Original Article

Ocular manifestations of *Rickettsia conorii* in South India

Manohar B Balasundaram, M Manjunath[1], Girish Baliga[1], Forum Kapadi[2]

Purpose: Among the major groups of rickettsiosis, the commonly reported diseases in India are: (a) Typhus group induced—scrub typhus, murine flea-borne typhus; (b) Spotted fever group induced—Indian tick typhus; and (c) Q fever. Though many scrub typhus outbreaks have been reported from India, only one outbreak of spotted fever—serologically proven Indian tick typhus (*Rickettsia conorii*)—has been reported. We report for the first time ocular manifestations of serologically proven *R. conorii* infection in a cluster of patients. **Methods:** In this retrospective study, case records patients with serologically proven Indian tick typhus (Rickettsia conorii) were reviewed for clinical manifestations and treatment outcomes. **Results:** In the months of February to April 2016, a cluster of 12 patients (23 eyes) visited us with defective vision. Examination showed multifocal retinitis; mostly bilateral; patients had a history of fever approximately 4 weeks prior to onset of symptoms. After excluding other causes of multifocal retinitis, a diagnosis of rickettsial retinitis was made after Weil–Felix test (WFT) was significantly positive, and enzyme-linked immunosorbent assay was positive for *R. conorii.* Course of the disease, visual outcome, and investigations are discussed. Doxycycline along with oral corticosteroids was effective in treating the condition. **Conclusion:** Systematic fundus examination should be part of the routine evaluation of any patient who presents with fever and/or skin rash living in or returning from a specific endemic area. Clinical clues to diagnosing ocular rickettsiosis could be multifocal retinitis predominantly involving the posterior pole and macular involvement in the form of serous macular detachment or macular hard exudates. A positive WFT still serves as a useful and cheap diagnostic tool for laboratory diagnosis of rickettsial disease. Doxycycline along with oral corticosteroids was effective in treating the condition.

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There are several reports of systemic rickettsiosis worldwide and in India. Among the major groups of rickettsiosis [Table 1], the commonly reported diseases in India are due to: (a) typhus group (TG)—scrub typhus caused by *Orientia tsutsugamushi* and murine flea-borne typhus caused by *Rickettsia typhi*, (b) spotted fever group (SFG)—Indian tick typhus (ITT) caused by *R. conorii*, and (c) Q fever caused by *Coxiella burnetii*.[1] Though many scrub typhus[2,3] outbreaks have been reported from India, only one outbreak of spotted fever—serologically proven ITT (immunoglobulin M (IgM) antibodies against *R. conorii*) has been reported.[4] As per Department of Health Research (DHR)/Indian Council of Medical Research (ICMR) guidelines, the case definition of rickettsial infection is as follows:

(a) Suspected/clinical rickettsial infection: Acute undifferentiated febrile illness of 5 days or more with or without eschar,
(b) Probable infection: Showing titers of 1:80 or above in OX 2, OX 19, and OXK antigens by Weil–Felix test (WFT) for diseases caused by members of TG and SFG, and
(c) Confirmed infection: Rickettsial DNA is detected in whole blood by polymerase chain reaction (PCR) or indirect immunoperoxidase assay (IPA) and immunofluorescence assay (IFA) positive.[1]

Only sporadic accounts of ocular manifestations of rickettsiosis have been reported from India.[5-7] We report ocular manifestations, treatment given, and visual outcome in a subset of patients with systemic rickettsial disease who attended the Uvea Clinic in our tertiary eye care center. To the best of our knowledge, this is the first incidence of a case series on ocular rickettsiosis (*R. conorii*) being reported as a cluster from India.

Methods

This study was undertaken at the Uvea and Retina Clinic at tertiary eye center in South India between the months of February 2016 and April 2016 and included 12 patients (21 eyes) who presented to us with defective vision.

Patients presenting with history of fever preceding ocular symptoms of defective vision. Retinitis was defined as elevated pale-yellow lesions, obscuring blood vessel view, focal and confluent, seen in the posterior pole of the retina with or without anterior uveitis, vitritis, and vasculitis. A probable diagnosis of rickettsial retinitis (RR) was made based on the above-mentioned ocular findings, a positive

Uvea and IOL, [1]Retina, [2]Resident, Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Salem, Tamil Nadu, India

Correspondence to: Dr. Manohar B Balasundaram, Cataract and Uvea Services, Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Salem, Tamil Nadu, India. E-mail: dr.mb@cbe.aravind.org

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WFT, and/or positive enzyme-linked immunosorbent assay (ELISA) immunoglobulin M (IgM) and IgG antibodies for *O. tsutsugamushi*/*R. conorii* and negative dengue and chikungunya serology. Only eight patients underwent ELISA IgM and IgG tests for both scrub typhus (*O. tsutsugamushi*) [Kit: Scrub Typhus Detect™ IgG and IgM ELISA, Inbios International Inc., Seattle, WA, USA], and spotted fever (ITT, *R. conorii*) [Kit: Vircell Microbiologists]. IFA and IPA are considered serological gold standards but are available only at laboratories with higher level of facilities and expertise, and hence were not done due to its nonavailability. Institutional Review Board and Ethical Committee approval was obtained before the study.

Results

All 12 patients were residents of Salem, Tamil Nadu, seen between the months of February–April 2016 with complaints of defective vision of 1–2 weeks duration. Unilateral involvement was seen in three patients and nine patients had bilateral involvement (total 21 eyes). Mean age of patients was 35 years (range 11–57 years). All patients gave a history of fever 4–6 weeks before the onset of defective vision. None of the patients gave history of skin rash or joint pain [Table 2].

On examination, best corrected visual acuity (BCVA) ranged from 20/20 to 20/2000. Ocular examination revealed 0.5–1+ AC reaction in 8/21 eyes, trace vitritis in 11/21 eyes, yellowish white lesions ranging from 1/2 DD to 3 DD along the arcades in all patients, suggestive of retinitis [Figs. 1a and 2a]. Four eyes had <3 lesions, 17 eyes had >3 lesions. Disc edema was seen in seven eyes. Hemorrhages along with retinitis were seen in 16 eyes. Retinal vascular sheathing was seen in seven eyes. Macular edema with star exudates was seen in 16 eyes [Figs. 1a and 2a].

Fundus fluorescein angiography (FFA) was done in all cases, which revealed early hypo fluorescence corresponding to retinitis patches that gradually turned hyper fluorescent at the border of the retinitis lesions with leakage in late phase [Fig. 1b]. No leakage was noted at the macula. Optical coherence tomography (OCT) showed increased inner retinal reflectivity [Fig. 2b] corresponding to the area of retinitis and confirmed serous macular detachment in 16 eyes.

WFT was performed in all 12 patients and interpreted as per manufacturer's instructions [Lister metropolis lab]. Titers of more than 1:80 were considered significant. Weil–Felix serology was positive in eight patients. Four patients were positive for OX19, two patients were positive for OX2 and OX19, and two patients were positive for OX2, OXK, and OX19.

ELISA IgM and IgG for *R. conorii* was positive in four cases out of eight patients. One patient was positive for IgM antibody, one patient was positive for both IgM and IgG antibody, and two patients were positive for IgG antibody only. ELISA IgM and IgG for *O. tsutsugamushi* (scrub typhus) was negative in all eight patients who were tested [Table 3]. All patients were treated with Tab. doxycycline 100 mg BD for 1 week, systemic steroids—tapering dose of oral prednisolone (40 mg for the first week and taper by 10 mg weekly), topical steroids if anterior chamber flare/cells were seen. Visual acuity recovery was good in all patients at final follow-up (range 20/20–20/60, follow-up of 3 months). Toxoplasma, chikungunya, dengue serology was negative in all patients.

Discussion

Rickettsial diseases are widely distributed throughout the world and many recent reports suggest to their continued presence in several parts of the Indian subcontinent, particularly, scrub typhus.[8-10] It has been reported from the states of Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala, and Tamil Nadu.[2,3,11] Dasari *et al*.[3] reviewed various outbreaks of rickettsial fever in India for the period 2000–2011. They found 11 published outbreaks, of which 10 were due to scrub typhus and only one was due to spotted fever—ITT.[4]

In our study group, all 12 patients (21 eyes) presented with visual impairment ranging between (20/2000–20/30), all had multifocal retinitis, and 16/21 eyes had serous macular detachment with macular star exudates and optic disc involvement as evidenced by disc edema, and disc leakage on FFA was seen in 7/21 eyes. Retinal vascular sheathing adjacent to the lesions was noted in 7/21 eyes. These findings are consistent with the study done by Kahloun *et al*. who analyzed visual loss associated with rickettsial disease in 16 eyes of 14 patients. In their study, they found white retinal lesions, suggestive of retinitis in 14/16 eyes, serous macular detachment in 11/14 eyes, and optic neuropathy in 7/16 eyes of their patients.[12] Posterior segment involvement in our cases was more profound than the findings described by Khairallah *et al*. in their study. In their prospective case series of 60 eyes from 30 patients with serology-proven Mediterranean-spotted fever (*R conorii*), white retinal lesions were seen in 18/60 patients, focal vessel sheathing in 5/60 patients, serous retinal detachment in 3/60 patients, macular star in 2/60 patients, and optic disc edema in one patient.[13] Kawali

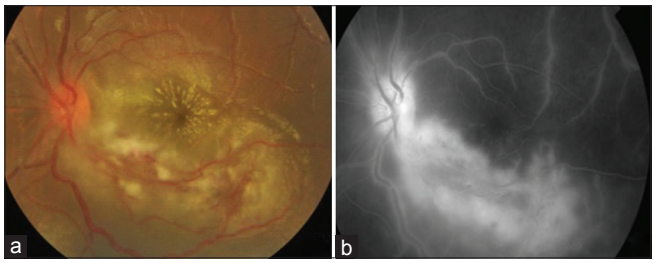

Figure 1: Patient No 1 presented with multifocal retinitis BE with macular edema (a). Early hypofluorescence with late hyperfluorescence and leakage at the borders of retinitis lesion was noted with vessel staining (b)

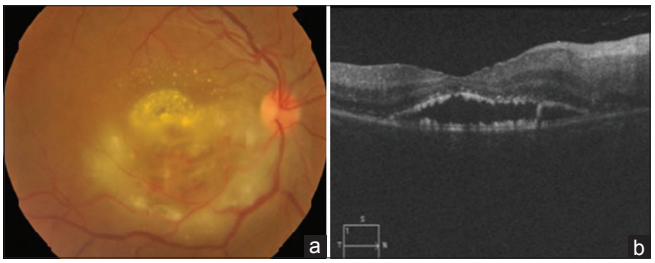

Figure 2: Patient No. 2 presented with multifocal retinitis BE (a) with macular edema in RE. OCT RE showed inner retinal hyper reflectivity corresponding to retinitis patches , few intraretinal hyper reflective dots with subretinal fluid (b)

et al.[5] in their retrospective study, which included 19 eyes of 10 patients who presented with fever, multifocal retinitis with macular edema, suggested that presumed RR is an epidemic, and its ocular manifestation could be an immune response to recent systemic rickettsial infection. Chawla *et al*. reported one case where patient presented with preceding history of fever and rash followed by bilateral ocular disease—multiple patches of retinal whitening 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.[6] Kamath *et al*.[7] reported an isolated case from South India with similar history and ocular features and WFT positivity.

Vasculitis is the basic pathogenic mechanism in rickettsiosis that is responsible for skin rash, microvascular leakage, edema, tissue hypoperfusion, and end-organ ischemic injury.[11] The retinal manifestations could be an immune response to systemic infection.[5] The deposition of immune complexes and inflammatory cells in the retina may lead to formation of white infiltrates.[6]

A suspected clinical case showing titers of 1:80 or above in OX 2, OX 19, and OXK antigens by WFT and an optical density (OD) >0.5 for IgM by ELISA are considered positive for TG and SFG of rickettsiae.[1] Other serological tests such as latex agglutination, indirect hemagglutination, dot blot immunoassay (including dipstick test), and the "gold standards" IPA and IFA are used in laboratory evaluation of suspected rickettsial infections.[1,11]

WFT, which was the first serological assay to be developed, involves antigens from three *Proteus* strains: *P. vulgaris* OX2, *P. vulgaris* OX19, and *P. mirabilis* OXK. Antibody reaction to OX19 identifies typhus group rickettsiae (*R. prowazekii* and *R. typhi*) and *R. rickettsii*, whereas reaction to OX2 identifies SFG rickettsiae and reaction to OXK identifies *O. tsutsugamushi*.[14] Either four-fold rise in agglutinin titer in paired sera or single titer of more than 1:320 is considered diagnostic for infection with these febrile agents.[8] Kamarasu *et al.* used antibody titers of 80 or more from single serum sample to indicate either spotted fever or scrub typhus infection.[15] WFT still serves as a useful and cheap diagnostic tool for laboratory diagnosis of rickettsial disease and the use of this test is accepted in conditions where definitive investigations are not available.[16] In our patients WFT showed positive titers in 8/12 patients. WFT was positive in all the other three reports of RR from India.[5-7]

ELISA for detection of IgM and IgG antibodies is highly sensitive and reproducible.[14] ELISA IgM/IgG for *R. conorii* was positive in 4/8 patients, out of which two patients were IgG positive, one was IgM positive and one patient was positive for both. ELISA IgM and IgG for scrub typhus (*O. tsutsugamushi*) was negative in all eight patients who were tested. All four patients positive for *R. conorii* by ELISA were negative for WFT. (It is known that WFT results may be negative during the early stages of the disease because agglutinating antibodies are detectable only during the second week of illness, and treatment in early stages of the disease may blunt or delay the serological response as could have happened in our cases.)

Table 1: DHR/ICMR-Classification of rickettsial diseases[1]

Diseases	Rickettsial agent	Vector	Mammalian host
Typhus group			
Epidemic typhus	*R. prowazekii*	Louse	Humans
Murine typhus	*R. typhi*	Flea	Rodents
Spotted fever group			
Indian tick typhus	*R. conorii*	Tick	Rodents, dogs
Rocky mountain spotted fever	*R. rickettsiae*	Tick	Rodents, dogs
Rickettsial pox	*R. akari*	Mite	Mice
Orientia group			
Scrub typhus	*O. tsutsugamushi*	Mite	Rodents
Others			
Q fever	*C. brunetti*	Nil	Cattle, sheep, goats
Trench fever	*R. quintana*	Louse	Humans

Table 2: Demography and ocular presentation of patients in the study

Age/Sex	Eye involved	BCVA at presentation		BCVA at final follow-up		Posterior segment	Disc edema	Vasculitis
		OD	OS	OD	OS			
11/F	OU	20/800	20/1000	20/20	20/20	MFR OU, MHES OU	OU	OU
32/F	OU	20/200	20/20	20/20	20/20	MFR OU, MHES OU	NO	OU
16/M	OU	20/30	20/20	20/20	20/20	MFR OU, MHES OU	NO	NO
25/M	OD	20/20	20/200	20/20	20/30	MFR OD, MHES OD	NO	NO
23/M	OS	20/80	20/60	20/20	20/20	MFR OS, MHE OS	NO	NO
35/M	OS	20/200	20/20	20/30	20/20	MFR OS, MHES OS	OS	OS
35/F	OU	20/40	20/60	20/20	20/20	MFR OU, MHE OD	NO	NO
16/M	OD	20/60	20/20	20/20	20/20	MFR OD, MHES OD	OD	NO
38/M	OU	20/40	20/60	20/20	20/20	MFR OU, MHE OU	NO	NO
20/M	OD	20/80	20/2000	20/20	20/30	MFR OD, MHES OD	OD	OD
43/M	OS	20/20	20/200	20/20	20/20	MFR OS, MHES OS	OS	OS
57/M	OU	20/80	20/2000	20/20	20/40	MFR OU, MHE OU	OU	OU

MFR: Multifocal retinitis, MHE: Macular hard exudates, MHES: Macular star

Table 3: Results of Weil-Felix test (WFT), ELISA for *R. conorii* (spotted fever-ITT) and *O. tsutsugamushi* (scrub typhus)

OX2	OXK	OX19	Subtype	ELISA for scrub typhus	ELISA for tick typhus (*R. conorii*)
1:80	1:320	1:80	Indeterminate	Not done	Not done
1:320	1:40	1:80	Spotted fever group	Not done	Not done
1:40	1:40	1:640	Typhus group	Not done	Not done
NIL	NIL	1:320	Typhus group	Negative	Negative
NIL	NIL	1:320	Typhus group	Negative	Negative
NIL	NIL	1:80	Typhus group	Negative	Negative
1:80	1:80	1:1280	Indeterminate	Negative	Negative
1:80	1:40	1:80	Spotted fever group	Not done	Not done
Nil	Nil	Nil	Negative	Negative	Positive
Nil	Nil	Nil	Negative	Negative	Positive
Nil	Nil	Nil	Negative	Negative	Positive
Nil	Nil	Nil	Negative	Negative	Positive

Early treatment is critical to outcome and must be started on the basis of clinical diagnosis. Doxycycline (100 mg every 12 h for 7–10 days) is the drug of choice for the treatment of rickettsial diseases.[1] Other tetracyclines, chloramphenicol (50–75 mg/kg/day), and fluoroquinolones are also effective. Both tetracyclines and chloramphenicol have potential significant adverse effects, especially in children. Macrolides, including clarithromycin, azithromycin can be used as alternative therapy in children and pregnant women. Additional therapeutic agents may be required for ocular disease; topical steroids and mydriatic drops for anterior uveitis, systemic steroids for severe ophthalmic involvement, such as extensive retinitis threatening the macula or optic disc, serous retinal detachment, macular edema, retinal vascular occlusion, severe vitritis, and optic neuropathy. All of our patients responded well to a combination of doxycycline and topical/oral steroids and systemic steroids with the resolution of retinitis and macular edema. Visual acuity recovery was good in all our patients (range 20/60–20/20) as there was no chorioretinal scarring, suggesting that the outer retina and retinal pigment epithelium layer were spared from involvement.

Clinical clues to diagnosing ocular rickettsiosis could be multifocal retinitis predominantly involving the posterior pole and localized along the arcades with strong predilection toward macular involvement in the form of serous macular detachment due to the proximity of these lesions to the fovea and positive WFT and negative serology for other infectious etiology. Systematic fundus examination should be part of the routine evaluation of any patient who presents with fever and/or skin rash living in or returning from a specific endemic area. Prevention is the mainstay of rickettsial diseases control. It consists of personal protection against tick bites in endemic areas (repellents, protective clothing, and avoidance of dogs, detection, and removal of an attached tick), improvement of sanitary conditions including the control of rat reservoirs and of flea or lice vectors.

Our study is limited by the sample size and by the fact that ELISA IgM, IgG was not done in all patients. Four-fold rise in titers could not be demonstrated by ELISA in our patients because of economic constraints. PCR for rickettsial DNA was not done in our cases, which is a specific test for diagnosis.

Conclusion

This is the first time that ocular manifestations of serologically proven *R. conorii* infection have been reported from India.

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Conflicts of interest

There are no conflicts of interest.

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