CASE REPORT

Varicella-zoster virus necrotising retinitis, retinal vasculitis and panuveitis following uncomplicated chickenpox in an immunocompetent child

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SUMMARY

A 4-year-old girl presented with acute left visual loss 4 weeks after uneventful chickenpox. She was found to have left necrotising retinitis and profound retinal vasculitis and vitritis. Aqueous humour was PCR positive for varicella-zoster virus. Combined intravenous and intravitreal antiviral treatment led to rapid improvement with settled retinitis, no vascular occlusion and good recovery of vision. Her recent coinfection with Epstein-Barr virus may have acted to provoke the retinitis.

BACKGROUND

Necrotising herpetic retinitis (NHR) is rare in children and most commonly associated with Herpes simplex type 2 (HSV2). Retinitis accompanying chickenpox is very rare. This case of varicella-zoster virus (VZV) necrotising retinitis with panuveitis in a 4-year-old child highlights the importance of careful fundal examination in childhood uveitis, the need for urgent high-dose antiviral treatment and a multidisciplinary approach.

CASE PRESENTATION

A 4-year-old girl of Japanese-Caucasian descent was referred to our uveitis clinic with a 10-day history of redness and a 4-day history of blurred vision in the left (L) eye. Four weeks previously she had developed chickenpox which had been mild and was now settled. She was otherwise well. She had no recent immunisations and no previous ophthalmic problems. She had no known contact with tuberculosis.

Visual acuity (VA) using Crowded Kays was 0.125 right (R) and 0.275 L with no objection to occlusion. Clinical examination revealed fine keratic precipitates in the L eye with 2+ anterior chamber cells. Dilated fundal examination revealed moderate vitritis with papillitis, temporal peripheral haemorrhagic, necrotising retinitis and severe exudative retinal vasculitis (figure 1). The R eye was normal.

INVESTIGATIONS

Investigation showed an elevated erythrocyte sedimentation rate of 26 mm/hour but a normal C reactive protein (1 mg/L). The white cell count was normal ($5.8 \times 10^9/L$) but the blood film was abnormal, showing rouleaux and some atypical

lymphocytes. A differential lymphocyte count revealed mild CD4 lymphopaenia at $371 \times 106/L$ with a reversed CD4/CD8 ratio (0.4). There were no autoantibodies. She was seropositive for Epstein-Barr virus (EBV) (PCR 4455iu/mL, IgM positive) indicating recently acquired infection. She was also PCR positive for VZV (low level). She was seronegative for HIV, HTLV-1,2, *Legionella* and cytomegalovirus. Aqueous humour was sampled and was PCR positive for VZV DNA (consistent with active infection) and negative for HSV 1 and 2, cytomegalovirus, EBV and toxoplasma. She was reviewed by a paediatric immunologist to exclude possible immunodeficiency; her immunoglobulins, vaccine responses, naïve T cell numbers and T cell function tested by proliferation assays were normal. Following a subsequent return of the CD4 count normal, it was concluded that the initial CD4 lymphopaenia was induced by viral infection.

DIFFERENTIAL DIAGNOSIS

Unilateral severe intraocular inflammation in a child, with a visible white focus of inflammation in the absence of ocular trauma, suggests endogenous infection with a HSV (most likely HSV2, less likely VZV, others); toxoplasmosis; fungus (most likely *Candida* or *Aspergillus*), bacteria including *Bartonella* or *Rickettsiae*. Other causes would include Behçet's disease and atypical endophytic retinoblastoma.

TREATMENT

Two-hourly prednisolone acetate 1% and cyclopentolate 1% three times per day were instilled

Figure 1 The left fundus at presentation, showing papillitis, widespread exudative retinal phlebitis and peripheral foci of haemorrhagic necrotising retinitis.

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Figure 2 The left fundus 16 months after presentation. The disc and retinal vasculature has returned to normal. There is peripheral atrophic retinal scarring.

topically, with oral aciclovir 400 mg four times per day (95 mg/kg/day). She was reviewed after 48 hours but VA had significantly worsened to L 0.6, with objection to occlusion and worsening vitritis. She was therefore admitted for intravenous aciclovir 325 mg three times per day (500 mg/m² body surface area (BSA)) for 10 days and received an intravitreal injection of foscarnet (1.2 mg in 0.05 mL). Oral prednisolone 1 mg/kg/day was added 2 days later and was tapered as inflammation settled. After discontinuation of intravenous antiviral she reverted to oral acyclovir 400 mg four times per day.

OUTCOME AND FOLLOW-UP

The uveitis, retinitis and retinal vasculitis all resolved gradually over a period of 3 months. The patient continued on oral aciclovir 400 mg twice daily for a total of 12 months with no recurrence of inflammation. The L VA 16 months after presentation was 0.02 LogMAR with peripheral retinal atrophy but a normal posterior pole (figure 2).

DISCUSSION

Necrotising herpetic retinopathy comprises a spectrum of disease from acute retinal necrosis (ARN, a peripheral, clear-edged, centripetally spreading retinitis usually in the immunocompetent) to progressive outer retinal necrosis, a multifocal outer retinitis with early posterior pole involvement, almost exclusively in the severely immunocompromised. Archetypical VZV-related ARN has a pathognomonic appearance, but variations in area involved lesion location and number, degree of associated arteriolitis and/or phlebitis and degree of uveitis are seen (sometimes depending on the responsible herpes virus). NHR mostly affects patients in the age range 20–60 years with a mean of 54 years.¹ Retinitis almost always accompanies reactivation of a herpes virus following previous systemic infection. The disease is very rare in children: two prospective 1 year surveys of ARN in the UK (2001–2002¹ and 2007–2008²) reported a total of 119 cases but no affected children under 10 years. HSV2 is the aetiological agent most likely to cause ARN in children.³

We could identify only three previous case reports of primary retinitis during or directly following chickenpox in children, in patients of 6 years,⁴ 4 years⁵ and 11 years⁶ of age. Our very young patient with proven VZV-associated NHR directly following uncomplicated chickenpox is a reminder that the clinician should be mindful of VZV as a cause of occlusive retinal vasculitis,

Learning points

- ▶ Necrotising retinitis is rare in children but typically presents with acute painful unilateral visual loss
- ▶ Toxoplasmosis is the most common cause of necrotising retinitis.
- ▶ Herpes simplex (HSV) type 2 is the most likely viral cause in a child but association with chickenpox is very rare
- ▶ Urgent systemic antiviral treatment is necessary for varicella-zoster virus-related or HSV-related necrotising retinitis, combined with intravitreal antiviral injection if required.
- ▶ Complications include retinal detachment, optic atrophy, contralateral eye involvement and meningoencephalitis. Associated immunodeficiency should be excluded.

especially if the clinical history suggests recent or previous chicken pox infection.^{4 6} Without treatment, the prognosis of NHR is poor, with progressive retinitis and ischaemia, optic neuropathy, complex retinal detachment, proliferative vitreoretinopathy and often, contralateral involvement; the outcome for these patients following vitrectomy remains poor.^{1 5 7} Prophylactic barrage laser to prevent rhegmatogenous retinal detachment has variable results and remains controversial^{1 8}

It has been suggested that NHR accompanying chickenpox can be less severe than that accompanying viral reactivation, with potentially good visual outcomes.⁴ Our patient did not have classical ARN but did have a clear area of peripheral retinitis with, unusually, extensive accompanying exudative retinal vasculitis. It was based on this clinical appearance that initially, high-dose oral antiviral treatment was attempted. However, the rapid worsening provoked both systemic and intravitreal treatment; although the visual outcome in this case was excellent, it may be prudent to commence with intravenous treatment in all cases.

Primary VZV infection may cause lymphopaenia that can persist for months after the initial infection, as seen in this case. In this case, there was also clear evidence of recently acquired EBV infection, which can alter cell-mediated immune responses.⁹ Coinfection has been reported to cause prolonged chickenpox¹⁰ and to precipitate vasculitic inflammations including Kawasaki disease¹¹ and glomerulonephritis.¹² It should be noted that EBV has also rarely been associated with NHR in a child.¹³ However, in our patient, the aqueous sample was negative for EBV DNA despite IgM positivity and there is no evidence of intraocular coinfection.

This case demonstrates that with early diagnosis and aggressive treatment, a good visual outcome can be achieved. As future VZV reactivation or retinal complications may occur, it is important to warn patients of relevant symptoms so that urgent attention can be sought if necessary. In patients at high risk from reactivation, immunisation with the shingles vaccine may be considered.

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