Deitz, Lucy I. Mudie, Amit K. Reddy, Alan G. Palestine

Department of Ophthalmology, University of Colorado Denver School of Medicine, Aurora, CO, USA

ARTICLE INFO

Keywords:
Idiopathic systemic capillary leak syndrome
Choroidal effusion
Secondary angle closure
Immune checkpoint inhibitor

ABSTRACT

Purpose: Immunotherapy has become an important addition to oncology treatment plans in recent years. As these therapies become more widely employed, many unique side effects have been reported. In ophthalmology the most well-documented side effects of immune checkpoint inhibitors (ICI) include uveitis, macular edema and dry eye syndrome. This manuscript describes a rare case of bilateral choroidal effusions and secondary angle narrowing in the setting of systemic capillary leak syndrome (SCLS) from an HLA-directed vaccine and an ICI, pembrolizumab, for the treatment of stage IV squamous cell carcinoma (SCC) of the lung.

Observations: A 67-year-old male with a history of stage IV SCC of the lung status-post pneumonectomy presented to the emergency department due to functional decline, anasarca, and dyspnea after receiving an HLA-directed vaccine in combination with pembrolizumab. Extensive workup revealed that his symptoms were secondary to SCLS. Ophthalmology was consulted due bilateral choroidal detachments seen on magnetic resonance imaging. B-scan ultrasound and ultrasound biomicroscopy revealed large, non-appositional choroidal effusions with anterior rotation of the ciliary body. Given minimal response to oral steroid therapy, sub-Tenon's triamcinolone acetonide, atropine, and intraocular pressure-lowering eyedrops were initiated with a good response.

Conclusions and Importance: Choroidal effusions and secondary angle closure can be rare complications of SCLS in the setting of ICIs. Clinicians must be aware of the potentials side effects of ICI therapy, as these medications become more commonly used.

1. Introduction

Systemic immune-related events are associated with immune checkpoint inhibitors (ICI) and occur due to nonspecific activation of the host immune system. They can present with inflammation systemically or in any organ. ICI-related ocular adverse events are rare, occurring in less than 1% of patients.[1] The most common ocular toxicities include uveitis and dry eye.[2] Systemic capillary leak syndrome (SCLS) is a rare but documented side effect of ICIs characterized by hypovolemic shock secondary to leakage of plasma from the intravascular space.[3] Complications of acute SCLS crisis are related to the massive peripheral edema. We described a rare presentation of bilateral choroidal effusions and secondary angle narrowing in the setting of SCLS from an HLA-directed vaccine and an ICI, pembrolizumab, for the treatment of stage IV squamous cell carcinoma (SCC) of the lung. Oncologists and ophthalmologists should be aware of these adverse outcomes in any patient undergoing treatment with these medications.

2. Case report

A 67-year-old male with a history of stage IV SCC of the lung status-post pneumonectomy and receiving an HLA-directed vaccine in combination with pembrolizumab, resulting in near complete remission of his malignancy, presented to the University of Colorado emergency

Abbreviations: AACG, Acute angle closure glaucoma; AC, Anterior chamber; CSC, Central serous chorioretinopathy; HLA, Human Leukocyte Antigen; ICI, Immune checkpoint inhibitors; IFN, Interferon; IL, Interleukin; IOP, Intraocular pressure; LPI, Laser peripheral iridotomy; MRI, Magnetic resonance imaging; PD-1, Programmed cell death protein 1; PCIOL, Posterior chamber intraocular lens; OCT, Optical coherence tomography; SCLS, Systemic capillary leak syndrome; SCS, Squamous cell carcinoma.

* Corresponding author. Sue Anschutz-Rodgers Eye Center, University of Colorado School of Medicine, 1675 Aurora Court, F731, Aurora, Colorado, 80045, USA.
E-mail address: alejandro.marin@cuanschutz.edu (A. Itzam Marin).

https://doi.org/10.1016/j.ajoc.2022.101777
Received 15 July 2022; Received in revised form 18 October 2022; Accepted 5 December 2022
Available online 14 December 2022

department one day following cycle 16 of his therapy. His symptoms and signs included rapid functional decline, diffuse edema of the face, scrotum and extremities, and shortness of breath due to pleural effusions. The patient had been enrolled in a study to receive 0.3 mg of the HLA-directed vaccine GNR-1201 once weekly for 4 weeks, followed by every 3 week dosing along with 200 mg pembrolizumab infusions per protocol.[4] Ophthalmology was initially consulted after an MRI brain showed bilateral choroidal detachments (Fig. 1). While the patient denied vision changes or eye pain upon presentation, he observed redness in both eyes that began after the first few infusion cycles progressing to blurry vision and eye pain worse on the left eye starting approximately after cycles 6–8 of combined therapy. He had been seen by an outside ophthalmologist one month prior and diagnosed as a narrow angle suspect. He was started on intraocular pressure (IOP)-lowering drops and underwent laser peripheral iridotomies (LPIs) in both eyes followed by cataract surgery in his right eye. Cataract surgery was planned in the left eye but not yet done. Initial examination with our ophthalmology team was notable for best corrected visual acuity of 20/25 in the right eye and 20/100 in the left. IOP was 20 and 17 mm Hg in the right and left eye, respectively. He was taking prednisolone acetate 1% three times daily in the right eye, dorzolamide 2% and brimonidine 0.2% three times daily in both eyes, and timolol 0.5% three times daily in the left eye. His pupils were symmetric and reactive without relative afferent pupillary defect. Anterior exam was notable for conjunctival corkscrew vessels in both eyes. The anterior chamber was shallow but quiet, and there were patent superior LPIs in both eyes. There was a posterior chamber intraocular lens (PCIOL) in the right eye and 3+ nuclear sclerotic cataract in the left. Dilated fundus examination demonstrated nasal and temporal non-appositional choroidal effusions without retinal tears or detachments in both eyes. The patient underwent extensive medical workup, which revealed negative infectious testing, hypotension and associated low serum protein of 5.1 g/dL (normal range 6.4–8.9 g/dL), and serum albumin of 2.8 g/dL (normal range 3.5–5.7g/dL). Urinalysis showed trace protein, however further evaluation revealed a normal glomerular filtration rate of >90 mL/min, and serum creatinine of 0.81 mg/dL (normal range 0.70–1.30 g/dL) with urine/protein creatinine ratio of 0.1 mg/day. The remainder of the workup included a normal echocardiogram and liver ultrasound without evidence of cirrhosis or transudative pleural effusions. Given these findings, the patient was diagnosed with SCLS secondary to the HLA-directed vaccine and pembrolizumab therapy. He was initiated on one mg/kg of oral prednisone. The patient also required intermittent short-term vasopressor support in the intensive care unit and was further stabilized with careful repletion of intravascular volume losses and albumin replacement, and was ultimately discharged on an oral corticosteroid taper.

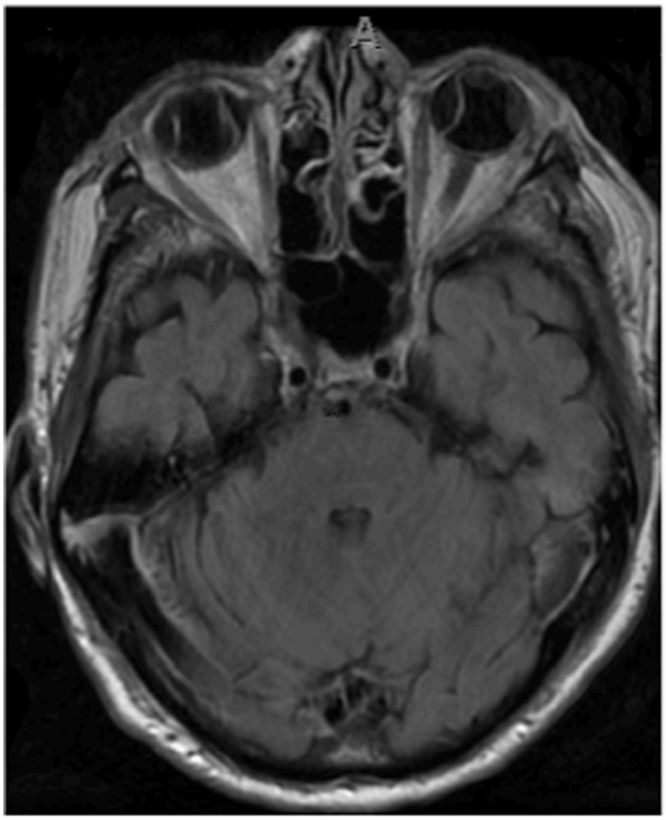

Fig. 1. Flare T2-weighted MRI demonstrating bilateral choroidal effusions.

Repeat ophthalmologic examination at one-week follow-up revealed stable corkscrew vessels in both eyes (Fig. 2A and B) and a shallow anterior chamber in the left eye, which deepened with cycloplegia. B-scan (Fig. 3) and ultrasound biomicroscopy (UBM) revealed large, non-appositional choroidal effusions with anterior rotation of the ciliary body (Fig. 4). Optical coherence tomography (OCT) demonstrated choroidal swelling with a pigment epithelial detachment and minimal sub-retinal fluid in both eyes (Fig. 5). Average sub foveal choroidal thickness was found to be 375μm on the right eye and 455μm on the left. The choroidal effusions improved minimally with oral dexamethasone 20 mg daily, so local corticosteroids with 40 mg sub-Tenon's triamcinolone acetonide (STA) was done in both eyes.

One month after STA, the patient was re-admitted to the hospital with worsening anasarca and hypotension in the setting of his oral corticosteroid taper, requiring pulse-dose intravenous corticosteroids. At this visit, the patient was re-evaluated by our team and was found to have improved visual acuity and normal IOP. Unfortunately, the patient subsequently developed acid-fast bacillus bacteremia, causing rapid systemic decline. The family elected to proceed with comfort care measures and the patient was pronounced deceased shortly after this.

3. Discussion

Choroidal effusion is a pathologic transudative accumulation of serum in the suprachoroidal space between the choroid and sclera. This contrasts with choroidal hemorrhage, which involves an accumulation of blood from choroidal vessel rupture. While the most common risk factor associated with choroidal effusion is incisional glaucoma surgery with over-filtration or bleb leak, any process that shifts flow from choroidal capillaries into the interstitial space may lead to an effusion.[5] SCLS is characterized by transient, severe, reversible hemoconcentration and hypoalbuminemia due to leakage of fluids and macromolecules from capillaries into tissues. Patients with SCLS rapidly develop shock and anasarca due to plasma extravasation.[6] Complications of acute SCLS crisis are thought to be related to the massive peripheral edema leading to multiple system dysfunction, which can include compartment syndrome of extremities, peripheral edema, hypercoagulability, pleural and pericardial effusions, as well as choroidal effusions as presented in our case.[6,7] The bilateral choroidal effusions seen in our patient are consistent with the pathophysiologic process of SCLS resulting in increased transudation throughout the choroidal capillary walls and fluid collection in the potential suprachoroidal space. The effusion caused anterior rotation of the ciliary body, mimicking angle narrowing and causing a rise in intraocular pressure. SCLS can be classified as idiopathic, drug-induced, and/or associated with inflammatory skin diseases.[7] It has also been well described following viral infections.[6] SCLS is an exceedingly rare but documented side-effect of ICIs.[3] Umeda et al.[7] suggested ICI-induced SCLS may be a result of increased inflammatory stimuli involving different pro-inflammatory pathways, including interferon IFN-γ, IFN-α, IL-6 and IL-8. We present a case of bilateral choroidal effusions and secondary angle narrowing in the setting of SCLS from an HLA-directed vaccine and ICI that targets the PD-1 receptor of lymphocytes, pembrolizumab. Given their novelty, there is a paucity of information regarding the adverse effects of HLA-directed vaccines.

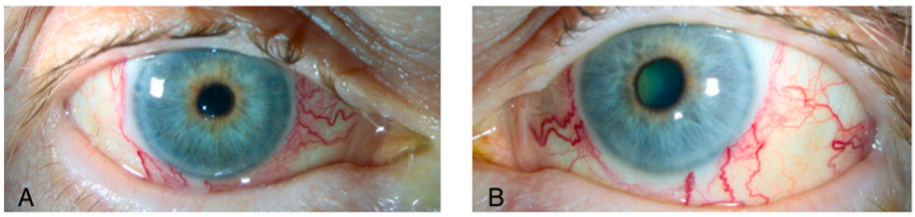

Fig. 2. A, B. External photos of the right (1) and left (2) eye from initial clinic visit showing conjunctival injection and corkscrew vessels.

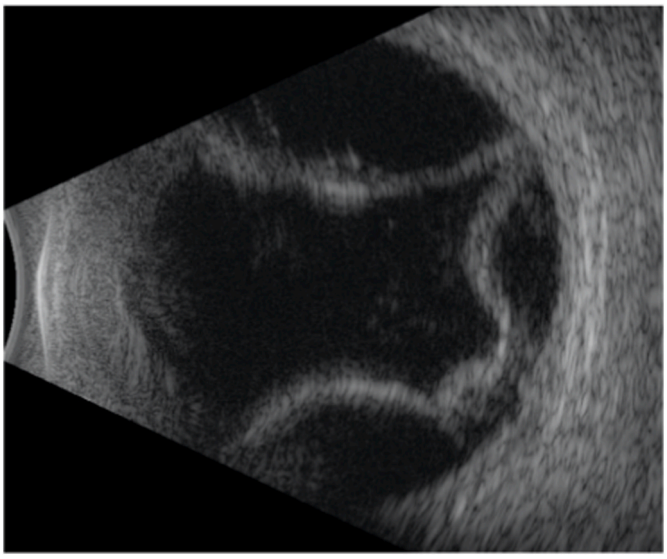

Fig. 3. B-scan ultrasound of the right eye from initial visit. T6E view showing large, serous choroidal detachment.

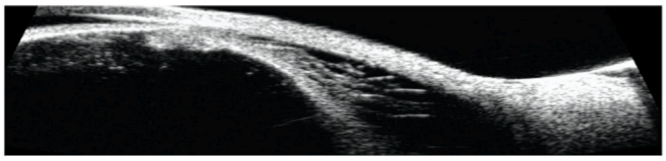

Fig. 4. UBM of the left eye from initial clinic visit. 3L view showing anteriorly rotated ciliary body and choroidal effusion.

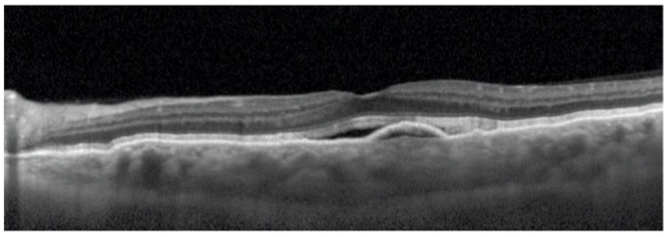

Fig. 5. Horizontal OCT of the left eye from initial clinic visit showing choroidal swelling with a PED and SRF.

However, in the preliminary results for the phase II clinical trial, the combination of pembrolizumab and GRN-1201 did not appear to increase the frequency of major treatment-related adverse events compared to pembrolizumab alone.[4]

There have been few cases demonstrating the ocular complications seen in SCLS. Those described so far include facial and periorbital edema,[8] bilateral acute angle closure (AAC) after hematotoxic snake bite,[9] and bilateral choroidal effusion following a viral infection.[10] Most of these cases reported improvement with topical and systemic steroids as well as IOP-lowering medications. Given the lack of improvement with systemic steroids in our patient, local therapy was administered in the form of STA, resulting in near complete resolution of choroidal effusions.

4. Conclusions

Although there have been separate reports of AACG[9] and bilateral choroidal effusion from SCLS,[11] there are no reports of ICI-induced SCLS leading to bilateral choroidal effusion with simultaneous secondary AAC. Our patient also received an HLA-directed vaccine as well an ICI. Given that SCLS has been reported with ICI use, we hypothesize that our patient's SCLS was related to his ICI, however it is possible that his HLA-directed vaccine also played a role. The uncertainty of the causative agent is a significant limitation of our case report. Furthermore, it is also important to note that given the poor clinical status of our patient we were unable to obtain further measurements including axial length, corneal thickness, and fluorescein angiography/optical coherence tomography angiography. Finally, our report of a single patient must be interpreted cautiously when generalizing to other populations.

It is well stablished that immunotherapy has radically changed the paradigm of cancer treatment and are known to cause fewer toxicities than conventional chemotherapy. However, their greater use has resulted in the discovery of new immune-related adverse effects.[12] As the use of pembrolizumab and other PD-1 inhibitors continue to expand, more eye-related adverse events are likely to occur. Further studies investigating potential exacerbating and protective factors for these important adverse related events would be useful to help prevent these conditions. We recommend prompt referral to ophthalmology for patients undergoing immunotherapy who develop any visual symptoms, in order to prevent potential delays in diagnosis and treatment.

Ethics approval and consent to participate

Not applicable.

Consent for publication

No personal identifying data included. No consent obtained.

Availability of data and materials

Not applicable.

Funding

No funding or grant support.

Authors' contributions

LIM, AGP, GAD followed the patient, acquired images, and interpreted the data. AIM, AGP, GAD, AKR made substantial contributions to conceptualization, design, and presentation of data. AIM, GAD contributed by writing up the manuscript. All authors read and

approved the final manuscript.

Presentations

Women in Ophthalmology Summer 2022 Symposium, Amelia Island, FL.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

References

1. Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One*. 2016;11(7), e0160221. https://doi.org/10.1371/journal.pone.0160221.
2. Dalvin LA, Shields CL, Orloff M, Sato T, Shields JA. Checkpoint inhibitor immune therapy: systemic indications and ophthalmic side effects. *Retina*. Jun 2018;38(6):1063–1078. https://doi.org/10.1097/IAE.0000000000002181.
3. Qin H, Vlaminck B, Owoyemi I, Herrmann SM, Leung N, Markovic SN. Successful treatment of pembrolizumab-induced severe capillary leak syndrome and lymphatic capillary dysfunction. *Mayo Clin Proc Innov Qual Outcomes*. Jun 2021;5(3):670–674. https://doi.org/10.1016/j.mayocpiqo.2021.01.004.
4. GRN-1201 with pembrolizumab in subjects with metastatic PD-l1+ NSCLC. ClinicalTrials.gov identifier. NCT 03417882. Updated June 14 https://ClinicalTrials.gov/show/NCT03417882; 2022. Accessed August 30, 2022.
5. Schuman JS, Greenfield DS. Ophthalmic surgery, lasers & imaging. *Ophthalmic Surg Laser Imag*. Jan-Feb 2003;34(1):6.
6. Siddall E, Khatri M, Radhakrishnan J. Capillary leak syndrome: etiologies, pathophysiology, and management. *Kidney Int*. Jul 2017;92(1):37–46. https://doi.org/10.1016/j.kint.2016.11.029.
7. Umeda Y, Hayashi H, Sugiyama S, Aoyama Y. Systemic capillary leak syndrome triggered by anti-programmed death 1 checkpoint inhibitor in psoriasis. *J Dermatol*. Nov 2020;47(11):1322–1325. https://doi.org/10.1111/1346-8138.15541.
8. Clarkson B, Thompson D, Horwith M, Luckey EH. Cyclical edema and shock due to increased capillary permeability. *Am J Med*. Aug 1960;29:193–216. https://doi.org/10.1016/0002-9343(60)90018-8.
9. Kulkarni C, George TA, Av A, Ravindran R. Acute angle closure glaucoma with capilllary leak syndrome following snake bite. *J Clin Diagn Res*. Oct 2014;8(10):VC01–VC03. https://doi.org/10.7860/JCDR/2014/10716.4924.
10. Cruz-Villegas V, Berrocal AM, Davis JL. Bilateral choroidal effusions associated with dengue fever. *Retina*. Aug 2003;23(4):576–578. https://doi.org/10.1097/00006982-200308000-00031.
11. Brewington BY, Kondapalli S, Kothari SS, Parikh SV, Cebulla CM. Choroidal effusion mimicking uveal melanoma: a novel presentation of idiopathic systemic capillary leak syndrome. *Ocul Oncol Pathol*. Dec 2021;7(6):390–395. https://doi.org/10.1159/000512765.
12. Choi J, Lee SY. Clinical characteristics and treatment of immune-related adverse events of immune checkpoint inhibitors. *Immune Netw*. Feb 2020;20(1):e9. https://doi.org/10.4110/in.2020.20.e9.