CASE REPORT

Primary Varicella Infection-associated Conjunctivitis: A Case-based Review and Insights into its Pathogenesis.

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Abstract
Primary varicella infection or chickenpox is a very common illness predominantly of childhood caused by the varicella zoster virus (VZV). Ocular involvement in chickenpox is relatively uncommon but is well documented in the literature. We present a case study of a healthy 6-year-old child developing unilateral serous conjunctivitis on day-2 of illness with spontaneous resolution by day-5. We narratively reviewed the findings of 2 larger case series in the English literature, highlighting ocular complications associated with chickenpox. Conjunctivitis is the second commonest ocular complication associated with chickenpox. Conjunctivitis associated with chickenpox generally runs a benign course and spontaneously resolve without anti-viral therapy. We reviewed the potential mechanisms of conjunctival involvement in chickenpox. These include epithelial homology to keratinocytes, the types of carrier T-lymphocyte involved in the secondary viraemic phase and VZV induced T-lymphocyte surface antigenic remodelling favouring ocular homing.

Keywords: *Immune-mediated cytopathy, secondary cell-associated viraemia, Υδ-T cells, T-helper regulatory cells, vesicular conjunctivitis.*

Introduction

The varicella zoster virus (VZV) is a human α-herpesvirus that causes chickenpox (primary infection) and herpes zoster (latent viral reactivation), both common illnesses in childhood and the elderly, respectively.

Primary varicella infection is a very common illness. Epidemiological studies indicate that over 95% of immunocompetent individuals aged 50 years and above are seropositive for this viral infection [1]. Clinically, primary varicella infection is a self-limiting illness characterised by the typical pruritic vesicular rash that erupts in crops over 5 to 7 days before crusting over and resolving within 10 days.

VZV demonstrates tropism for T-lymphocytes and keratinocytes with establishment of latency in neurons. However, the virus can occasionally disseminate to other tissues. The mechanism of this dissemination is still currently obscure.

Ocular involvement in primary varicella infection is uncommon. We report a case of a healthy 6-year-old child who developed a self-limiting unilateral conjunctivitis in the course of a primary varicella infection.

Case presentation

A 6-year-old boy with no chronic illness, achieving all his neurodevelopmental milestones and is fully vaccinated as per immunisation schedule (Ministry of Health Malaysia) presented with a sudden onset polymorphic vesiculo-papular rash. These skin eruptions were pruritic and initially involved the trunk and groin, but rapidly spread to involve the face, including both eyelids, within 24 hours.

Clinical examination on day 1 of the illness revealed multiple vesiculo-papular cutaneous eruptions with surrounding erythematous flare, demonstrating a centrifugal dominant pattern [Figure 1a to c]. He was otherwise reasonably well apart from irritability due to pruritus and a low-grade fever (37.5°C). There were no palpable lymphadenopathies and no mucosal lesions detected. The rest of his physical examination was unremarkable. A diagnosis of primary varicella infection (chickenpox) was made. He was quarantined, and his kindergarten was notified. He was commenced on supportive therapy with paracetamol as required, chlorpheniramine 1mg twice daily, and topical cetrimide 2% lotion body wash followed by calamine lotion (15% calamine, 5% zinc oxide) application once daily.

On the second day (day-2) of illness, new vesiculo-papular lesions appeared, also involving the hands and feet, including bullae on the dorsal right thumb [Figure 3a]. Interestingly, right-sided conjunctivitis was also observed. There was no ocular pain or pruritus, and his visual acuity was intact. Examination revealed right conjunctival inflammation with epiphora [Figure 2a, 2b]. Conjunctival injection mainly involved the bulbar conjunctiva with relative sparing of the palpebral conjunctiva and absence of conjunctival follicles. No pre-auricular nodes were palpable. His cornea was clear with no anterior chamber abnormalities and normal pupillary reflexes. This clinical picture was consistent with an asymptomatic serous conjunctivitis secondary to primary varicella infection. A 'watchful waiting' approach was adopted, and no specific therapy was initiated.

He remained well and by day 5 of illness, the right-sided conjunctivitis completely resolved [Figure 2c]. The final crops of cutaneous lesion also erupted this day, while the right thumb bullae turned haemorrhagic. [Figure 3c]. No cutaneous or mucosal bleeding was identified. Two percent fusidic acid ointment was applied twice daily to the haemorrhagic bullae to cover for secondary bacterial infection for 3 days. All lesions, including this bulla, dried up by day-10 and he made an uneventful recovery.

Discussion

VZV-associated ocular complications are relatively common in the setting of herpes zoster ophthalmicus (viral re-activation affecting the ophthalmic branch of the trigeminal nerve). This is more likely if the nasociliary branch of the

trigeminal nerve is affected (Hutchinson's sign). Ocular complications associated with primary varicella infection are uncommon and are restricted to occasional case series in the literature. The ocular complications of primary varicella infection can be classified into early or late complications:

i. Early complications: These complications occur concurrent with the skin eruptions and are thought to be directly mediated by the virus (secondary viraemia). These include palpebral (eyelid) lesions, conjunctivitis, superficial keratitis, and uveitis.
ii. Delayed complications: These complications occur after a significant period post cutaneous eruption and are more likely to be mediated by an immune process (hypersensitivity or autoimmune) or as a sequela of ocular inflammation. These include conditions such as interstitial keratitis, early cataracts, secondary glaucoma, oculomotor palsy, retinopathy and optic neuritis.

Eyelid and conjunctival lesions are the commonest ocular complications accompanying primary varicella infection. Findings of 2 larger case series are summarised below [Table 1].

In an earlier Canadian case series by Jordan DR *et al* [2], conjunctival pox was identified as the commonest conjunctival manifestation associated with primary varicella infection. Interestingly, the majority (75%) of these pox lesions were peri-limbal. Only one case of conjunctivitis was identified as a unilateral follicular conjunctivitis with pre-auricular lymphadenopathy. All patients experienced spontaneous full resolution within 14 days. Conversely, a later case series by Yap A *et al* conducted in New Zealand identified conjunctivitis as the commonest conjunctival lesion [3]. Duration of the ocular symptoms was not specified, but all patients in this series received topical prophylactic antibiotics and lubricants and none required topical antivirals. An isolated Turkish case reported bilateral serous conjunctivitis in a 9-year-old boy treated with topical 3% acyclovir and prophylactic netilmicin 0.3% [4]. Conjunctivitis developed on day 7 of rash eruption and recovered within 2 weeks.

Based on data from the medical literature combined with our experience, it is inferred that primary varicella-associated conjunctivitis is a benign phenomenon and usually runs an uncomplicated course without requiring specific anti-viral therapy.

The mechanism of ocular involvement in primary varicella infection has not been fully elucidated. The VZV is unique as it is highly cell-associated due to strong interaction between viral surface glycoproteins with intra-cellular receptors (mannose-6-phosphate and insulin-degrading enzyme, which are both abundantly localised in endosomes) [5]. Infective cell-free VZV virions are only found in cutaneous blisters due to downregulation of mannose-6-phosphate receptors in mature keratinocytes [6].

For primary varicella infection to spread from the site of inoculation (lymphoid tissue of the Waldeyer's ring), it requires a carrier cell, which are known to be $CD4^+$ T-lymphocytes. Interestingly, memory T-helper cells ($CD4^+$ $CD45RO^+$) are preferentially infected and are highly permissive for VZV invasion and replication [7]. Many of these infected memory T-lymphocytes also express surface homing markers to the skin, namely cutaneous lymphocyte antigen (CLA) and chemokine receptor 4 (CCR-4), which may explain the cutaneous tropism of this virus [7]. Hitchhiking these memory T-lymphocytes enables dissemination of the VZV to host keratinocytes in an asymptomatic phase of primary cell-associated viraemia. Once disseminated to keratinocytes, the VZV is initially suppressed by interferon-β produced by neighbouring keratinocytes. After a period of 7 to 10 days, VZV specific proteins (including IE62 and ORF61) overwhelms interferon-β suppression, allowing rapid viral replication, subsequently leading to a symptomatic phase of secondary cell-associated viraemia [8][9]. This phase is clinically recognised as the classic vesiculo-papular skin eruption of chickenpox. It is during this eruptive

phase that the VZV may potentially disseminate to other organs such as the lungs, nervous system and eyes.

- Mechanism of ocular involvement:

The pathophysiology of primary varicella-associated conjunctivitis in our case is more likely to be bystander inflammation rather than direct viral cellular invasion. There were eyelid vesicles in our case. Interferon-ϒ released by cytotoxic T-lymphocytes infiltrating the eyelid can signal in a paracrine fashion, inducing inflammatory monocytes to cause surrounding conjunctival inflammation. Conjunctival pox or vesicular conjunctivitis is clinically consistent with cellular conjunctival infection and VZV induced cytolysis. Altered conjunctival vesicles may take on an atypical appearance. This was highlighted by an American case report describing multiple pale tarsal conjunctival lesions secondary to ruptured conjunctival vesicles [10]. Other possible mechanisms of conjunctivitis in primary varicella infection:

i. Homology of conjunctival epithelial cells to keratinocytes:

Conjunctival involvement is the second commonest ocular manifestation (after the eyelid) of primary varicella infection. Many areas of the conjunctiva (particularly limbal, bulbar and outer palpebral) are lined by stratified squamous epithelia. Keratinocytes are also stratified squamous cells but are fortified with keratin (keratinized). This cellular homology may allow for skin homing memory T-lymphocytes to migrate to the conjunctiva. This may explain the predominant bulbar inflammation in our case.

ii. Type of T-lymphocytes infected in the secondary viraemic phase

The nature of T-lymphocytes involved in the secondary viraemic phase has not been scientifically characterised. Since most primary varicella infection is limited to the skin, they can be deduced to be memory $CD4^+$ T-lymphocytes with skin homing markers, identical to cells involved in the primary viraemic phase. This is consistent with the observation that children (predominantly harbouring naïve T-lymphocytes) have relatively few skin lesions compared to adults (predominantly harbouring memory T-lymphocytes) who usually present with several hundred skin lesions [11].

However, it is possible that other types of T-lymphocytes may also harbour the VZV to allow spread to distant organs. The conjunctiva associated lymphoid tissue (CALT) is predominantly populated by tissue-resident memory T-lymphocytes (TRM of both $CD4^+$ and $CD8^+$ cells). However, these cells are unlikely to be the VZV carriers as they are non-migratory cells. Interestingly, the limbal conjunctiva is populated by an unusual population of T-cells predominantly ϒδ-T cells and a small population of Tregulatory cells (Tregs).

Based on the observations by Jordan *et al* that majority of conjunctival pox lesions were peri-limbal, it is likely that ϒδ-T cells may be the VZV carrier-cells. Other possibilities would include transient surveillance naïve T-cells ($CD4^+$ $CD45RA^+$) entering the CALT and conjunctival Tregs ($CD4^+CD25^+$). Similarly, other types of carrier T-lymphocytes may allow dissemination to different organs. Predominant tissue T-lymphocyte populations are characterised below [Table 2]

iii. Induction of ocular homing cell surface molecule expression

Human tonsillar T-lymphocytes experimentally infected with VZV has been demonstrated to induce alterations in their surface membrane protein expression [11]. Sen *et al* utilized single cell mass cytometry, demonstrating surface expression downregulation of CCR7 and upregulation of CD11a and CD49d in both infected memory and naïve T-cells [11]. This surface antigenic profile indicates cellular reconfiguration favouring tissue migration. Furthermore, approximately 35 to 40% of infected T-cells in this study expressed skin homing markers (CLA and CCR4). This study did not investigate presence of other tissue homing markers such as α4β7 (gut) and CD44 (extra-

cellular matrix). Induction of ocular specific tissue homing receptors on VZV infected cells is theoretically a possible explanation for ocular involvement in primary VZV infection. However, further studies are required to corroborate this hypothesis.

Conclusion

Although uncommon, conjunctivitis is one of the commonest ocular manifestations of primary varicella infection. The pathogenic mechanism underlying this condition is still obscure. Primary varicella-associated conjunctivitis is a benign phenomenon and usually runs an uncomplicated course of spontaneous recovery without requiring anti-viral therapy. It's prudent for physicians to monitor for the appearance of further complications such as keratitis (pseudo-dendrites or stromal infiltrates) and anterior uveitis, which may then require anti-viral therapy.

Ethical declaration

Verbal informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images. The parents were assured of the patient's anonymity.

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Figure 1a: Multiple vesiculopapular lesions in the anterior chest. Figure 1b: skin lesions of the posterior trunk Figure 1c: bullae of right lower chest with typical erythematous flare. All pictures were taken on day-1.

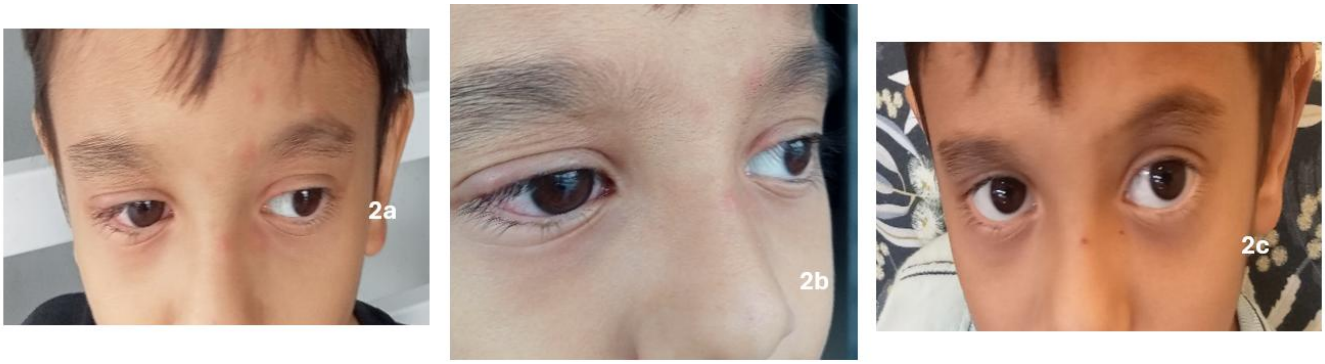

Figure 2a: Right sided conjunctivitis with epiphora noted on day-2. Figure 2b: Close up of the right-sided conjunctivitis. Note the conjunctival injection and bilateral eyelid lesions. Figure 2c: Spontaneous resolution of the right-sided conjunctivitis on day-5. Note the resolution of facial skin lesions with crusting.

Figure 3a: Right dorsal thumb bullae on day-2. Figure 3b: the same bullae turned haemorrhagic on day-5. Figure 3c: Note the bullae resolution leaving a hypopigmented scar, typical of dermo-epidermal skin lesions. This picture was taken on day-28.

Table 1. Ocular complications reported in larger case series.

Ocular complications	Jordan DR *et al* 1984 [3]		Yap A *et al* 2020 [4]	
	Frequency	therapy	Frequency	therapy
Conjunctival lesions	9		15	
• conjunctivitis	1	nil	10*	Top antibiotics and lubricants
• conjunctival pox	8	nil	5	Top antibiotics and lubricants
Eyelid lesions	15		5	
• vesicular lesions	14	nil	3	Top antibiotics
• preseptal cellulitis	1	PO cloxacillin	2	IV antibiotics
Uveitis	6	TCS	7- 12*	TCS ± antiviral
Keratitis	2	nil	3	TCS ± antiviral

Abbreviations: PO (oral), Top (topical), IV (intravenous), TCS (topical corticosteroids). * Yap *et al* reported the frequency as 'number of eyes' instead of number of patients.

Table 2. Predominant T-lymphocyte population of some organ tissues known to be affected in primary varicella infection.

Tissue	Predominant T-lymphocyte population	Remarks
Skin	TRM (both $CD4^+$ and $CD8^+$)	Commonest tissue involved in primary VZV infection
Lung	TRM (both $CD4^+$ and $CD8^+$)	Commonest extra-cutaneous tissue involved in primary VZV infection (commoner in adults) [12].
Liver	MAIT cells	Significant in primary VZV infection involving immunosuppressed patients. Particularly in ALL patients' post-chemotherapy [13].
Conjunctiva (CALT)	TRM (both $CD4^+$ and $CD8^+$)	Cellular densities significantly higher in the adenoid layer with a $CD4^+$ predominance over $CD8^+$ cells by a ratio of 12:1 [14].
Conjunctiva (limbus)	ϒδ-T cells	Limbal T-cells guard and preserves the corneal stem cell population.
Brain/meninges	TRM ($CD4^+$)	Rarely involved in primary varicella infection but carries a high mortality if untreated.

Abbreviations: TRM (tissue-resident memory T-cells) MAIT (mucosal-associated invariant T-cells) ALL (acute lymphoid leukaemia)

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