Rickettsial disease: An underestimated cause of posterior uveitis

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Abstract

Rickettsioses are worldwide distributed infectious disease caused by intracellular small Gram-negative bacteria transmitted to humans by the bite of contaminated arthropods, such as ticks. Systemic disease typically consists of a triad of high fever, headache, and skin rash. It usually has a self-limited course, but severe, life-threatening complications can sometimes occur. It may be clinically difficult to differentiate rickettsial diseases from other febrile illnesses. Rickettsial infection has been largely underestimated as a cause of infectious uveitis for long decades in the past. Conversely, recent data show that ocular involvement is much more common than previously thought, with retinitis, retinal vasculitis, and neuroretinitis being the most typical and frequent findings. Early clinical diagnosis of rickettsial disease, while awaiting laboratory test results, is essential for prompt initiation of appropriate antibiotic treatment to prevent systemic and ocular morbidity. The prevention remains the mainstay of rickettsial infection control.

Keywords:

Arthropod-borne diseases, infection, posterior uveitis, retinitis, rickettsioses, vasculitis

Introduction

Rickettsioses are worldwide distributed zoonoses with variable geographical distribution that are caused by intracellular small Gram-negative bacteria and transmitted to humans by the bite of contaminated arthropods, mostly ticks. Systemic involvement is typically characterized by a triad of high fever, headache, and skin rash. Although the prognosis of rickettsial disease is usually good, severe, life-threatening complications can sometimes occur.[1] Rickettsial diseases, especially noneschar forms, are frequently underdiagnosed and confused with other febrile illnesses.[2] On the other hand, rickettsial infection has been considered as a very rare cause of infectious uveitis in literature.[3] Ocular involvement actually is common in patients with rickettsiosis, but since it is frequently asymptomatic and self-limited, it may be easily overlooked.[4] It is also not unusual for rickettsial ocular disease to be misdiagnosed as other uveitic entity. Recent data show that the rate of symptomatic posterior segment inflammation cases ascribed to rickettsial disease is increasing, mainly due to climate changes and globalization and to a better recognition of typical ocular changes.[5] Early clinical diagnosis of rickettsial disease, while serological confirmatory testing is pending, is of utmost importance for prompt initiation of appropriate therapy to improve outcomes. The prevention remains the mainstay of rickettsial infection control.[1]

Epidemiology

Rickettsial agents are generally classified into three major categories: The spotted fever group, the typhus group, and the scrub typhus group. The spotted fever group includes mediterranean spotted fever (MSF), rocky mountain spotted fever (RMSF), and numerous other rickettsial. MSF, also called "boutonneuse" fever or tick-borne rickettsiosis is caused by *Rickettsia conorii* and is prevalent in Mediterranean countries and Central Asia, including India. RMSF, which is caused by *Rickettsia rickettsii*, is endemic in America, especially in the south-eastern and south-central United States.

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RMSF and MSF occur most commonly in spring or summer (between April and September). The other multiple rickettsial species belonging to the spotted fever group vary in their geographic distribution.

The typhus group includes Epidemic typhus and Murine typhus. Epidemic typhus, which is caused by the organism *Rickettsia prowazekii*, is usually encountered in areas of crowded population with poor hygiene conditions, as occurs during wars and natural disasters. Murine typhus, which is caused by *Rickettsia typhi*, is found worldwide in warm-climate countries. Scrub typhus, which is caused by *Orienta tsutsugamushi*, is a zoonosis found in the Far East. A more recent classification has categorized more than 20 species within the genus Rickettsia into four groups, including the ancestral group, the typhus group, the spotted fever group, and a transitional group.[1,5-7]

Pathophysiology

The pathogenic sequence of events that occur in rickettsial infection begins with the inoculation of the rickettsial pathogen by the feeding tick or mite or scratched into the skin from infected louse or flea feces deposited on the skin. The rickettsiae then spread via lymphatic vessels to the regional lymph nodes and hematogenously throughout the body. Specific surface cells antigens play an important role in rickettsial adhesion to host cells and in their invasion. Rickettsiae, *in vivo*, preferentially infect microvascular endothelial cells in humans as well as in animal models. As a consequence, a host-immune response is triggered, leading to disseminated inflammation, impairment of endothelial barrier function, and altered vascular permeability. Infected endothelium will be induced to express prothrombotic, proadhesive, and proinflammatory genes, resulting in systemic vasculitis.[1,5] Since the pathophysiologic basis for rickettsial disease is vasculitic, most common ocular lesions involve the retinal and optic disc vasculature.[4,8]

Systemic Disease

The incubation period for rickettsial disease varies between 2 and 21 days. The initial presentation typically includes high fever with abrupt onset, headache, and myalgia. A maculopapular skin rash, hallmark of rickettsial infection, usually appears 3–5 days after the onset of fever. It involves the palms of the hands and the soles of the feet. Its absence should not rule out a possible rickettsial infection, especially during the 1st week of illness. A local skin lesion, termed "tache noire" (black spot), at the inoculating site may be seen in several rickettsial infections including MSF, caused by *R. conorii* infection. Most patients will recover within 10 days without any sequelae. However, severe life-threatening complications including major neurological manifestations and multi-organ involvement occur in 5%−6% of patients with MSF, and the mortality rate is 2% to 3%.[1,2,9,10]

It is noteworthy that rickettsial disease is reported to be consistently underdiagnosed in clinical practice. The diagnosis of rickettsial disease was missed in 57.9% of patients with MSF, in 87% of patients with RMSF, and in 66.5% of patients with scrub typhus.[2]

Ocular Disease

Retinitis and retinal vascular involvement, with or without mild vitritis, is the most common ocular findings in patients with rickettsial disease, but an array of other ocular manifestations also may occur [Tables 1 and 2].

Retinitis

Bilateral or rarely unilateral multifocal or unifocal white retinal lesions have been reported to be a common and typical clinical

Table 1: Ophthalmic manifestations of rickettsial infection

Ocular structure	Clinical findings
Adnexa and anterior segment	Parinaud's oculoglandular syndrome
	Keratitis
	Nongranulomatous anterior uveitis
	Iris nodule
Posterior segment	Mild vitritis
	Mutifocal or unifocal superficial retinitis
	Retinal hemorrhages
	Retinal vascular sheathing, retinal vascular leakage
	Branch retinal artery occlusion
	Hypofluorescent choroidal lesions
	Endogenous endophthalmitis
Optic nerve	Optic disc edema, optic neuritis, neuroretinitis, ischemic optic neuropathy
Other neuro-ophthalmic structures	Third and sixth ocular nerve palsy

Table 2: Multimodal imaging findings in rickettsial disease

Imaging modality	Findings
Fundus photography	Unifocal or multifocal inner retinitis
	White retinal lesions, variable in size and number, involving the posterior pole or the peripheral retina, typically adjacent to retinal vessels
	Progressive resolution of lesions with no visible chorioretinal scarring
	Associated findings: Retinal vascular sheathing, retinal hemorrhages, ischemic whitening due to BRAO
Fluorescein angiography	Early hyopofluorescence and late staining of large retinal lesions and isofluorescence or moderate hypofluorescence of small retinal lesions
	Retinal vascular leakage
	Branch retinal artery occlusion
ICG-angiography	Hypofluorescent choroidal lesions
SD/SS OCT	Increased internal reflectivity of retinal lesions, with posterior shadowing, without sublesional choroidal thickening or retinal pigment epithelium elevation
	Macular edema
	Serous retinal detachment
OCT angiography	Flow deficit areas involving the superficial and deep retinal vascular plexus in case of associated occlusive retinal vasculitis

OCT: Optical coherence tomography, ICG: Indocyanine green, BRAO: Branch retinal artery occlusion, SD: Spectral domain, SS: Swept source

finding in rickettsial disease including MSF, RMSF, and murine typhus.[9-14] Recent data show that rickettsial disease was the most common cause of acute multifocal retinitis associated with febrile illness, accounting for 68.5% of cases[11] [Figure 1]. Rickettsial acute multifocal retinitis typically presents in the form of white retinal infiltrates involving the inner retinal layers, located adjacent to retinal vessels, and varying in number, size, and location. Small lesions in the posterior fundus may strikingly resemble cotton-wool spots. Large retinal lesions are usually associated with macular edema and serous retinal detachment (SRD).[4] Fluorescein angiography (FA) shows early hypofluorescence and late staining of large retinal lesions and a slight hypofluorescence or isofluorescence of small retinal lesions. Optical coherence tomography (OCT) demonstrates focal hyperreflectivity and thickening primarily involving the inner retinal layers with or without associated posterior shadowing. OCT is also useful in the detection of associated macular edema and SRD[4] [Figure 2].

Rickettsial retinitis has a typical self-limited evolution in most cases, with resolution of retinal lesions without visible chorioretinal scarring. A localized retinal nerve fiber layer defect and focal retinal thinning are typically seen on OCT as sequelae of retinal infiltrate.[11]

The pathogenesis of rickettsial retinal involvement remains speculative. Retinitis could develop as a consequence of multiplication of rickettsial microorganisms within retina. Alternatively, immune response to bacteremia might induce immune complexes and inflammatory cells to form white infiltrates through the deposition in retinal vessels.[4]

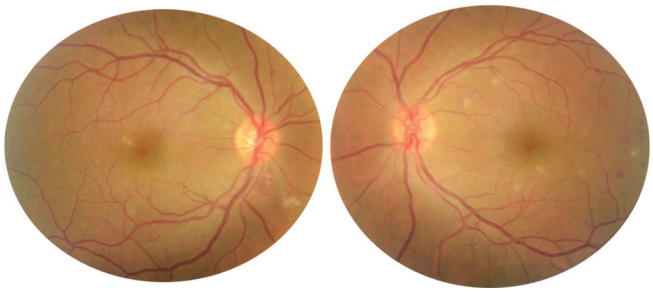

Figure 1: Fundus photography in a 30-year-old male with rickettsial disease shows multiple superficial small white retinal lesions and a few retinal hemorrhages

Retinal Vasculitis

The marked tropism of rickettsial organisms for retinal vasculature is evidenced by the frequent occurrence of retinal vascular involvement. This may include focal or diffuse retinal vascular sheathing, arterial plaques similar to toxoplasmic Kyrieleis arteritis, superficial, deep, or white-centered retinal hemorrhages, and retinal vascular leakage on FA, mostly in the vicinity of white retinal lesions. Vascular occlusive events may occur, usually in the form of asymptomatic or symptomatic branch retinal arteriolar occlusion that is usually intimately related to a white retinal inflammatory lesion.[15] Rickettsial disease has been reported to be the second-leading cause of inflammatory branch retinal artery occlusion (22.2%), after ocular toxoplasmosis.[16] Central retinal artery occlusion and retinal vein occlusions have been less commonly reported.[4,17-22] Besides FA, OCT angiography allows a noninvasive, detection, and evaluation of retinal occlusive changes involving the superficial and deep retinal vascular plexus associated with rickettsial retinitis[23] [Figure 3].

Optic Disc Involvement

Optic nerve involvement is common, reflecting the tropism of rickettsial organisms for optic disc vasculature besides retinal vasculature. It may include optic disc edema, optic-disc hyperfluorescence, optic neuritis, neuroretinitis, and ischemic optic neuropathy.[4,12,14,17,24-28] Rickettsial disease has been reported to be the second-leading cause of neuroretinitis (19.2%), after cat-scratch disease.[29]

The overall visual prognosis appears to be good in patients with rickettsial optic neuropathy. However, optic disc pallor and permanent visual loss may complicate rickettsial optic disc involvement, mainly in ischemic optic neuropathy.[8,16]

Other Ocular Manifestations

Parinaud's oculoglandular syndrome presenting as swollen eyelids, conjunctival hyperemia, and chemosis with mucopurulent discharge has been reported in association with rickettsial infection.[30] Other ocular manifestations of rickettsial disease include keratitis, nongranulomatous anterior uveitis, iris nodule, hypofluorescent choroidal lesions on fluorescein or indocyanine green angiography,

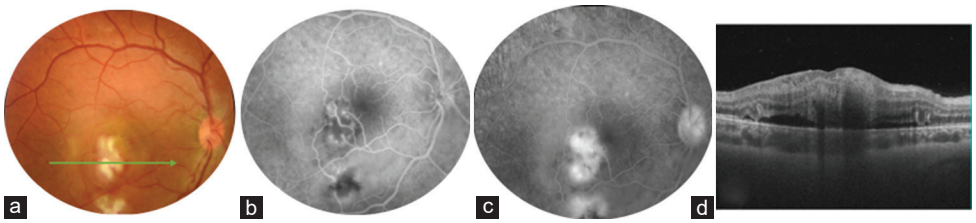

Figure 2: Multimodal imaging findings in a 19-year-old male with rickettsial disease. (a) Fundus photograph of the right eye shows two large white retinal lesions along the inferotemporal vascular arcade with associated retinal hemorrhages, macular edema and serous retinal detachment. (b and c) Fluorescein angiography shows early hypofluorescence and late staining of the retinal lesions with adjacent retinal vascular leakage. (d) Swept source optical coherence tomography scan through the superior retinal lesion demonstrates a focal area of retinal thickening with increased inner layer reflectivity and posterior shadowing associated with serous retinal detachment

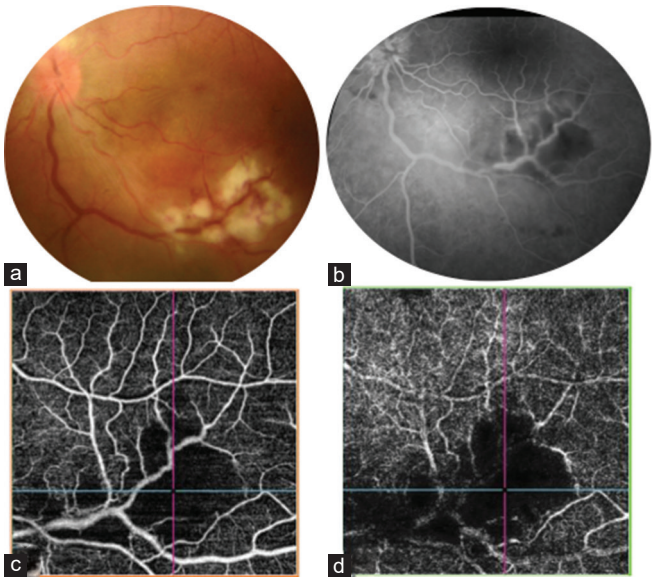

Figure 3: Multimodal imaging findings of the left eye of the same patient in figure 2. (a) Fundus photograph shows a large white retinal lesion along the inferotemporal vascular arcade with associated retinal hemorrhages. (b) Fluorescein angiography shows early hypofluorescence of the retinal lesion with adjacent retinal vascular leakage. (c and d) Swept source OCT angiography (6 mm × 6 mm) shows flow deficit areas in the superficial and deep capillary plexus. OCT: Optical coherence tomography

endogenous endophthalmitis, and third or sixth cranial nerve palsies.[4,25,31-34]

Diagnosis

Diagnosis of rickettsial infection is usually suspected on the basis of clinical features (ocular and systemic) and epidemiologic data (history of living in or traveling from an endemic area for rickettsiosis during spring or summer). It is confirmed by positive indirect immunofluorescent antibody test results. Positive serologic criteria usually include either initial high antibody titer or a fourfold rise of the titer in the convalescent serum.[1,35] Case confirmation with serology might take 2–3 weeks and it may be negative in the early course of the disease. Other laboratory tests, such as serologic testing using Western blot or detection of rickettsiae in blood or tissue using polymerase chain reaction may be useful in selected cases.[1]

In a patient suspected as having rickettsial systemic disease, a systematic fundus examination, revealing frequently abnormal, fairly typical findings, can help to establish the diagnosis while serologic testing is pending.[4]

Differential Diagnosis

The differential diagnosis of rickettsial infection includes numerous systemic infectious and noninfectious diseases manifesting with febrile illness, such as typhoid fever, measles, rubella, enteroviral infection, meningoccemia, disseminated gonococcal infection, secondary syphilis, leptospirosis, cat scratch disease, Q fever, infectious mononuleosis, arbovirus infection, COVID-19, Kawasaki disease, Behçet disease and other systemic vasculitic disorders, idiopathic thrombocytopenic purpura, and drug reaction.

Specific epidemiological data, history, systemic symptoms and signs, and ocular findings can help differentiate rickettsial ocular disease from other infectious or noninfectious causes of retinitis, retinal vasculitis, or optic neuropathy. The differential diagnosis includes toxoplasmosis, cat scratch disease, Q fever, syphilis, herpetic disease, Chikungunya, Dengue, Behçet's disease, and sarcoidosis. Small retinal infiltrates in the posterior fundus should be differentiated from cotton-wool spots that may be associated with a wide variety of ocular and systemic conditions.[12,14,24]

Management

Early empirical antibiotic treatment should be given for any suspected rickettsiosis. Doxycycline (100 mg every 12 h for 7–10 days) is the drug of choice for the treatment of rickettsial disease. Antibiotic treatment for systemic disease may be terminated 48 h after the patient is afebrile. Antibiotic treatment for severe ocular involvement may be prolonged for 2–4 weeks.[8,23] Other tetracyclines, chloramphenicol, and fluoroquinolones are also effective. Macrolides, including clarithromycin, azithromycin, and particularly josamycin can be used as alternative therapy in children and pregnant women.[1,36] Additional therapeutic agents may be required for ocular disease: Topical antibiotics for conjunctivitis or keratitis; topical corticosteroids and mydriatics for anterior uveitis; systemic corticosteroids for severe ophthalmic involvement, including extensive retinitis threatening the macula or optic disc, SRD, macular edema, retinal vascular occlusion, severe vitritis, and optic neuropathy; and anticoagulant agents for retinal vascular occlusions. The role of antibiotic therapy, as well as that of oral corticosteroids, on the course of posterior segment involvement, remain unknown. The effect of anticoagulants on the course of retinal occlusive complications is also unclear.[4,12,14,24]

Prognosis

The prognosis of systemic infection is good in most cases, and patients will recover within 10 days without any sequelae. However, severe complications may occur including interstitial pneumonitis, meningoencephalitic syndrome, acute renal failure, myocarditis, and disseminated intravascular coagulation.[1,10]

Ophthalmic manifestations of rickettsial disease have a self-limited course in most patients, disappearing between the 3rd and 10th week after the first examination. Posterior segment involvement has a good overall visual outcome. Foci of retinitis usually disappear without causing scarring in 3–10 weeks. A retinal nerve fiber layer defect and focal retinal thinning resulting from resolved retinal infiltrates are found on OCT [Figure 4]. The causes of persistent visual impairment include residual central retinal pigment epithelial

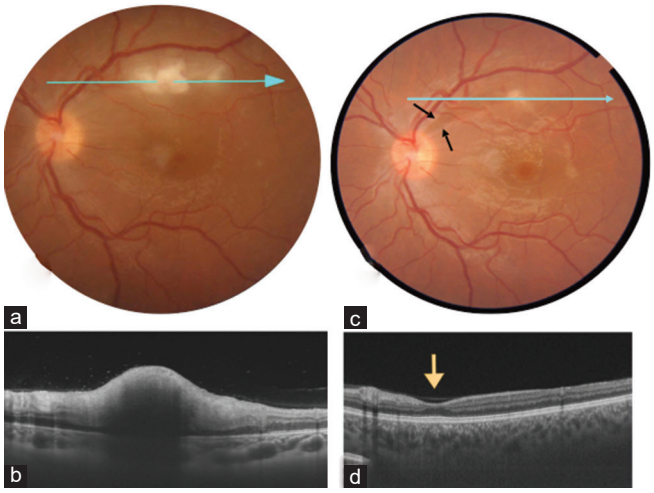

Figure 4: Funds photograph (a) of the left eye of a 28-year-old male with rickettsial disease showing a large retinal lesion in the posterior pole adjacent to the superotemporal arcade. (b) OCT shows a focal area of retinal thickening with inner layer hyperreflectivity and posterior shadowing. (c and d) Funds photograph and OCT of the same patient 3 weeks after treatment with oral doxycycline and systemic corticosteroids show the resolution of the retinal infiltrate associated with the development of a retinal nerve fiber layer defect (black arrows) and a focal retinal thinning with a fovea-like aspect (yellow arrow). OCT: Optical coherence tomography

changes, macular ischemia, optic atrophy, and choroidal neovascularization.[8]

Prevention

The 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. Antibiotic prophylaxis after an arthropod bite is not recommended.

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Conflicts of interest

There are no conflicts of interest.

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