Rickettsial retinitis: Direct bacterial infection or an immune-mediated response?

Rohan Chawla, Gadkar Amit Pundlik, Rama Chaudhry, Chandan Thakur

Infectious retinitis postfebrile illness is known to be caused by chikungunya, dengue, West Nile virus, Bartonella, Lyme’s disease, Rift Valley fever, rickettsia, Herpes viruses etc. Rickettsia is Gram-negative bacteria transmitted by arthropods vectors. Ocular involvement is common including conjunctivitis, keratitis, anterior uveitis, panuveitis, retinitis, retinal vascular changes, and optic nerve involvement. Retinitis lesions in rickettsia can occur because of an immunological response to the bacteria or because of direct invasion and proliferation of bacteria in the inner retina. We report such a case of bilateral rickettsial retinitis proven by serology which worsened on systemic steroids and responded dramatically to therapy with oral doxycycline and steroid taper. We thus believe that direct bacterial invasion plays a major role in the pathogenesis of rickettsial retinitis.

Key words: Retinitis, rickettsial, vasculitis

Rickettsial infections are caused by a variety of obligate intracellular, Gram-negative bacteria. According to recent classification, genus Rickettsia belongs to phylum Alphaproteobacteria, order Rickettsiales, and family Rickettsiaceae. Ocular involvement is common but often asymptomatic. All ocular structures can be involved, but posterior segment involvement is more common and most severe. Common posterior segment manifestations are inner retinitis with associated vasculitis and mild vitritis. There are various speculations regarding the pathogenesis of rickettsial retinitis. The cotton wool spot-like retinal lesions could result from intraretinal multiplication of organisms or alternatively due to immune complex deposition along retinal vessels.

We report clinical findings and management details of a patient with rickettsial retinitis.

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Case Report

A 22-year-old male presented with diminution of visual acuity in left eye for the past 1 month and right eye for 5 days, preceded by fever with rash 3 weeks before visual symptoms. Diagnosed as having retinitis in another center, he was on oral valacyclovir and oral corticosteroids. Despite 3 weeks of therapy, his vision kept worsening with further fresh involvement of the right eye.

At presentation, his visual acuity was 6/60 and he was able to count fingers held close to his face in right (OD) and left (OS) eyes, respectively. Both eyes had 2+ anterior chamber cells with minimal vitritis. Multiple patches of retinal whitening were seen at the posterior pole involving the macula in the OS and in the nasal retina in the OD. A few flame-shaped intraretinal hemorrhages adjacent to these patches and hard exudates at the macula were also present. The vessels adjacent to the whitish areas showed perivascular exudation [Fig. 1a and b].

Fluorescein angiography of the white retinal lesions showed early hypofluorescence and late hyperfluorescence with disc leakage [Fig. 1c and d]. Optical coherence tomography (OCT) through the patches of retinitis revealed significant inner retinal hyperreflectivity with multiple hyperreflective dots in the retina and vitreous along with serous detachments at the fovea [Fig. 1e and f].

Considering a diagnosis of infectious retinitis that could worsen on a combination of antiviral and steroid therapy, we started tapering his steroids and empirically added oral doxycycline 100 mg twice a day. Oral doxycycline 100 mg was given twice a day for 3 weeks followed by once a day for the next 3 weeks. A complete blood count with erythrocyte sedimentation rate was done which was within normal limits. Dengue, chikungunya, toxoplasma, Lyme serology, Weil–Felix titer (WFT), Bartonella immunofluorescent assay, X-ray of the chest, Mantoux test, HIV, and venereal disease research laboratory tests were performed. Diagnostic workup was negative for all infectious etiologies except for a WFT of 1:80 for OXK. This test was done at a laboratory outside our institute. It was positive for OXK which was suggestive of scrub typhus (*Orientia tsutsugamushi*). Although the WFT is used widely for screening of rickettsial infection in developing countries due to its low cost and easy availability, it lacks specificity. The indirect immunofluorescent antibody (IFA) assay is considered the gold standard for diagnosis of rickettsial infection, but it is not routinely available in most of the laboratories in our country. Thus, for confirmation, we got further tests done at our microbiology laboratory at the All India Institute of Medical Sciences, New Delhi, India. IgM ELISA (inBios, USA) and IFA assay (Fuller lab, USA), all were negative for scrub typhus. While IgM ELISA (Fuller lab, USA) was positive for typhus group, this was further confirmed by gold standard IFA (Fuller lab, USA). Based on this, we diagnosed it as a case of rickettsial retinitis. At 1-month follow-up, his visual acuity in OD improved to 6/9 with resolution of all retinitis lesions [Fig. 2a-c]. OCT showed marked resolution of the retinitis [Fig. 2e]. OS developed a vitreous hemorrhage and could not comment on the posterior...
Ultrasound did not show retinal detachment.

Three months following resolution of retinitis, we performed a vitrectomy in OS. In this eye too, all the patches of retinitis had resolved leaving a few pigmentary changes at the macula [Fig. 2d]. OCT showed resolution of macular edema with disruption of ellipsoid zone [Fig. 2f]. The exact cause of the vitreous hemorrhage could not be determined. The authors did not find any occluded vessels or neovascularization or featureless retina. We can only conjecture that the hemorrhage developed from inflamed superficial retinal vessels as the area and severity of involvement of the inner retina was quite significant in this eye. The patient improved to a visual acuity of 6/60 in this eye following vitrectomy.

Discussion

Focal or multifocal retinitis post febrile illness is known to be caused by chikungunya, dengue, West Nile virus (WNV), Bartonella, Lyme’s disease, Rift Valley fever, rickettsia, and retinitis caused by herpes viridae family and so on. Diagnosis of rickettsial infection is usually suspected on the basis of clinical features (ocular and systemic) and epidemiologic data. WFT lacks high sensitivity and specificity but serves as an inexpensive screening test for rickettsial diseases. WFT titers more than 1:80 are considered significant for a presumptive diagnosis of rickettsiosis. ELISA techniques, particularly immunoglobulin M (IgM) capture assays are probably the most sensitive tests available for ricketsia. Our patient had a positive Weil–Felix reaction and further confirmation was based on IgM ELISA and IFA.

OCT of cases of rickettsial retinitis predominantly shows inner retinal involvement (as seen in our case) in contrast to other organisms such as VZV, CMV, and toxoplasma where there is full thickness involvement of the retina.

The pathogenesis of postfever retinitis of various etiologies has been speculated by some authors to be of immunological origin. The deposition of immune complexes and inflammatory cells in the retina may lead to formation of white infiltrates. The treatment of choice recommended for this is corticosteroids. An article from India by Kawali A et al. nicely describes cases of rickettsial retinitis. The authors of this study propose that the lesions could be an immune response to a systemic infection.

On the other hand, rickettsial organisms are known to invade small blood vessels causing endothelial injury and tissue necrosis. In addition, glutamic acid which is found abundantly in retina is known to be involved in the pathogenicity of rickettsia. Due to marked angiotrophism of rickettsial organisms, it has been reported that the white retinal lesions in rickettsial retinitis could be a result of multiplication of organisms in inner retina.

It is imperative to start oral antibiotics such as doxycycline to treat this active infective component.

Conclusion

Considering the initial worsening of retinitis in our case on oral steroids and antiviral therapy, followed by a dramatic response to oral antibiotics, we feel that direct invasion of the inner retina by rickettsia has a significant role to play in retinitis caused by this organism. Thus, we recommend initiating therapy with an appropriate antibiotic and the judicious use of steroids in cases of probable rickettsial retinitis.
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Conflicts of interest
There are no conflicts of interest.

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