

Case report

A case of hypertrophic herpes simplex virus affecting the eyelid and cornea masquerading as IgG4-related disease

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A B S T R A C T

Purpose: To report a case of hypertrophic herpes simplex virus (HSV) of the eyelid and cornea masquerading as IgG4-related disease.

Observations: A 37-year old African American female with a past medical history of human immunodeficiency virus (HIV) on highly active antiretroviral therapy (HAART) and a recent history of treated genital herpes, presented with an ulcerative lesion of the left upper and lower eyelids, and severe ocular inflammation with symblepharon. Initially, eyelid biopsy revealed findings consistent with IgG4-related disease, and the patient was treated with high dose oral prednisone. After one week of therapy, there was no improvement in the patient's symptoms, and she subsequently developed a corneal epithelial defect which progressed to chronic ulceration. Repeat biopsy and corneal cultures revealed herpes simplex virus type 2. The patient was treated with high dose acyclovir, and the lid lesion improved. The conjunctival inflammation and corneal epithelial defect resolved but symblepharon restricting her eye movement remained. She also developed corneal vascularization and opacification causing severe vision loss.

Conclusions and importance: Chronic hypertrophic herpes simplex virus infection is a rare condition reported in patients with HIV. While there have been few reports of hypertrophic HSV affecting the eyelid, this is the first reported case of hypertrophic HSV affecting the eye, resulting in severe vision loss.

1. Introduction

Herpes simplex virus (HSV) is a double stranded DNA virus that commonly affects the skin, mucous membranes, and eye. HSV type 1 typically affects the ocular and oral regions while type 2 typically affects the genital area. Primary ocular infection by HSV-1 usually manifests as a blepharoconjunctivitis. After initial infection, the virus can establish latency in the trigeminal ganglia, and when reactivated, can cause epithelial and/or stromal keratitis and endothelitis.^{1,2} This manifestation of HSV type 1 can cause recurrent inflammation, scarring, and decreased vision and is one of the leading causes of corneal blindness in the developed world.

HSV type 2 is a common cause of sexually transmitted infection of the genital area, but is uncommonly encountered in the eye. When it is present in the eye, it usually manifests in the posterior segment, with uveitis and acute retinal necrosis.³ HSV type 2 in the anterior segment is extremely rare, but has been reported to cause keratitis in infants who were infected through a placental or maternal genital tract route.^{4,5} HSV type 2 affects the genital area far more commonly, and in patients

with HIV, may demonstrate atypical presentations, such as hypertrophic lesions resistant to antiviral therapy.^{6–13} There have been two cases of HSV type 2 causing a similar presentation in the eyelid but in both cases the eye remained unaffected.^{14,15} We report the first case of chronic hypertrophic HSV infection of the eyelid with associated conjunctivitis and keratitis ultimately resulting in severe vision loss. Interestingly, our first biopsy was negative for HSV and positive for IgG4-related disease.

2. Case report

A 37-year old African American woman with a past medical history of HIV on HAART presented with a two-month history of a growing, painless lesion of the left medial canthus and upper and lower eyelids. She reported that the lesion began as a pustule and continued to worsen despite treatment with erythromycin ointment. The patient also reported a recent history of treated genital herpes for which she was on a prophylactic oral dose of valacyclovir 1000 mg daily. She denied any history of trauma, insect bites, or recent travel. She denied history of

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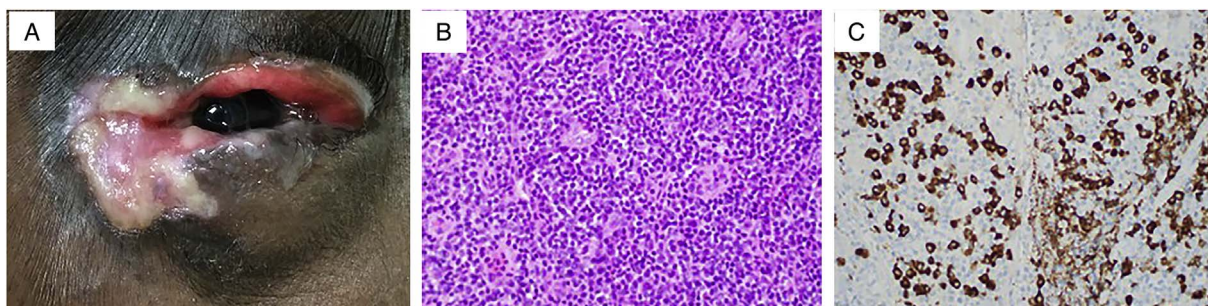


Fig. 1. A: Photograph of ulcerative lesion centered at left medial canthus. B: Biopsy shows dense polytypic plasma cell infiltrate in background of fibrosis, acute and chronic inflammation (hematoxylin & eosin stain, 400). C: Immunohistochemistry of the biopsy shows IgG4 plasma cell infiltrate (> 100 per high-power field) with IgG4:IgG ratio $> 40\%$ (immunostain, $\times 400$).

diabetes mellitus. On examination, the patient was afebrile. Her best corrected visual acuity was 20/20 in the right eye and 20/100 in the left eye. There was an ulcerative lesion centered at the medial canthus (Fig. 1A). The lid margin architecture was distorted and there was significant madarosis. Anterior segment examination revealed severe conjunctival inflammation with nasal and inferior symblepharon and mucous discharge. Pupillary response, intraocular pressure, and fundoscopic examination of the left eye were within normal limits. The examination of the right eye was entirely within normal limits. Computerized tomography (CT) scan of the orbits with contrast revealed preseptal involvement consistent with the medial canthal pathology as well as enlargement of the left lacrimal gland. HIV viral load was undetectable at less than 20 copies/ml, and CD4 level was low at 10% (normal 25–58%). Laboratory studies were significant for antinuclear antibody (ANA) and anti-ro (SSA) positivity. Indirect immunofluorescence antinuclear antibody test (IF-ANA) detected a strongly positive 241 AU/ml (normal, 100 AU/ml) speckled pattern. Complete blood count, anti-neutrophil cytoplasmic antibody (ANCA), angiotensin converting enzyme (ACE), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and treponemal IgG were negative. Serum IgG subclass 4 level was 35.7 mg/dL (normal 2.4–121 mg/dL).

Culture of the lesion was positive for moderate growth of latex positive staphylococcus, which was thought to be a contaminant. With malignancy being on the differential diagnosis, an incisional biopsy of the lid lesion was performed which revealed a dense polytypic plasma cell infiltrate fibrosis, and phlebitis (Fig. 1B). Biopsied tissue was not processed by immunofluorescence to evaluate for ocular cicatricial pemphigoid given that there were greater than 100 IgG4-positive plasma cells per high power field with IgG4/IgG ratio $> 40\%$ consistent with IgG4-related disease (Fig. 1C). Stains for acid-fast bacilli, bartonella, and fungus were negative. Because the clinical appearance seemed atypical for IgG4-related disease, the specimen was sent to the pathology department at another institution for a second opinion. The diagnosis of IgG4-related disease was confirmed. At this point the patient was admitted to the hospital with a presumed diagnosis of IgG4-related inflammatory disease and a systemic work up for site involvement elsewhere proved negative.

The patient was started on oral prednisone 1 mg/kg day and tobramycin/dexamethasone ophthalmic ointment was applied four times daily to the lid lesion. The patient was followed closely by the departments of Ophthalmology, Dermatology, Rheumatology, and Infectious Disease. After 1 week of corticosteroid therapy, there was no improvement of the lid lesion, and the cornea and conjunctiva became progressively more inflamed. She developed a corneal epithelial defect (Fig. 2A) with stromal haze, and the visual acuity in the left eye dropped to counting fingers at 3 feet. Erythromycin ophthalmic ointment was applied to the cornea and conjunctiva hourly. The patient was also started on oral azathioprine 100 mg daily. The patient then developed symptoms of generalized weakness and was found to have severe metabolic acidosis secondary to diabetic ketoacidosis. She was

admitted to the intensive care unit for an insulin drip and fluid resuscitation.

Given no improvement in the appearance of the lid lesion and enlargement of the corneal epithelial defect (Fig. 2B), a second biopsy of the eyelid was performed. This time pathology revealed syncytial and scattered epithelial cells with a viral cytopathic effect including smudged, “ground glass” intranuclear inclusions in a background of acute inflammation and necrosis (Fig. 3A). HSV immunostain revealed scattered HSV positive cells (Fig. 3B). Culture swab of the cornea was also positive for HSV-2. The department of infectious disease noted the lesion’s striking similarity to HIV-associated chronic hypertrophic herpes and the patient was started on intravenous acyclovir 1200 mg every 8 hours. Oral prednisone (60 mg) was continued given the intense ocular inflammatory response, and ganciclovir ophthalmic ointment was applied to the eye six times daily.

After starting high dose antiviral therapy, the patient’s eyelid lesion began to show signs of improvement, and it continued to improve during her 2-week hospital stay. Her corneal and conjunctival inflammation improved, but the epithelial defect enlarged, and the cornea became progressively vascularized. Her vision was stable at counting fingers at 3 feet, and her posterior segment examination remained normal. Since her corneal sensation was intact and her cornea was not exposed, it was thought that her persistent epithelial defect was most likely secondary to limbal stem cell deficiency in the setting of severe, chronic inflammation. She was followed closely over a period of two months following discharge from the hospital and continued on aggressive ocular lubrication. The epithelial defect resolved during this time but the cornea became progressively vascularized and opacified. The symblepharon also remained, restricting her eye movements. The lid lesion improved with minimal scarring and residual hypopigmentation of skin (Fig. 4).

3. Discussion

Recent reports have demonstrated that the epidemiology of herpes simplex virus throughout the world is changing.¹⁶ While classically thought to be an infection acquired during childhood, HSV-1 is now increasingly acquired later in life, among adolescents and older adults. Also, while it was once thought that HSV-1 reactivates only from the trigeminal ganglia and HSV-2 from the sacral ganglia, the opposite has also been demonstrated. Genital herpes can be caused by HSV-1, which can partly be explained by the increase in the practice of oral-genital sex versus genital-genital sex in teenagers.¹⁷ Likewise, HSV-2 has been shown to involve the eye, specifically in the form of acute retinal necrosis (ARN). ARN may be associated with a history of congenital HSV-2 infection, and it has been postulated that the recent rise in congenital HSV infection will lead to an increase in the prevalence of ARN in the future.¹⁸ While the link between ARN and HSV-2 has been well established, little has been reported on HSV-2 affecting other areas of the eye, particularly the anterior segment. Our patient not only was biopsy positive for HSV-2 in the eyelid, but she also had HSV-2 positive corneal

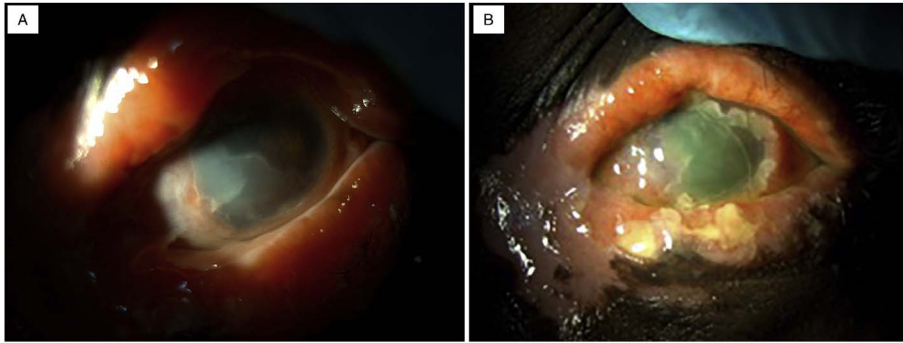


Fig. 2. A: Photograph of corneal epithelial defect. B: Photograph of enlarged corneal epithelial defect.

cultures.

In patients co-infected with HIV, atypical HSV presenting as chronic hypertrophic genital ulcers have been reported, an entity which universally affects the genital area, is notably difficult to treat, but can respond to high dose antiviral therapy.^{6–12} These lesions have been reported in both the severely immunosuppressed as well as patients who are stable on antiretroviral therapy.⁶ All reported cases have involved the genital area with histopathologic findings including hyperplasia of the epidermis with multinucleated keratinocytes and a dense inflammatory infiltrate with prominent plasma cells. The lesions are universally difficult to manage, because of their resistance to first line antiviral agents at their usual doses. High-dose intravenous antivirals have been shown to be effective. Topical 5% imiquimod has also been reported to be effective after treatment failures with oral and IV antivirals.⁷

Our patient developed a chronic hypertrophic HSV lesion of the eyelid with severe conjunctivitis and keratitis. While our initial biopsy was negative for HSV-2, this has often been the case with hypertrophic HSV. Small biopsies are often inconclusive or provide misleading information, as it may be difficult to demonstrate the virus in the presence of chronic extensive granulation tissue.^{19,20} Our repeat biopsy was in fact positive for HSV-2, and this in conjunction with the experience of our infectious disease colleagues secured the diagnosis. As with other reported cases of hypertrophic HSV, our patient had a prolonged hospital course with a slow response to treatment. She did not respond to standard antiviral therapy but improved on high-dose IV acyclovir.

In this case, our initial biopsy was negative for HSV, and positive for IgG4. IgG4-related disease is a recently recognized systemic inflammatory disorder that is now being diagnosed with increased frequency. Often affecting the salivary & lacrimal glands, key distinguishing features include lesions with histopathologic findings of IgG4 positive plasma cell infiltration, fibrosis, and obliterative phlebitis.²¹ Other diagnostic criteria for IgG4-related disease include elevated serum IgG4 levels. However, at least one-third of patients with IgG4-related disease have normal serum IgG4 levels. Therefore, an elevated serum IgG4 level is not necessary for the diagnosis. In addition, IgG4

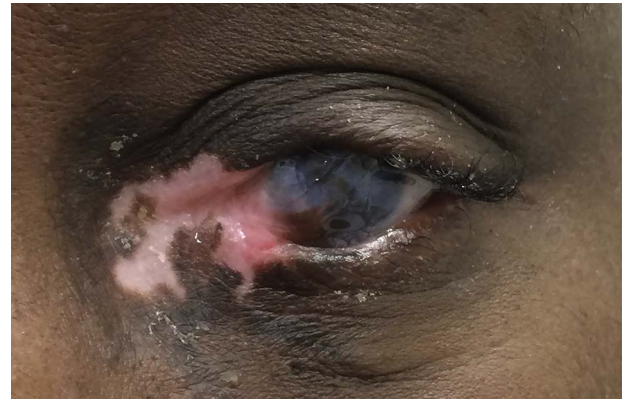


Fig. 4. Photograph of improved eyelid lesion with residual symblepharaon and corneal opacification.

expression in tissue is non-specific for IgG4-related disease as inflammation, infection, and neoplasm can manifest with tissue enriched IgG4 plasma cells. For example, in patients with recurrent HSV-1 infection, IgG4 production is increased in response to HSV membrane and glycoprotein antigen.^{22,23}

Our patient had an initial histologic diagnosis of IgG4 related-disease based on the microscopic findings. The diagnosis was corroborated by two different pathologists. But given the atypical clinical presentation and when she failed to respond to oral prednisone, a repeat biopsy was performed confirming hypertrophic HSV. Hypertrophic HSV and IgG4-related disease share some histopathologic features. Sbidian et al. reported that hypertrophic HSV is characterized by a predominant polyclonal lymphoplasmacytic infiltration.¹³ We propose that our initial histopathologic findings were likely an inflammatory reaction to HSV-2 that shares many similarities to IgG4-related disease.

In our review of the literature, there have been two other reports of HSV-2 affecting the eyelid, both presenting as chronic lesions in immunocompromised individuals. The first case, reported by Strum et al. was of a rapidly enlarging eyelid ulcer in a patient with HIV.¹⁴ The

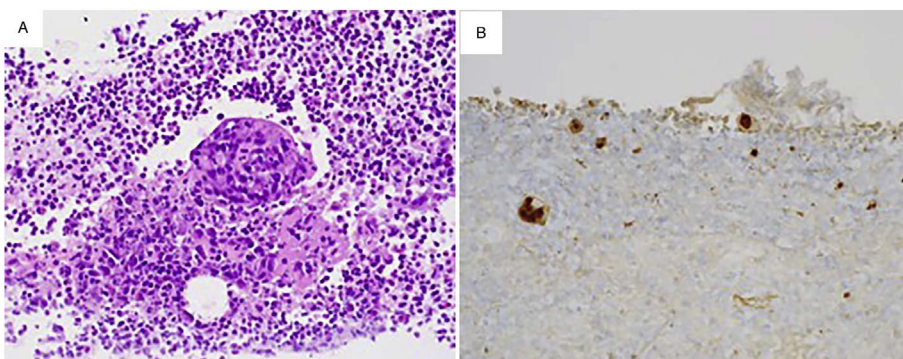


Fig. 3. A: Hematoxylin & eosin stain shows syncytial and scattered epithelial cells with viral cytopathic effect (smudged, “ground glass” intranuclear inclusions) in a background of acute inflammation and necrosis (hematoxylin & eosin stain, x 400). B: Herpes simplex virus immunostain highlighting scattered herpes simplex virus positive cells (immunostain, x 400).

lesion was initially thought to be a malignancy, but pathology revealed HSV types 1 and 2. The second case, reported by Blieden et al. was described as a case of herpes simplex vegetans in a patient with congenital T-cell deficiency.¹⁵ Two consecutive biopsies were inconclusive. Complete excisional biopsy revealed herpetic dermatitis with exuberant epidermal hyperplasia with marked chronic and acute inflammatory reaction and granulation tissue. The patient was treated with valacyclovir and the lesion resolved. Although neither of these reports classify the lesions as chronic hypertrophic HSV, they appear to be clinically similar to our case. Herpes simplex vegetans and chronic hypertrophic herpes simplex are likely different names for the same clinical entity. Both of these cases were confined to the eyelid and did not affect the globe or cause vision loss.

In addition to the eyelid biopsy, our patient also had a corneal culture positive for HSV-2. HSV-2 very rarely affects the anterior segment of the eye. In rural South Africa, a study was conducted to investigate the microbial profile of infectious keratitis amongst individuals with HIV. Corneal swabs were tested for herpes simplex virus type 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VZV) and adenovirus DNA by real-time polymerase chain reaction (PCR) and for bacteria and fungi by culture. HSV-1 and VZV were most commonly implicated while HSV-2 was not detected in any of the patients.²⁴ While rare, HSV-2 has been shown to cause keratitis in babies born with congenital HSV.^{4,5} In adults, one author reported on 5 patients with severe keratoconjunctivitis caused by HSV-2.²⁵ Our patient presented with a severe cicatrizing conjunctivitis and keratitis associated with chronic eyelid ulceration. We conclude that HSV-2 should be considered in the differential diagnosis of ocular inflammatory disease, particularly in patients with HIV. In addition, it is important to remember that IgG4 can be expressed in inflammatory and infectious states other than IgG4-related disease. It is widely accepted that corticosteroids can worsen epithelial herpetic keratitis by enhancing proliferation of the virus. It is possible that our use of oral corticosteroids for biopsy confirmed IgG4-related disease worsened her ocular condition. Corticosteroids were continued after the diagnosis of hypertrophic HSV was confirmed given the patient's severe ocular inflammation. It is unclear whether discontinuation of corticosteroids would have resulted in an improved outcome. After our patient's lid lesion and ocular surface inflammation improved, she developed corneal vascularization and opacification likely from limbal stem cell deficiency in the setting of chronic inflammation at the limbal area. Visual rehabilitation will be a challenge, as a corneal transplant is unlikely to survive in this setting. Limbal stem cell transplantation or keratoprosthesis may be surgical options to consider in the future.

4. Patient consent

Consent to publish the 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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Conflict of interest

The following authors have no financial disclosures: PD, RS, DBL, DL, AR.

Authorship

All authors attest that they meet the current ICMJE criteria for

Authorship.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.joc.2017.12.002>.

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