Rickettsial Diseases

104

Moncef Khairallah, Rim Kahloun,
and Riadh Messaoud

Contents

Core Messages

- Rickettsioses are worldwide-distributed diseases caused by obligate intracellular small gram-negative bacteria, usually transmitted to humans by the bite of arthropods, such as ticks.
- They are clinically characterized by the triad of high fever, headache and general malaise, and skin rash.
- Diagnosis of rickettsial infection is based on clinical features and epidemiologic data and is confirmed by positive serologic testing and/or PCR.
- Diagnosis relies on a high index of suspicion.
- Ocular involvement is common and is frequently asymptomatic, including retinitis, retinal vascular changes, and optic disc involvement.
- Doxycycline is the drug of choice for the treatment of rickettsial diseases, but other antibiotics may be used. Additional topical antibiotics and corticosteroids may be required to treat ocular disease.
- Although prognosis of systemic infection is good in most cases, rickettsioses may be severe and potentially lethal.

Electronic supplementary material The online version of this chapter (doi:10.1007/978-3-540-75387-2_104) contains supplementary material, which is available to authorized users. Additional case reports to this book can be downloaded from http://extras.springer.com

M. Khairallah, MD (✉) • R. Kahloun, MD
Faculty of Medicine, Department of Ophthalmology, Fattouma Bourguiba University Hospital, University of Monastir, Monastir 5019, Tunisia
e-mail: Moncef.khairallah@rns.tn; rim.korbaa@gmail.com

R. Messaoud, MD
Department of Ophthalmology, Taher Sfar University Hospital, Mahdia, Tunisia
e-mail: messaoud_riadh@yahoo.fr

M. Zierhut et al. (eds.), *Intraocular Inflammation*,
DOI 10.1007/978-3-540-75387-2_104, © Springer-Verlag Berlin Heidelberg 2016

104.1 Definition

Rickettsioses are zoonoses caused by obligate intracellular small gram-negative bacteria. Most of them are transmitted to humans by the bite of contaminated arthropods, such as ticks. Rickettsiae are classified into three major groups: the spotted fever group, the typhus group, and the scrub typhus group [31, 35].

The spotted fever group includes rickettsiae that cause Mediterranean spotted fever (MSF), Rocky Mountain spotted fever (RMSF), and numerous other rickettsioses. MSF, also called "boutonneuse" fever or tick-borne rickettsiosis, is caused by the organism *Rickettsia conorii* and is prevalent in Mediterranean countries and Central Asia, including India. RMSF is caused by *R. rickettsii*, being endemic in parts of North, Central, and South America, especially in the southeastern and south-central United States. The other multiple rickettsial species involved in the spotted fever group vary in their geographic distribution. Epidemic typhus is caused by *R. prowazekii* and is usually encountered in areas of crowded population with poor hygiene conditions, as during wars and natural disasters. Murine typhus is caused by *R. typhi*, being found in warm-climate countries worldwide. Scrub typhus is caused by *Orientia tsutsugamushi* and is found in the Far East [31, 35].

104.2 Clinical Manifestations

104.2.1 General Disease

A rickettsial disease should be suspected during spring or summer, in the presence of the triad of high fever, headache and general malaise, and skin rash in a patient living in or traveling back from a region endemic for rickettsioses. A local skin lesion, termed "tache noire" (black spot) may develop at the site of arthropod bite in MSF and several other rickettsioses (Fig. 104.1). A history of outdoor activities, occupational exposure, or tick attachment is frequent [31, 35].

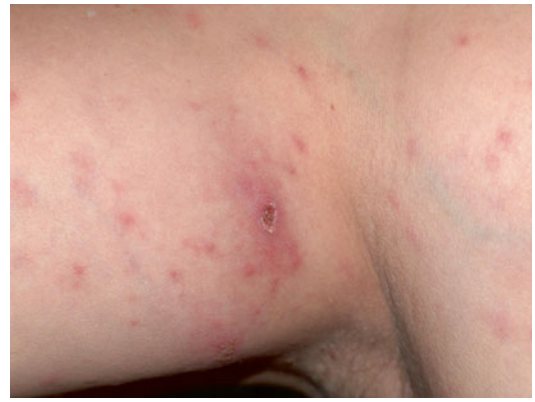

Fig. 104.1 A maculopapular skin rash in a patient with Mediterranean spotted fever. Note the presence of a "tache noire"

104.2.2 Ocular Disease

Ocular involvement is common in patients with rickettsiosis, but since it is frequently asymptomatic and self-limited, it may be easily overlooked. It may be associated with complaints such as decreased vision, scotoma, floaters, or redness. Retinitis, retinal vascular involvement, and optic disc changes are the most common ocular findings, but numerous other manifestations may occur [1–7, 9–30, 32, 33, 35–48].

Retinitis

Retinitis is observed in at least 30 % of patients with acute MSF [25]. It presents in the form of white retinal lesions, typically adjacent to retinal vessels. These lesions may vary in number (from one to more than five per eye), size (very small to large), topography (posterior fundus or periphery), and retinal layer location (superficial or full-thickness involvement) (Fig. 104.2).

Associated mild or moderate vitritis is commonly observed. Fluorescein angiography shows early hypofluorescence and late staining of large acute white retinal lesions (Fig. 104.2) and isofluorescence or moderate hypofluorescence of small active retinal lesions throughout the whole phase of dye transit [25]. Serous retinal detachment (SRD), accurately detected by

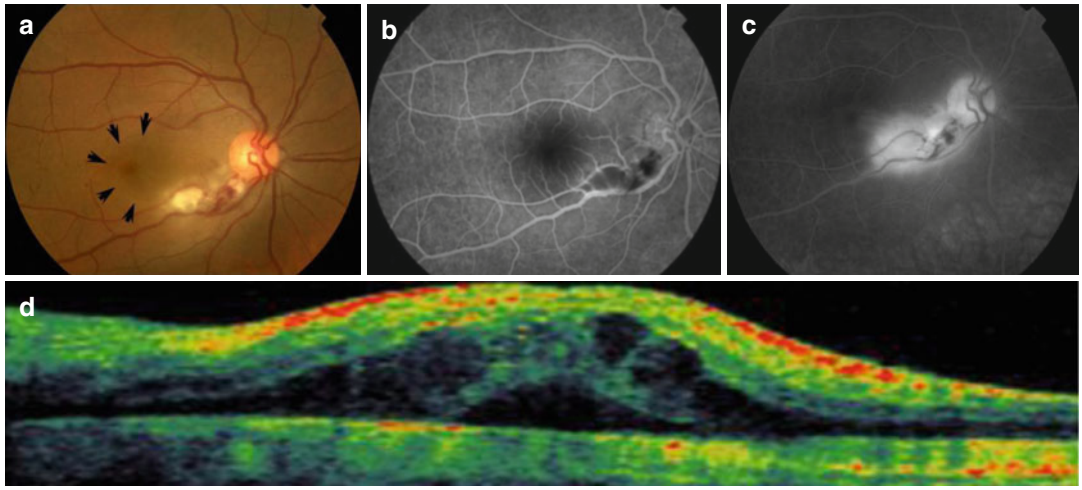

Fig. 104.2 (**a**) Color fundus photograph of a 35-year-old man with Mediterranean spotted fever shows white retinal lesions adjacent to the inferior retinal vascular arcade close to the optic disc associated with retinal hemorrhages and a serous retinal detachment involving the center of the macula (*arrows*). Fluorescein angiography shows early hypofluorescence (**b**) and late staining of the retinal lesions, retinal vascular leakage, and optic disc hyperfluorescence (**c**). (**d**) OCT confirms the presence of subretinal fluid and shows associated retinal thickening and intraretinal cysts

optical coherence tomography (OCT), frequently accompanies large foci of rickettsial retinitis (Fig. 104.2).

There are reports of multiple small white retinal lesions in other rickettsioses, including RMSF, Queensland tick typhus, and murine typhus [2, 11, 17, 19, 21, 29, 39, 41, 45]. Some small white retinal lesions in posterior pole have been interpreted as cotton-wool ischemic spots [4, 45]. Multiple lesions similar to those seen in multiple evanescent white dot syndrome (MEWDS) have been reported [12, 28].

Retinal Vascular Involvement

Numerous retinal vascular lesions may occur in patients with rickettsial disease. They include focal or diffuse vascular sheathing, vascular leakage, intraretinal, white-centered, or subretinal hemorrhages (Figs. 104.3 and 104.4), and retinal vascular occlusions associated with transient or permanent visual loss, including branch (Fig. 104.5) and central artery occlusion, and branch retinal vein occlusion or subocclusion that may lead to retinal neovascularization and vitreous hemorrhage [1, 4, 18, 25, 33, 36, 47].

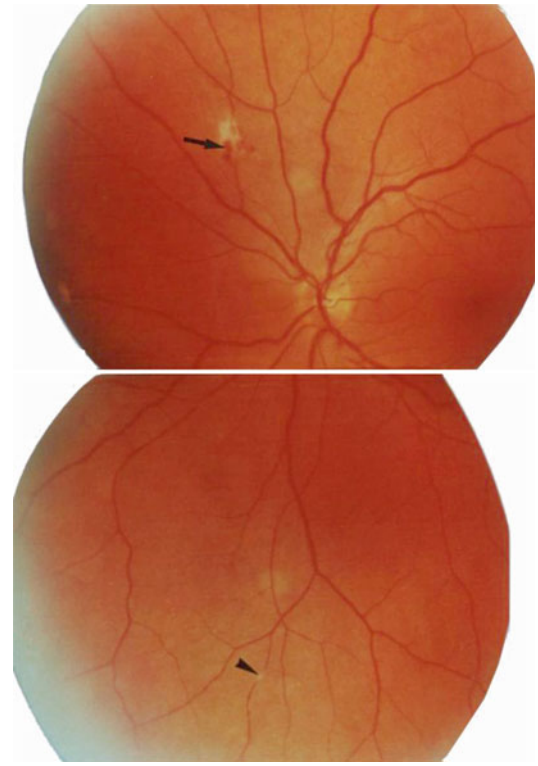

Fig. 104.3 This patient with MSF has a juxtavascular white retinal lesion associated with retinal hemorrhages in the superior midperiphery (*arrow*) and a focal vascular sheathing in the inferior periphery (*arrowhead*)

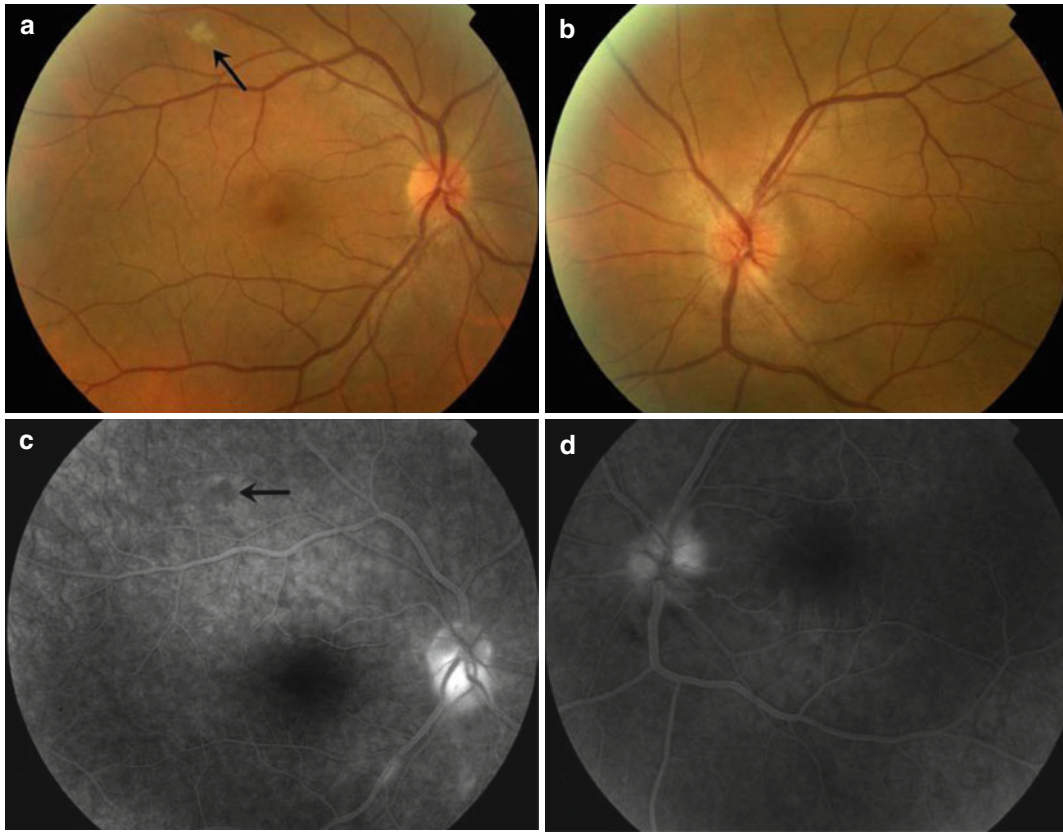

Fig. 104.4 A 47-year-old man with acute murine typhus complained of sudden decrease in visual acuity in his left eye. Visual acuity was 20/20 in the right eye and 20/40 in the left eye. There was a relative afferent pupillary defect in the left eye. (**a**) Fundus photograph of the right eye shows a 500 μm white retinal lesion (*arrow*). (**b**) Fundus photograph of the left eye shows optic disc edema with peripapillary hemorrhages. (**c**) Late-phase fluorescein angiogram of the right eye shows hypofluorescence of the white retinal lesion seen on funduscopy (*arrow*), leakage of dye from the inferior temporal vein, and optic disc staining. (**d**) Late-phase fluorescein angiogram of the left eye shows optic disc staining

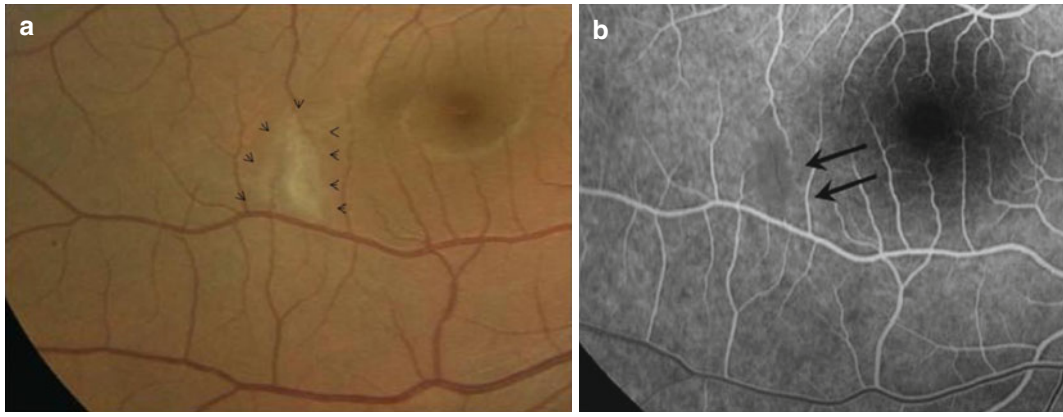

Fig. 104.5 (**a**) Color fundus photograph of the right eye of a 30-year-old woman with rickettsiosis shows an area of retinal whitening sparing the fovea (*arrowheads*). (**b**) Early-phase fluorescein angiogram confirms the diagnosis of branch retinal arteriolar occlusion sparing the fovea (*black arrows*)

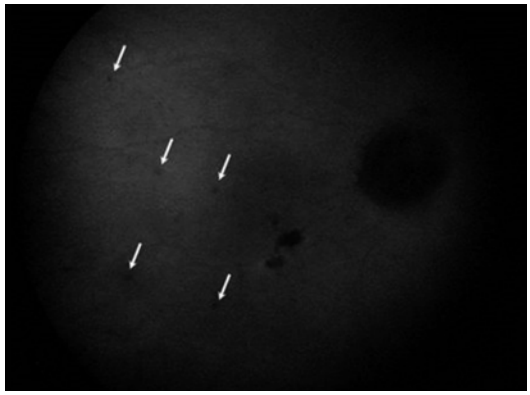

Fig. 104.6 Late-phase indocyanine green angiogram of the left eye of a patient with MSF without ocular complaints shows small well-delineated hypofluorescent lesions (*arrows*), without corresponding abnormalities on clinical examination or fluorescein angiography

Other Retinochoroidal Changes

They include cystoid macular edema and hypofluorescent choroidal lesions on fluorescein and indocyanine green angiography (Fig. 104.6). Other indocyanine green angiography findings include areas of hyperfluorescence, choroidal vascular filling defects, and choroidal vascular staining [19, 25, 46]. A case of endogenous endophthalmitis caused by *R. conorii* has been reported [32].

Optic Nerve Involvement

Optic disc involvement, with or without subsequent visual loss, has been described in association with rickettsial infection, including optic disc edema, optic disc staining, optic neuritis (Fig. 104.4), neuroretinitis, and ischemic optic neuropathy [4, 7, 9, 15, 25, 26, 46, 48].

Other Ophthalmic Manifestations

Anterior segment manifestations of rickettsiosis include bilateral or unilateral conjunctivitis (port of entry infection) [5, 16, 30, 38], conjunctival petechiae and subconjunctival hemorrhages, keratitis [9], nongranulomatous anterior uveitis [5, 6, 25, 43], and iris nodules [10]. Third and six cranial nerve palsies have also been reported.

104.3 Etiology and Pathogenesis

For most of the organisms of the spotted fever and the typhus groups, target cells are the endothelial cells of blood vessels. Invasion of vascular endothelial cells by the organism causes endothelial injury and tissue necrosis, with subsequent development of a host mononuclear-cell tissue response and stimulation of coagulation process, resulting in a systemic occlusive vasculitis [35], which may involve retinal, choroidal, and optic disc vasculature.

104.4 Diagnosis

Diagnosis of rickettsial infection is usually based on clinical features and epidemiologic data, being 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. Case confirmation by serology might take 2–3 weeks [8, 34]. Other laboratory tests, such as serologic testing using Western blot or detection of rickettsiae in blood or tissue using polymerase chain reaction (PCR), may be useful in selected cases, mainly in the early phase of the illness [44].

Ocular examination revealing frequently abnormal, fairly typical findings may be helpful in diagnosing a rickettsial disease, particularly in incomplete and atypical systemic presentation, while serologic testing is pending [21].

104.5 Differential Diagnosis

It includes numerous systemic infectious and noninfectious diseases manifesting as an exanthematous febrile illness, such as typhoid fever, measles, and rubella; enteroviral infection; meningococcemia; disseminated gonococcal infection; secondary syphilis; leptospirosis; infectious mononucleosis; arboviral infection, mainly Chikungunya, Kawasaki disease, and Behçet's disease; and other systemic vasculitic disorders.

Idiopathic thrombocytopenic purpura and drug reactions may also be considered.

Rickettsial infection should also be considered in the differential diagnosis of retinitis, retinal vascular involvement, optic disc changes, or any intraocular inflammatory condition in a patient living in or returning from a specific endemic area, especially during spring or summer.

104.6 Treatment

Early treatment is critical to outcome and must be started on the basis of clinical diagnosis. Doxycycline (100 mg *bid* for 7–10 days) is the drug of choice for the treatment of rickettsial diseases. Antibiotic treatment may be terminated 48 h after the patient is afebrile. Tetracycline (25–50 mg/kg/day *qid*), chloramphenicol (50–75 mg/kg/day *qid*), and fluoroquinolones (ciprofloxacin 500 mg *tid*) are also effective. Macrolides, including clarithromycin, azithromycin, and particularly josamycin (50 mg/kg/day), can be used as alternative therapy in children and pregnant women [1].

In addition to systemic antibiotics, topical antibiotics for conjunctivitis or keratitis and topical steroids and mydriatic agents for anterior uveitis may be used. Systemic steroids may be considered for severe ophthalmic involvement, such as extensive retinitis threatening the macula or optic disc, SRD, macular edema, retinal vascular occlusion, severe vitritis, and optic neuropathy. Anticoagulant agents may be used in retinal vascular occlusions, but their effect on the course of retinal occlusive complications still remains unclear [1].

Prevention is the mainstay for control of rickettsial diseases: personal protection against tick bites in endemic areas (repellents, protective clothing, avoiding dogs, detection and removal of an attached tick) and improvement of sanitary conditions including the control of rat reservoirs and of flea or lice vectors.

104.7 Prognosis

Although prognosis of systemic infection is good in most cases, rickettsioses may be severe and potentially lethal.

Ophthalmic manifestations of rickettsioses have a self-limited course in most patients, disappearing between the third and tenth week after the first examination. Typically, all inner white retinal lesions clear without scars. Retinal pigment epithelium changes develop in eyes with resolved full-thickness white retinal lesions. Retinal neovascularization has been reported after resolution of retinitis [25]. Visual acuity returns to baseline in most patients. Persistent decreased vision may occur due to retinal changes secondary to macular edema or SRD, retinal artery or vein occlusion, foveal chorioretinal scar, choroidal neovascularization, or optic neuropathy.

Take-Home Pearls

- A routine, careful dilated fundus examination, complemented with fluorescein angiography in selected cases, is recommended in patients with clinically suspected rickettsial disease. It may assist in early diagnosis and institution of prompt and appropriate therapy, especially in incomplete and atypical presentations of systemic disease.
- Ocular involvement commonly has a self-limited course but may be associated with transient or persistent decrease in vision.
- Because of their good ocular penetration, fluoroquinolones may be a good alternative to doxycycline.
- Prevention is the mainstay of rickettsial infection control.

References

1. Adan A, Lopez-Soto A, Moser C et al (1988) Use of steroids and heparin to treat retinal arterial occlusion in Mediterranean spotted fever. J Infect Dis 158:1139–1140
2. Agahan AL, Torres J, Fuentes-Páez G et al (2011) Intraocular inflammation as the main manifestation of Rickettsia conorii infection. Clin Ophthalmol 5:1401–1407
3. Alio J, Ruiz-Beltran R, Herrera I et al (1992) Rickettsial keratitis in a case of Mediterranean spotted fever. Eur J Ophthalmol 2:41–43
4. Alio J, Ruiz-Beltran R, Herrero-Herrero JI et al (1987) Retinal manifestations of Mediterranean spotted fever. Ophthalmologica 195:31–37
5. Bazin R (2002) Rickettsial diseases. In: Foster F, Vitale A (eds) Diagnosis and treatment of uveitis. WB Saunders, Philadelphia, pp 297–304
6. Bloch-Michel E, Ginnepain M, Edlinger E et al (1983) Fièvre boutonneuse méditerranéenne: à propos de la physiopathologie des manifestations uvéales. Bull Mem Soc Fr Ophtalmol 95:566–570
7. Bronner A, Payeur G (1973) Hemorrhagic papillitis and rickettsiosis. Bull Soc Ophtalmol Fr 73:355–358
8. Brouqui P, Bacellar F, Baranton G et al (2004) Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. Clin Microbiol Infect 10:1108–1132
9. Castanet J, Costet C, Dubois D et al (1988) Neuropathie optique au cours d'une fièvre boutonneuse méditerranéenne. Presse Med 17:439–440
10. Cherubini TD, Spaeth GL (1969) Anterior nongranulomatous uveitis associated with Rocky Mountain spotted fever. First report of a case. Arch Ophthalmol 81:363–365
11. Duffey RJ, Hammer ME (1987) The ocular manifestations of Rocky Mountain spotted fever. Ann Ophthalmol 19:301–306
12. Esgin H, Akata F (2001) Bilateral multiple retinal hyperfluorescent dots in a presumed Rickettsia conorii infection. Retina 21:535–537
13. Fontaine M, Saraux H, Ganen J (1960) Rickettsioses et uvéites. Bull Mem Soc Fr Ophtalmol 73:491–499
14. François J (1968) Rickettsiae in ophthalmology. Ophthalmologica 156:459–472
15. Granel B, Serratrice J, Rey J et al (2001) Impaired visual acuity in Mediterranean boutonneuse fever. Presse Med 30:859
16. Helmick CG, Bernard KW, D'Angelo LJ (1984) Rocky Mountain spotted fever: clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis 150:480–488
17. Hudson HL, Thach AB, Lopez PF (1997) Retinal manifestations of acute murine typhus. Int Ophthalmol 21:121–126
18. Kahloun R, Mbarek S, Khairallah-Ksiaa I et al (2013) Branch retinal artery occlusion associated with posterior uveitis. J Ophthal Inflamm Infect 3:16
19. Khairallah M, Ben Yahia S, Toumi A et al (2009) Ocular manifestations associated with murine typhus. Br J Ophthalmol 93(7):938–942
20. Khairallah M, Ben Yahia S, Attia S (2010) Arthropod vector-borne uveitis in the developing world. Int Ophthalmol Clin 50:125–144
21. Khairallah M, BenYahia S, Jelliti B et al (2009) Diagnostic value of ocular examination in Mediterranean spotted fever. Clin Microbiol Infect 15(Suppl 2):273–274
22. Khairallah M, Chee SP, Rathinam SR et al (2010) Novel infectious agents causing uveitis. Int Ophthalmol 30:465–483
23. Khairallah M, Jelliti B, Jenzeri S (2009) Emergent infectious uveitis. Middle East Afr J Ophthalmol 16:225–238
24. Khairallah M, Kahloun R, Ben Yahia S et al (2013) New infectious etiologies for posterior uveitis. Ophthalmic Res 49:66–72
25. Khairallah M, Ladjimi A, Chakroun M et al (2004) Posterior segment manifestations of Rickettsia conorii infection. Ophthalmology 111:529–534
26. Khairallah M, Zaouali S, Ben Yahia S et al (2005) Anterior ischemic optic neuropathy associated with rickettsia conorii infection. J Neuroophthalmol 25:212–214
27. Lebas M, Bernaerts-Lebas M (1963) Rickettsioses et affections oculaires. Bull Soc Belge Ophtalmol 135:437–441
28. Lu TM, Kuo BI, Chung YM et al (1997) Murine typhus presenting with multiple white dots in the retina. Scand J Infect Dis 29:632–633
29. Lukas JR, Egger S, Parschalk B et al (1998) Bilateral small retinal infiltrates during rickettsial infection. Br J Ophthalmol 82:1217–1218
30. Martin A, Juarez C, Calbo F et al (1985) Estudio clinico-epidemiologico de 164 casos de fiebre botonosa. Rev Clin Esp 176:333–339
31. McDade JE (1998) Rickettsial diseases. In: Collier L, Balows A, Sussman M (eds) Topley and Wilson's microbiology and microbial infections, vol 3, 9th edn. E. Arnold, London, pp 995–1011
32. Mendivil A, Cuartero V (1998) Endogenous endophthalmitis caused by Rickettsia conorii. Acta Ophthalmol Scand 76:121–122
33. Nagaki Y, Hayasaka S, Kadoi C et al (2001) Branch retinal vein occlusion in the right eye and retinal hemorrhage in the left eye in a patient with classic Tsutsugamushi disease. Jpn J Ophthalmol 45: 108–110
34. Omezzine Letaief A, Kaabia N, Chakroun M et al (2005) Clinical and laboratory features of murine typhus in central Tunisia: a report of seven cases. Int J Infect Dis 9:331–334

35. Parola P, Raoult D (1998) Rickettsioses éruptives. In: Encyclopedie Mèdicale Chirurgical – EMC. Elsevier, Paris, pp 1–20
36. Paufique L, Bonnet M, Lequin et al (1964) Thromboses vasculaires rétiniennes et rickettsioses. Bull Soc Ophtalmol Fr 64:410–415
37. Pinna A, Sechi LA, Serru A et al (2000) Endogenous panuveitis in a patient with Rickettsia conorii infection. Acta Ophthalmol Scand 78:608–609
38. Pinna A, Sotgiu M, Carta F et al (1997) Oculoglandular syndrome in Mediterranean spotted fever acquired through the eye. Br J Ophthalmol 81:172
39. Presley GD (1969) Fundus changes in Rocky Mountain spotted fever. Am J Ophthalmol 67: 263–267
40. Priego M, Blazquez JC, Serrano C et al (2000) Retinal vasculitis secondary to Mediterranean boutonneuse fever. Enferm Infecc Microbiol Clin 18:249–250
41. Raab EL, Leopold IH, Hodes HL (1969) Retinopathy in Rocky Mountain spotted fever. Am J Ophthalmol 68:42–46
42. Restat S, Lenoble P, Nasica X et al (1999) La fièvre boutonneuse méditerranéenne: a propos d'un cas. J Fr Ophtalmol 22:554–561
43. Rizo AE, Muniz O, Auladell C et al (1992) A case of bilateral uveitis secondary to Mediterranean spotted fever. Clin Infect Dis 14:624–625
44. Santibáñez S, Portillo A, Santibáñez P et al (2013) Usefulness of rickettsial PCR assays for the molecular diagnosis of human rickettsioses. Enferm Infecc Microbiol Clin 31:283–288
45. Smith TW, Burton TC (1977) The retinal manifestations of Rocky Mountain spotted fever. Am J Ophthalmol 84:259–262
46. Vaphiades MS (2003) Rocky mountain spotted fever as a cause of macular star figure. J Neuroophthalmol 23:276–278
47. Verdot S, Estavoyer JM, Prost F et al (1986) Atteinte oculaire en phase aiguë de fièvre boutonneuse méditerranéenne. Bull Soc Ophtalmol Fr 86:429–431
48. Zhang J, Pau D, Lee AG (2011) Postinfectious optic neuropathy in endemic typhus. J Neuroophthalmol 31:342–343