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Unilateral conjunctival Classic Kaposi Sarcoma following a COVID 19 booster

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ABSTRACT

Purpose: We describe a case of Classic Kaposi's sarcoma in a functionally monocular patient following a COVID19 vaccine booster and provide compelling evidence that suggests the booster was a relevant co-factor in the initiation of the disease process.

Observations: The patient presented with red, irritated conjunctival area described as "bubbling" in her right eye. While her past medical history includes hypercholesterolemia and hypertension, she had no history of a compromised immune system. Her ophthalmologic history is more complex including treatment for glaucoma. The patient has 20/20 uncorrected vision OD and LP OS. Due to her ocular co-morbidities, the patient initially received interferon alpha 2-B qid for 6 weeks. However, topical therapy failed to decrease the size of the conjunctival lesions. After referral to Radiation Oncology, the right eye/orbit was treated with electron beam therapy for 1 month which caused a marked decrease in the size and vascularity of the conjunctival lesions. A slow improvement continued during followup.

Conclusion and importance: In that the vaccine booster preceded the cancer, it appears etiologic to the appearance of Kaposi's sarcoma. The patient's monocular vision and glaucoma complicated her treatment. This case expands on current concepts of cofactors needed for the development of Kaposi's sarcoma in that vaccine booster administration was relevant to tumor progression and both clinical and mechanistic evidence is presented to support this hypothesis.

1. Introduction

Kaposi Sarcoma (KS) is a low-grade vascular tumor associated with KS herpesvirus/human herpesvirus 8 (KSHV/HHV8) infection in lymph or blood vessels.[1] HHV8 infection is necessary but not sufficient for KS to develop as additional factors (genetic, immunologic, and environmental) are also required.[2]

KS lesions typically appear on the skin or mucosal surfaces, and thus can involve the conjunctiva. There are four clinical-epidemiologic variants of KS: Classic (*Mediterranean*), Endemic (*African*), Iatrogenic (*Transplant related*), and acquired immunodeficiency syndrome (AIDS) associated (*Epidemic*). Classic KS primarily effects elderly individuals of Mediterranean and Eastern European descent. Males are more frequently affected than females, with a ratio of as high as 15:1.[3] Classic KS is characterized by the development of purpuric papules that appear on the extremities and progress proximally. Involvement of the mucosal membranes occurs in approximately 10 % of patients.[3] Iatrogenic or drug-induced KS occurs in immunocompromised patients and those receiving immunosuppressive therapy. Iatrogenic KS occurs in patients following organ transplantation who require systemic immunosuppressive therapy. In a recent report of 137 patients with KS, the most common presenting forms were Classic (64 %) and Iatrogenic (37 %).[4]

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However, as a female the "Classic" form is unlikely.

Ophthalmic involvement can occur with any of the KS subtypes. Conjunctival KS lesions appear as a red to pink tumors.[5] Diagnosis of KS is confirmed by biopsy showing characteristic spindle-shaped tumor cells on histology.[3] KS histology is fairly consistent across all subtypes and changes as the tumor evolves from the initial early-patch stage to the well-developed tumor stage. The early-patch stage is characterized by abnormal vessels lined by thin endothelial cells. Sparse chronic inflammatory cells, extravasated red blood cells, and hemosiderin-laden macrophages may be variably seen. The well-developed tumor is defined by fascicles of spindle-shaped cells often interspersed with a variable chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and dendritic cells in addition to hemosiderin-laden macrophages. Typically, lesions are devoid of marked cellular pleomorphism, necrosis, or a significant number of mitotic figures. KS lesions may stain with over 100 different primary antibodies, more common ones including factor VIII–related antigen, CD31 (PECAM-1), and CD34; and in advanced KS, CD34,CD31, D2-40, LYVE-1, VEGFR-3, and Prox-1. Important in the immunochemical definition is the identification and localization of HHV8 within KS cells, using the most diagnostically relevant immunostaining technique, LNA-1.[16] Treatment of KS depends on the patient's age, general health, current medications and immune status. Small, isolated KS lesions can be excised at biopsy. Larger or multifocal tumors may be treated systemically or regionally.[5]

Herein, we report a case of unilateral KS isolated to the conjunctival surface that appeared after a COVID19 booster.

2. Case report

A 75-year-old Egyptian woman presented to the Stony Brook Ophthalmology clinic for a second opinion regarding the treatment of a conjunctival lesion OD. Her past medical history was notable for hypercholesterolemia, and hypertension. She had no history of a compromised immune system (systemically). Her past surgical history included appendectomy (1969) and removal of a benign adrenal tumor (1995).

Her ophthalmologic history is complex. The patient has moderately advanced uveitic glaucoma OU, chronic iridocyclitis OU, posterior vitreous detachment OU, epiretinal membrane OU, pseudophakia OU, pseudophakic bullous keratopathy OS, cystoid macular degeneration OS, presumed ocular histoplasmosis syndrome (POHS) and dry eye disease (DED). Her past ocular surgeries included bilateral phacoemulsification with PCIOL, bilateral trabeculectomy with mitomycin C, laser trabeculoplasty OD, YAG capsulotomy OS, Descemet's stripping endothelial keratoplasty OS, seton implant OS and penetrating keratoplasty OS. Prior to her presentation reported here, she had not had a surgical procedure in either eye for over five years. Her moderately advanced glaucoma was treated with latanoprost OD. She also used loteprednol and cyclosporin drops OU for DED.

The patient's chief complaint was of a red, irritated conjunctival area OD that she described as "bubbling." The appearance and the symptoms developed a few weeks following the COVID vaccine booster (Pfizer). On exam, uncorrected vision was 20/20–2 OD and LP OS. The vision in the left eye was stable, and was decreased due to corneal opacification from a failed graft and glaucoma). Applanation IOP was 11 mmHg OU. She had a diffuse avascular bleb in the superior quadrant. However, her anterior segment showed elevated nodular and plaque-like conjunctival lesions OD with some involvement of the bleb area (Fig. 1A). Ultrasound biomicroscope examination confirmed thickened conjunctival lesions OD with the largest lesion measuring 1.68 mm in height (Fig. 1B).

Prior to her presentation in our clinic, her primary ophthalmologist had biopsied the conjunctiva as the lesions did not respond to topical antibiotic therapy. Histopathology was consistent with KS (Fig. 2).

The patient was referred for ophthalmic oncology (PTF) and hematology oncology for a systemic evaluation. Laboratory testing confirmed the patient was HIV-negative. No other systemic involvement was seen clinically or with positron emission tomography (PET scan).

Patient course: Due to her ocular co-morbidities and moderately advanced glaucoma in her only seeing eye, excisional biopsy of the affected conjunctival tissues was not felt to be prudent. Removal of the

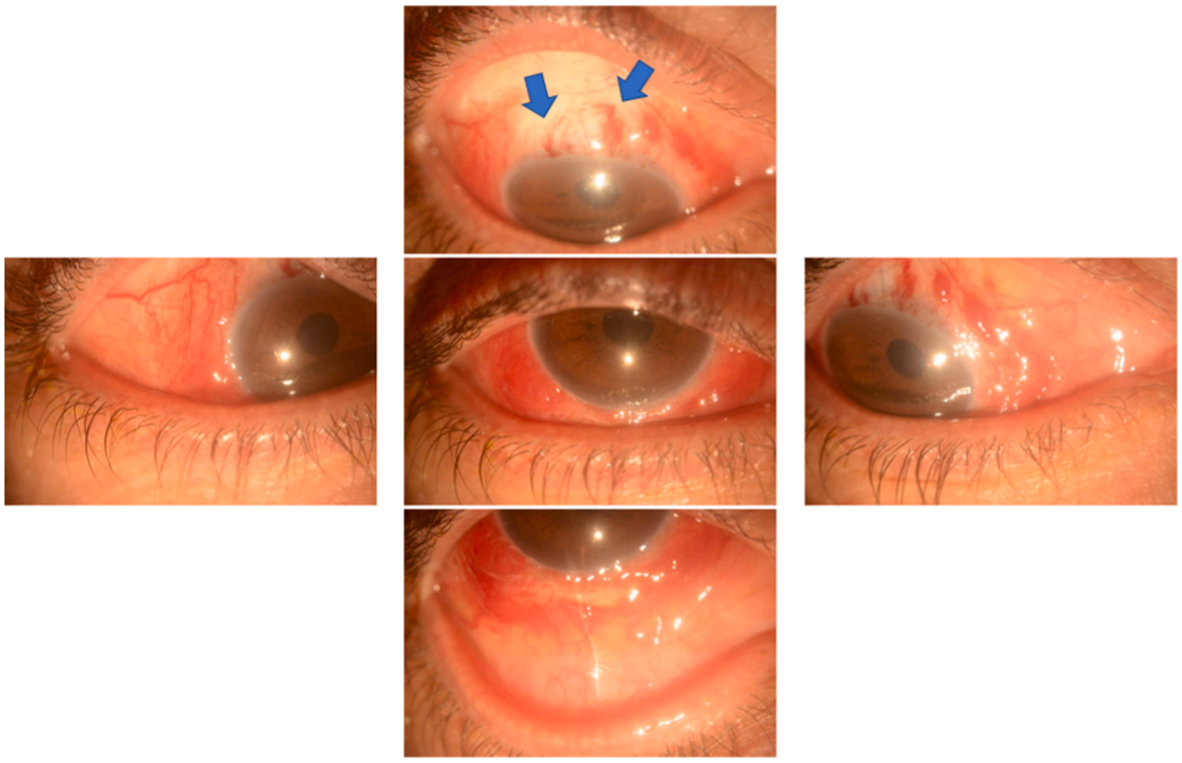

Fig. 1 A. Baseline anterior segment photos showing thickened vascular tumor in the primary gaze positions. Note involvement of bleb area with presumed tumor (blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

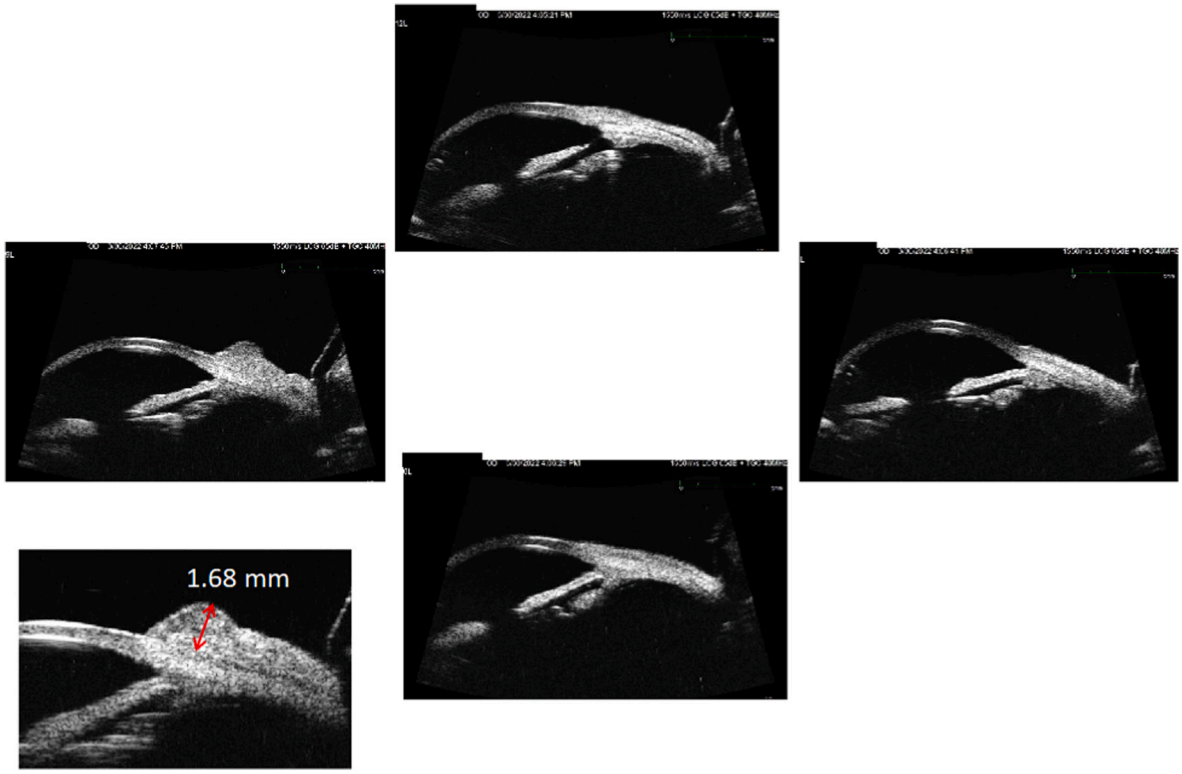

Fig. 1 B. Baseline anterior segment ultrasound biomicroscope images showing thickened vascular tumor in the primary gaze positions. Thickest area measured 1.68 mm in height inset (image taken at 8:00).

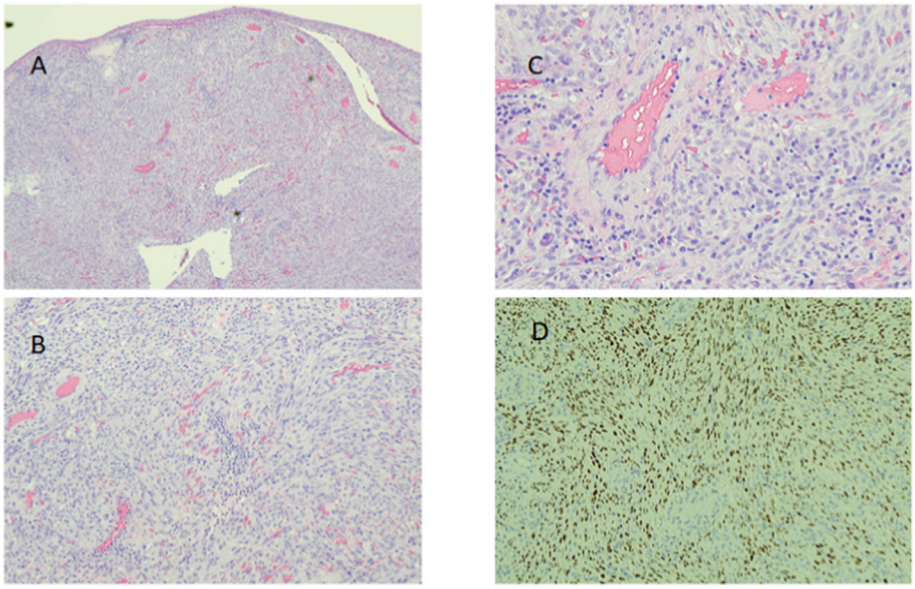

Fig. 2. Histopathologic image of biopsied conjunctival tissue. Figure A, B, C low medium and high power fields showing irregular vascular spaces with proliferating atypical endothelial cells and scattered mitoses. In addition, extravasated red blood cells are identified. The overlying conjunctival epithelium shows early squamous metaplasia (Fig A). Neighboring variable accompanying chronic inflammation is also noted (Figure B, C). Figure D shows positive immunostaining with HHV8 within the vascular proliferation which were also CD34 positive. Findings support the diagnosis of Kaposi sarcoma. Lesional cells were negative for AE1/AE3, Me lan-A, and S-100. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

involved conjunctiva would have eliminated her bleb and made the placement of another glaucoma drainage device difficult to cover. Instead, the patient was initially started on interferon alpha 2-B (1000000 units/ml) qid for 6 weeks. At the conclusion of this topical therapy, her uncorrected acuity remained 20/20 OD, but the conjunctival lesions had not regressed from the initial presentation (Fig. 3). The patient was then referred to Radiation Oncology (SR) for evaluation and management. The right eye/orbit was treated with electron therapy (20 Gray in 10 fractions) over a period of 1 month. Following radiation therapy, there was a marked decrease in the size and vascularity of the conjunctival lesions. A slow improvement in her appearance continued over the next three months (Figs. 4 and 5).

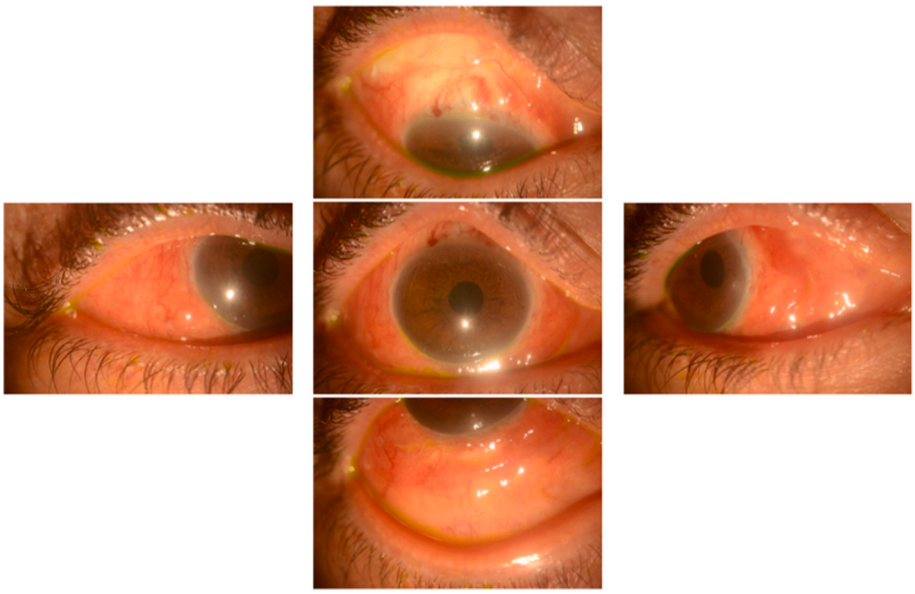

Fig. 3. Slit lamp photos showing anterior segment appearance 6 weeks following topical therapy with interferon alpha 2-B (1000000 units/ml) qid. There is little to no change in lesion size from baseline.

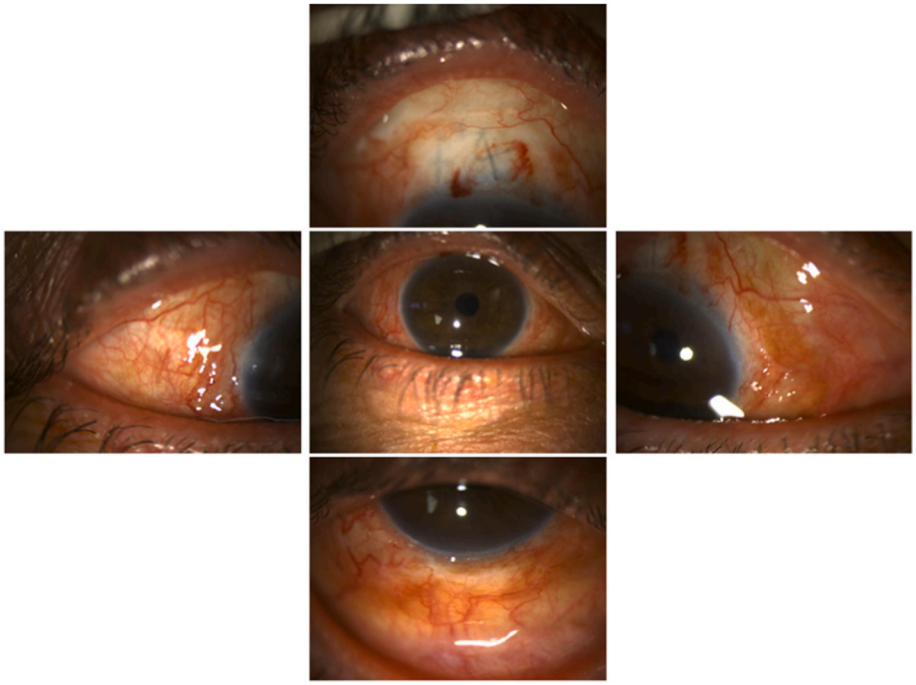

Fig. 4. Slit lamp photos showing anterior segment appearance shortly after treatment with electron therapy (20 Gray in 10 fractions). The size and vascularity of the conjunctival lesions has begun to decrease.

3. Discussion

Human Herpesvirus-8 (HHV8) infection alone is insufficient for the development of KS. It requires some degree of host immune dysfunction or local inflammatory milieu.[6,7] In this particular case, it appears that COVID19 vaccination acted as one of the additional co-factors necessary to induce KS in that there was no other clear cause other than the temporal relationship between booster vaccine and development of KS.

Of the four clinical-epidemiologic classifications, the patient is a female and has a presentation that most closely fits the Iatrogenic form. Although the patient is of Mediterranean descent (Egyptian) and of the appropriate age, Classic KS affects males far more frequently than females and typically is characterized by development of purpuric papules that initially appear on the lower extremities and progress proximally. Iatrogenic or drug-induced KS may present as localized muco-cutaneous lesions and typically occurs in immunocompromised patients receiving immunosuppressive therapy, most commonly patients following organ transplantation or those with other immunocompromised states.

Although our patient presented with a localized muco-cutaneous lesion, her health was excellent and she was not using any systemic immunosuppressive agents.

Although we believe the COVID19 vaccine booster acted as a cofactor to induce progression of HHV8 infection to KS disease in this

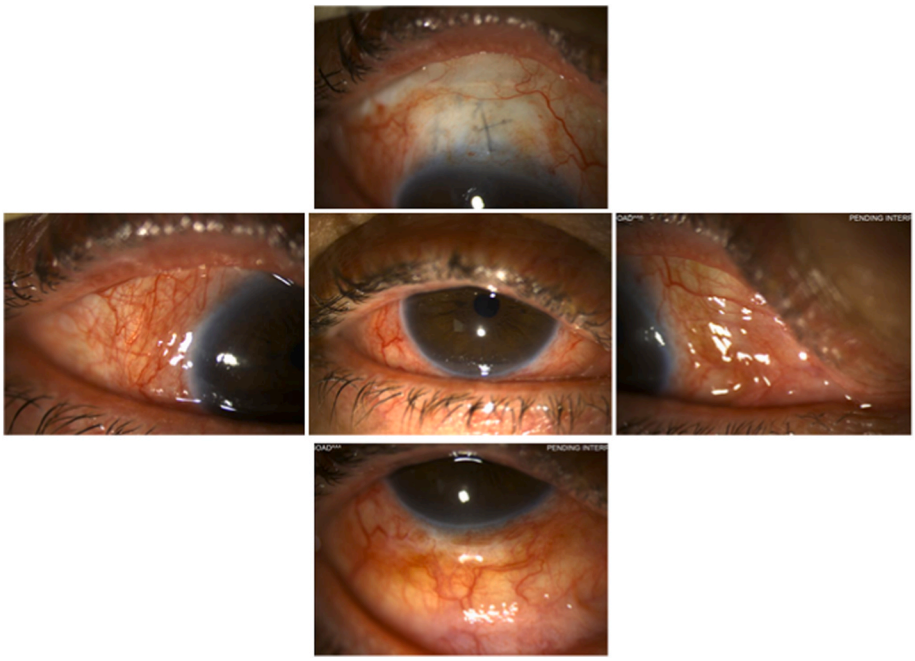

Fig. 5. Slit lamp photos showing anterior segment appearance 3 months following treatment with electron therapy (20 Gray in 10 fractions). The size and vascularity of the conjunctival lesions has decreased dramatically. There are no areas of conjunctival thickening.

case, we cannot rule out the contribution of her other ocular co-morbidities acting as additional co-factors. The patient's history of Presumed Ocular Histoplasmosis Syndrome (POHS) and Dry Eye Disease (DED) for which she was using topical loteprednol and cyclosporin may also have played a contributory role. It is possible that the patient's POHS or history of iridocyclitis indicate a local inflammatory milieu exists that could have contributed to disease progression. We think this is unlikely as the patient's POHS and iridocyclitis were quiet without any recent activity requiring treatment for years. In addition, there are no reported cases of KS related to POHS infection in the literature. However a definitive conclusion cannot be made as a single case report of Histoplasma capsulatum and KS in a skin lesion of a patient with HIV related KS has been described.[8]

The patient was also using two topical anti-inflammatory drugs for DED which have immunosuppressive properties. Although systemic cyclosporin has been associated with KS, it is unlikely that the patient's topical use was the cause of KS progression in this case. The use of topical cyclosporin A has been extensively reported and studied since 1980, and a comprehensive review of the literature found no reports of KS or other malignancy caused by topical use of the medication.[9] Similarly, although progression of KS has been associated with immunosuppression from systemic steroids, there are no reports in the literature of KS progression resulting from topical use of loteprednol. For these reasons, we do not believe that the patient's KS presentation fits clearly into the iatrogenic category.

Although it is not possible to definitively prove a causative role for booster vaccine in the development of neoplasm in this case, many factors make this probable. The KS developed in the weeks following a COVID19 booster during which time there were no other predisposing illnesses or medical conditions that occurred. Beyond this temporal association, there are also case reports of KS development following COVID19 infection.[10,11]

There is also mechanistic data to support this assertion. In a report by Chen et al., the SARSCoV-2 virus was demonstrated to induce KS in a human iSLK.219 cell line.[12] They demonstrated that cells transfected with both the spike protein and nucleid capsid protein of the virus demonstrated a lytic reactivation of KS. It is therefore plausible that the Pfizer or Moderna vaccines, both of which are based on building the virus's spike protein,[13] may be able to induce a similar effect causing an in vivo KS reactivation. However, this assertion is only speculative at this point and should not be used to discourage vaccination. There are no other case reports of KS in the literature as a result of vaccination which is still recommended in patients with KS.[14] We hypothesize that COVID19 vaccination and the local immunosuppression caused by topical loteprednol and cyclosporin were the major co-factors needed to induce the localized conjunctival KS in this case.

The specific clinical location of the tumor also presented unique challenges as the patient was functionally monocular with moderately advanced glaucoma in her seeing eye. In consideration of her diffuse disease and the presence of a functioning trabeculectomy, surgical removal of the effected tissues, a viable treatment option for some cases (which had been recommended to the patient elsewhere), was not felt to be the best alternative in this case due to concerns about how this would impact her glaucoma control. Instead, at first, a nonsurgical approach with medication (topical interferon) with a poor response. Therefore, electron beam radiation therapy was employed with good effect to control the local disease.[15] The conjunctiva of the right eye was treated with radiation to a total dose of 20 Gy in 10 fractions with 2 Gy fraction daily. The treatment was performed by using 6 MeV election beams directly en face to the involved conjunctiva and eyelid. The treatment course was uneventful. There was no loss of eyelash or eyebrow Fortunately, neither treatment negatively impacted the function of her bleb and her IOP remains well controlled at last follow up. The patient continues to remain disease free and undergoes frequent monitoring for KS recurrence and any change in her glaucoma status.

4. Conclusions

This report presents a unique and challenging case of ocular KS in a functionally monocular patient following COVID19 vaccine booster. We hypothesize that vaccine booster in addition to local administration of loteprednol and cyclosporin was relevant to KS progression in this case because our patient does not fit any of the 4 classic clinico-epidemiologic types of KS, and because of the temporal association with COVID19 booster administration. In addition, we present other clinical and mechanistic data to support this assertion. It deserves repeating that no other case

reports of KS in the literature as a result of COVID19 vaccination exist and that vaccination is still recommended in patients, even those with a history of KS.[14] For the ophthalmologist who discovers conjunctival Kaposi's sarcoma, it is important to coordinate care with a team consisting of a medical/ophthalmic oncologist (and/or HIV-specialist), and radiation oncologist. This report helps expand the current understanding of potential cofactors needed in addition to HHV8 infection for the development of KS.

Consent

Consent to publish this case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors contributed to the Writing-review and editing of this case report. EW and RH also wrote the original draft and JS provided the methodology for this case report.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this case report.

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