Severe bilateral retinal vasculitis as a delayed manifestation of rickettsial infection

Abeyagunawardena IA¹*, Sirisena KKSN¹, Vitharana BHN⁰, Thuvarakan P¹, Karunatilake RMSH¹

Abstract

Ophthalmic manifestations of rickettsial infections are reported as mostly asymptomatic and self-limiting. A 27-year-old woman, 29 weeks pregnant, recently treated for rickettsial infection, presented ten days following discharge with visual blurring and was diagnosed to have severe bilateral retinal vasculitis. Rickettsial antibody testing (indirect immunofluorescence assay) revealed Rickettsia conorii IgG titer >1:128. Antinuclear antibody, retroviral, syphilis and toxoplasmosis screens were negative. Bilateral intra-vitreous triamcinolone, azithromycin and prednisolone were administered. However, despite some improvement, a residual visual deficit remained. This case report highlights the possibility of debilitating visual loss following rickettsial infections, need for ophthalmic screening at diagnosis and prompt treatment initiation.

Keywords: rickettsia, spotted fever, retinal vasculitis

Introduction

Rickettsial diseases are caused by obligate intracellular bacteria of Orientia and Rickettsia genera and remain a significant cause of morbidity and mortality in the developing world.(1) Scrub typhus, caused by Orientia tsutsugamushi and spotted fever have been reported in Sri Lanka.(2,3) Many types of spotted fever group rickettsioses have been emerging in Sri Lanka. However, diagnostic tests in Sri Lanka for spotted fever frequently use group-specific antigens of Rickettsia conorii and may therefore be misinterpreted as exposure to Rickettsia conorii.(4)

Ocular manifestations caused by rickettsial disease are reported as generally self-limiting and asymptomatic.(5) We report a pregnant woman in Sri Lanka, presenting with rapidly progressing bilateral visual loss culminating in a diagnosis of severe bilateral retinal vasculitis as a delayed manifestation of spotted fever rickettsiosis infection. Retinal vascular disease may be seen in pregnancy with gestational hypertension, diabetes and pre-eclampsia. However, causes for retinal vasculitis are mainly infections (tuberculosis, syphilis, cytomegalovirus, herpes simplex virus, varicella zoster virus, toxoplasmosis and rickettsia) and systemic diseases (systemic lupus erythematosus, Behcet's disease and sarcoidosis).(6,7)

Case presentation

A 27-year-old previously healthy woman in her second pregnancy with a period of gestation of 29 weeks, presented with fever, myalgia and a maculopapular rash, to a local hospital in Sri Lanka.
The rash was non-blanching and was noted three days following the onset of fever and had progressed from involving the arms and legs to the whole body sparing the face. She was from the south, an area endemic to scrub typhus. Since the rash was suggestive, she was diagnosed clinically to have scrub typhus and treated with intravenous ceftriaxone and azithromycin for five days. Testing for rickettsial infection at this acute stage had not been performed due to the lack of testing facilities. Her full blood count revealed a white blood cell count of 10.9 x 10³/uL (4.0-10.0 x 10³/uL), haemoglobin level of 11.0 g/dL (11.0-16.0 g/dL) and platelet count of 236 x 10³/uL (150-450 x 10³/uL). Her c-reactive protein (CRP) was 52 mg/L. Her fever settled by day two and she was discharged with oral cefixime. Ten days following discharge, she developed visual blurring of the right eye which progressed to involve the left eye in two days. Fundoscopy revealed bilateral cotton wool spots. Best corrected visual acuity was 6/60 on the right eye and 6/36 in the left eye.

She had no oral ulcers, photosensitive rashes, arthralgia, alopecia or any other evidence of connective tissue disease. She was afebrile and her pulse rate and blood pressure were normal. The cardiovascular, respiratory and neurology system examinations were normal. There were no abnormalities in the abdominal examination (a single live foetus with a symphyseal-fundal height appropriate for the gestation). She was initially pulsed with intravenous methylprednisolone 1g daily for 3 days at the local hospital on suspicion of connective tissue disease and commenced on oral prednisolone 1mg/kg daily with azathioprine 50 mg daily. She was transferred to a tertiary care hospital, for further evaluation approximately 3 weeks after the first presentation.

At the tertiary care hospital, her CRP was found to be 1.3 mg/L and electrolytes while liver enzymes, renal functions and urine full report were normal with no proteinuria. Her antinuclear antibody (ANA) test was negative.

Her antibody levels tested using immunofluorescence assay (IFA) for rickettsial diseases revealed a titre >1:128 for *Rickettsia conorii* IgG revising the diagnosis to spotted fever (Diagnostic cut off titre > 1:128). Antibodies to *Orientia tsutsugamushi* were negative. This was a convalescent sample taken approximately four weeks after the initial onset of symptoms. Retroviral screening and VDRL testing for syphilis were negative. Toxoplasmosis IgM was negative.

Azathioprine was withheld and bilateral intra-vitreous triamcinolone was administered, first to the right eye. Figure 1A depicts fundal images revealing multiple cotton wool spots with macular oedema and bilateral macular star. Optical coherence tomography (OCT) of the patient is depicted in figure 1B showing bilateral diffuse retinal oedema with cystoid macular oedema.

Upon confirmation of rickettsial infection she was commenced on azithromycin 500 mg daily for further fourteen days and prednisolone tapering regimen with a starting dose of 40 mg daily. She reported some improvement in vision following two weeks of treatment. However, regrettably, three months on, she continued to have residual visual deficit.

**Discussion**

The opthalmic manifestations caused by rickettsial disease are mostly reported to have a self-limited asymptomatic course resolving by 3rd- 10th week of illness without causing scarring.(5) Retinal findings are more commonly reported in spotted fever than scrub typhus.

A case series and a study, involving patients diagnosed with spotted fever found that retinal vasculitis is present in 55.9% of cases, frequently venous and mostly asymptomatic. Focal arterial sheathing, venous sheathing, branch retinal artery occlusion and cotton-wool spots were noted. Both studies mention that due to the frequency of occurrence, retinal vasculitis could be considered a clinical sign of spotted fever in areas of endemicity. (8,9) Another study including 50 serologically confirmed rickettsial disease, reported 54% with ocular involvement where most patients were asymptomatic.(10)

Early antibiotic therapy with doxycycline 100 mg 12 hourly for 7-10 days is the treatment of choice for rickettsial infection with macrolides used in pregnant women.(5) The antibiotic treatment for severe ocular involvement may be extended for 2-4 weeks. There is currently no consensus guideline for the management of the opthalmic manifestations of rickettsial disease in Sri Lanka.

A case report describing optic neuritis following *Rickettsia conorii* infection reported significant improvement with oral doxycycline 200 mg daily for 15 days in combination with 1 mg/kg/day corticosteroids tapered over 4 weeks.(11) However, another case report of bilateral rickettsial retinitis reported worsening of sight with systemic steroids which responded dramatically to therapy with oral
doxycycline and tapering off of steroids.\(^{(12)}\)

Post-infectious causes of retinal vasculitis were not initially considered in the index patient and she was treated with methylprednisolone pulses with autoimmune aetiology in mind which led to an unfortunate delay in initiating appropriate antibiotics. Hence, this case highlights the importance of considering infectious causes at the forefront in a patient presenting with retinal vasculitis. As retinal changes may be similar, in a pregnant patient, diabetes, hypertension and pre-eclampsia need to be excluded by checking the blood sugar levels, blood pressure, urine for proteinuria, and other organ functions.\(^{(6)}\)

Rickettsial infections are diagnosed using indirect immunofluorescence antibody assays. However, this investigation is not widely available in Sri Lanka.\(^{(13)}\) The absence of an acute stage antibody level to demonstrate a four-fold rise to be diagnostic of acute spotted infection was a limitation of this case report. However, other possible causes of retinal vasculitis were excluded.

**Conclusion**

This patient developed debilitating ocular symptoms two weeks after spotted fever indicating the possibility of severe delayed manifestations of retinal vasculitis in rickettsial infections. The presence of retinal involvement provides a diagnostic clue for spotted fever rather than scrub typhus, in areas with no access to serology.

This case sheds light on the importance of early detection of rickettsial ophthalmic involvement by routine screening, the need to consider infectious causes in a patient presenting with retinal vasculitis at the outset itself and the need for a consensus management guideline for the management of retinal vasculitis in rickettsial disease in Sri Lanka.

**Declarations**

**Author contributions**

All authors contributed to data interpretation and writing the manuscript. All authors read and approved the final manuscript.

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**Figure 1** - Fundal images depicting bilateral cotton wool spots with macular oedema and bilateral macular star (A) and Optical coherence tomography showing bilateral diffuse retinal oedema with cystoid macular oedema (B)
Conflicts of interest

The authors declare that they have no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author details

¹National Hospital, Sri Lanka

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