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Two cases of uveitis associated with severe transaminitis during a *Rickettsia typhi* outbreak in Los Angeles County

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ABSTRACT

Purpose: To report the clinical presentation, multimodal imaging, and management of two patients with *Rickettsia typhi* infection who presented with transaminitis and bilateral uveitis.

Observations: We report two cases of murine typhus-associated uveitis in the setting of a *Rickettsia typhi* outbreak in Los Angeles County. In case 1, a 29-year-old Hispanic female presented with scotoma of the right eye and bilateral floaters after 2 weeks of persistent fevers, maculopapular rash, and arthralgia. Clinical examination and optical coherence tomography (OCT) revealed vitreous cell and scattered white spots in both eyes at the level of the inner retina, and a cotton wool spot inferiorly in the left eye. Multiple hyperautofluorescent spots were seen on widefield fundus autofluorescence (FAF). Retinal vascular leakage and optic disc hyperfluorescence were visualized on widefield fluorescein angiography (FA). These findings were concerning for a white dot syndrome (WDS). The patient was started on oral prednisone 30 mg daily. Serologic testing during the convalescent phase returned positive for *R. typhi* infection and she was started on doxycycline. 3 weeks later, she reported complete resolution of scotoma and significant improvement of bilateral floaters.

In the second case, a 42-year-old Hispanic male presented with sudden bilateral increased floaters and blurry vision after 12 days of persistent fever and headache. Clinical examination revealed trace flare with 1+ cell in the anterior chamber, 1+ vitreous cell, and multiple white dots in both eyes at the level of the inner retina. FAF showed scattered hyperautofluorescent spots in both eyes. FA demonstrated late retinal vascular leakage with bilateral hyperfluorescent optic discs. He was started on oral prednisone 40mg, prednisolone acetate 1% drops, and cyclopentolate 1% drops daily. 2 weeks later, serologic titers returned positive for murine typhus and he was started on doxycycline with gradual taper off of steroids. He subsequently had complete resolution of floaters, blurry vision, and the inner retinal white spots.

Conclusions and Importance: Murine typhus-associated uveitis may present with scotoma and increased floaters in the setting of persistent fevers and transaminitis, with pre- or inner retinal white spots seen on fundus examination. Ophthalmologists may aid in prompt diagnosis and initiation of antibiotic therapy, which can shorten the course of the disease and in turn, reduce the risk of severe complications.

1. Introduction

Murine or endemic typhus is a systemic flea-borne illness caused by *Rickettsia typhi*, a gram-negative obligate intracellular bacterium. The main culprit in transmission to humans is the rat flea (*Xenopsylla cheopis*), although another flea vector, the cat flea (*Ctenocephalides felis*), can transmit a closely related and serologically indistinguishable organism, *Rickettsia felis*, from opossums and cats.[1] The typical symptoms of murine typhus, including high fevers (>38 °C), headache, arthralgia, and a maculopapular rash sparing the palms and soles, are nonspecific and overlap with a number of other infectious syndromes, making a prompt diagnosis challenging. Although typically self-resolving, complications such as splenic rupture, neurologic deficits, and death have been reported.[2–4] It has also been implicated in inflammation of multiple

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layers of the eye, most commonly the retina, optic nerve, and vitreous.[5] Here, we report two cases of murine typhus-associated uveitis which were included as part of a Los Angeles County Department of Public Health report of a murine typhus outbreak in the city.

2. Case report

2.1. Case 1

A 29-year-old Hispanic female presented to the emergency department with 2 weeks of persistent fevers and arthralgia, and complaints of a new-onset stationary "black spot" in her right eye and bilateral floaters for which ophthalmology was consulted. She had been seen 1 week prior in urgent care for fever of 38.9 °C associated with pharyngitis and had completed a 7-day course of amoxicillin. Physical exam revealed a maculopapular rash on her torso but was otherwise unremarkable. Her medical history was noncontributory. She had no prior ophthalmic history and had no prior ocular trauma or infection. She worked at a school, had 4 dogs and 2 cats at home, and lived in the suburbs. She denied recent travel and sick contacts. Rapid strep test and throat culture were negative. Laboratory investigations showed elevated transaminases (ALT 375 U/L, AST 313 U/L) with elevated GGT 97 IU/L, ESR 53 mm/hr, CRP 82.9 mg/L. Chest CT was unremarkable. Rickettsial titers were also ordered. Ophthalmology and rheumatology were consulted for further work-up. She was evaluated by a rheumatologist, received methylprednisone (IM 80 mg), and was started on prednisone (PO 20 mg daily) for suspicion of adult-onset Still's disease. However, ferritin levels were not consistent with Still's disease. Further rheumatologic work-up, including C3/C4, ANA, rheumatoid factor, ANCA, and CCP IgG, were unremarkable.

On ophthalmic examination, best corrected visual acuity (BCVA) was 20/20 bilaterally. Intraocular pressures, Amsler grid, and pupillary reactions were within normal limits bilaterally. Slit lamp examination of both eyes was unremarkable. Bilateral white scattered pre- or inner retinal spots and a cotton-wool spot inferiorly in the left eye were visualized on fundus examination (Fig. 1a). Optical coherence tomography (OCT) demonstrated vitreous opacities anterior to the fovea in both eyes, with no ellipsoid zone changes. Multiple hyperautofluorescent spots were seen on widefield fundus autofluorescence (FAF) (Optos, Dunfermline, United Kingdom). Retinal vascular leakage and optic disc hyperfluorescence were visualized on widefield fluorescein angiography (FA) (Optos, Dunfermline, United Kingdom) (Fig. 2a).

Given the ocular findings, her oral prednisone dose was increased to 30 mg daily. Serologic test results returned 2 days later with elevated titers of EBV (573 copies/mL) and *Rickettsia typhi* (IgG ≥1:256; IgM 1:128). Doxycycline (100 mg, oral, bid) was started. Repeat titers obtained 2 weeks later during the convalescent phase showed a rise in *R. typhi* titers (IgG 1:2048; IgM 1:1024) and EBV viral load (651 copies/mL). On reexamination 3 weeks later, fundus examination showed complete resolution of white choroidal spots bilaterally, with no retinal tears or holes. Prednisone was slowly tapered off over the course of 1 month. At week 11, OCT demonstrated trace vitreous opacities bilaterally, improved from her previous OCT. The patient reported complete resolution of scotoma in the right eye and significant improvement of floaters in both eyes.

2.2. Case 2

A 42-year-old Hispanic male presented to the emergency department with new-onset of conjunctival injection and bilateral increased floaters and was sent to the ophthalmology department with concern for retinal detachment. He had two prior clinic visits for an illness that began 12 days earlier with complaints of persistent fevers up to 39.2 °C, frontal headache, upper molar pain, and myalgia, all of which had since resolved. Testing performed on the 9th day of illness showed a mild leukocytosis, a platelet count of 102,000/mcL, elevated transaminases (ALT 188 U/L, AST 228 U/L), microscopic hematuria, and hepatosplenomegaly on abdominal ultrasound.

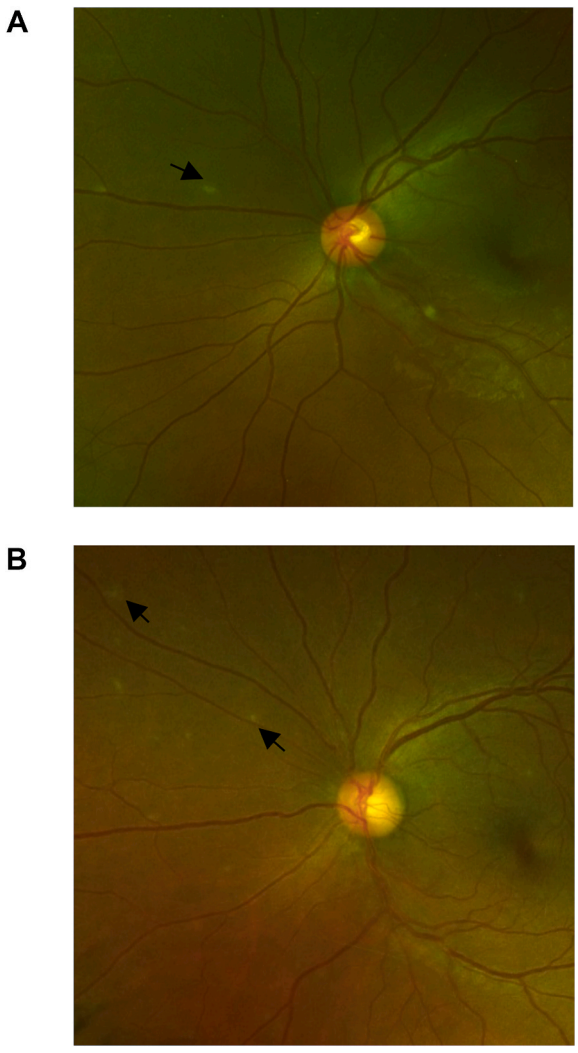

Fig. 1. Fundus exam findings. Multiple white spots (black arrows) seen on fundus examination associated with Rickettsia typhi infection in the left eye of patient 1 (A) and patient 2 (B).

Physical exam was unremarkable, with no tenderness to palpation over the sinuses. Past medical history was unremarkable, with no prior ophthalmic trauma. He worked in an office, lived near downtown Los Angeles, and stated that he occasionally provided a foster home for dogs. He had not had the most recent influenza vaccine, and denied recent travel, sick contacts, and intravenous drug use.

On presentation to the ophthalmology clinic, BCVA was 20/20 OU, although he reported blurrier vision than usual. Intraocular pressures and extraocular motility were within normal limits bilaterally. Slit lamp examination demonstrated faint flare with 1+ cell in the anterior chamber bilaterally. Fundus examination revealed 1+ cell in the vitreous, and multiple white spots at the level of the inner retina (Fig. 1b), with no retinal tears or holes bilaterally. A hyperfluorescent optic disc associated with retinal vascular leakage was appreciated bilaterally in late frames on widefield FA (Fig. 2b). Bilateral scattered hyperautofluorescent lesions were seen on FAF (Fig. 3a and b).

Based on his clinical findings and recent persistent fever, the differential diagnoses included white dot syndrome (WDS), infectious chorioretinitis, or a post-viral inflammatory process. He was started on cyclopentolate 1% drops, prednisolone 1% drops, and oral prednisone 40 mg daily after ruling out syphilis or tuberculosis infection, and

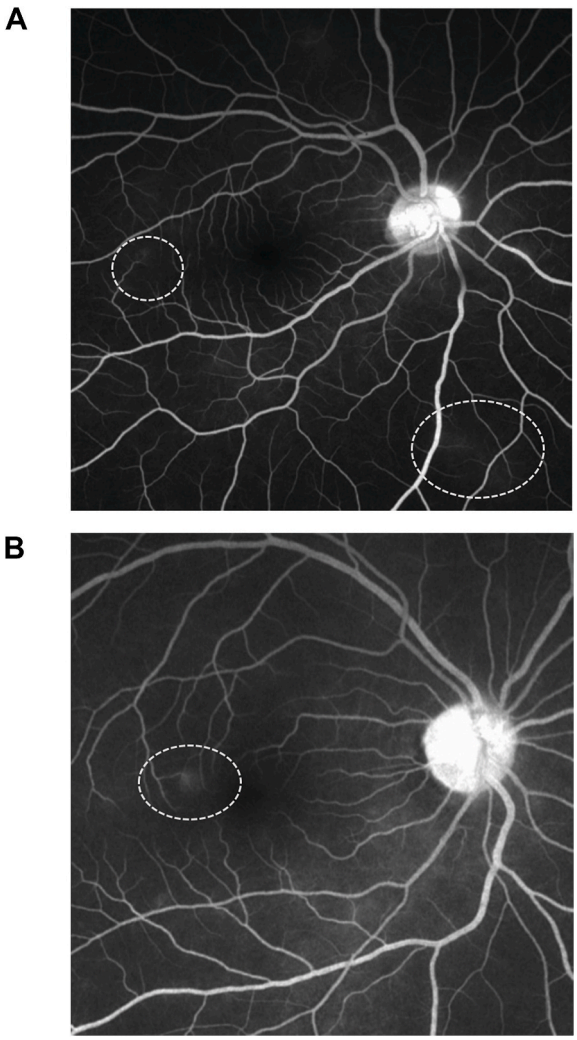

Fig. 2. Fluorescein angiography findings. (A) Patient 1 with subtle areas of retinal vascular leakage (circled) and a hyperfluorescent optic disc seen in a late frame on fluorescein angiography of the right eye. (B) Patient 2 with subtle areas of retinal vascular leakage (circled) and a hyperfluorescent optic disc seen in a late frame on fluorescein angiography of the right eye.

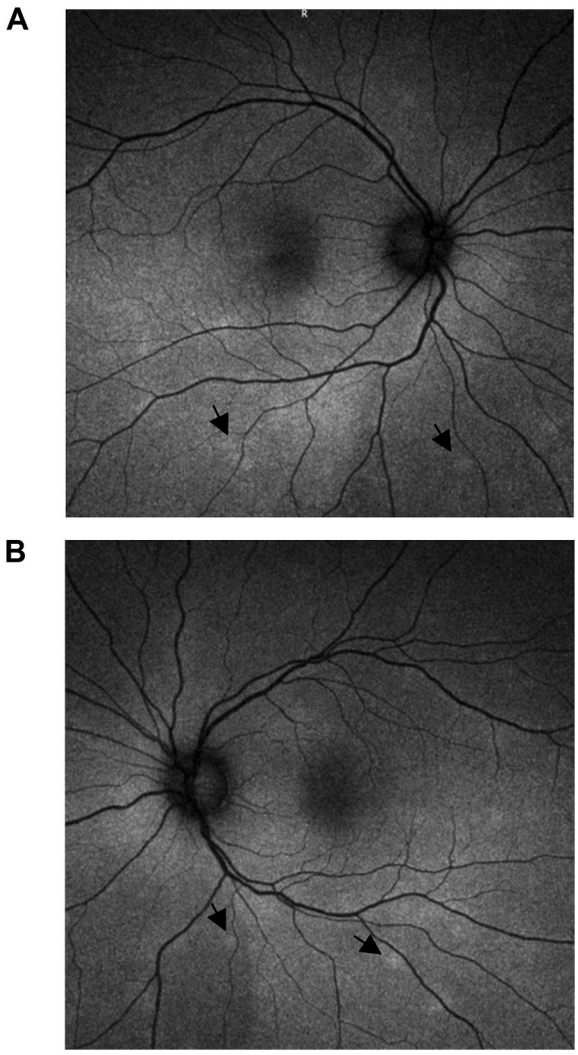

Fig. 3. Fundus autofluorescence findings. Patient 2 with multiple hyperautofluorescent spots seen on fundus autofluorescence in the right eye (A) and left eye (B) (black arrows point to characteristic lesions).

serology for rickettsial disease was also checked given the similar presentation and positive test result in patient 1 who was seen 2 days prior. Titers returned positive for *R. typhi* (both IgG and IgM were >1:256 when tested 4 weeks after illness onset) and he was subsequently started on doxycycline. He reported significant improvement in floaters 1 week later. Slit lamp examination showed resolved flare in the anterior chamber bilaterally. Fundus examination showed improving white spots bilaterally. At follow-up 7 weeks after the onset of ocular manifestations, fundus examination showed clear vitreous, complete resolution of white spots, with no RPE changes or retinopathy, and the patient reported his vision had returned to baseline.

3. Discussion

Murine typhus is an emerging cause of infectious eye disease, and its changing ecology and ubiquity of mammalian reservoirs portend further outbreaks in the future. There has been an upward trend in the incidence of murine typhus in Los Angeles County, with 14 cases reported in 2006 and most recently, 149 cases in 2018.[6] While traditionally associated with rodent fleas, opossums and cats have been identified as important reservoirs of infection, particularly in suburban settings.[1] Infection occurs in humans and other mammals after cutaneous inoculation by flea feces, with subsequent invasion of vascular endothelial cells of small blood vessels, causing a host mononuclear response and resulting in a systemic small-vessel lymphohistiocytic vasculitis.[7] While usually following a benign course, systemic complications of splenic rupture, meningoencephalitis, and severe pulmonary involvement in murine typhus have been reported.[2–4]

Ocular manifestations of murine typhus previously reported in literature include conjunctivitis, mild to moderate vitritis, white retinal lesions and vascular leakage, and post-infectious optic neuropathy.[7–10] Patients may complain of scotoma, sudden increase in floaters, and decreased visual acuity. The white lesions seen on fundus exam appear hyperautofluorescent on FAF, suggestive of acute underlying chorioretinal inflammation.[11] The exact pathophysiology of these retinal lesions is unclear, but has been speculated to be secondary to an immunologic process.[10] It is possible that the endovascular tropism of rickettsial organisms and subsequent accumulation of host mononuclear cells and formation of immune complexes result in deposition of perivascular cellular aggregates or formation of microgranulomata,[12] seen as white lesions on fundoscopy.

We suspect that murine typhus is underdiagnosed due to its nonspecific presentation and at times asymptomatic ocular manifestations. In many cases, exposure to fleas is not recollected by patients. The interval between the onsets of systemic symptoms to ocular

manifestations was 12–14 days in the two cases reported herein, which is similar to the reported range of 6–22 days in prior studies.[10] It is worth noting that the triad of fever, headache, and maculopapular rash presents in less than 33% of reported cases.[13] Furthermore, the non-pruritic maculopapular rash may be overlooked in patients with darker skin pigmentation, which may impede appropriate and prompt diagnosis. Patients presenting with ocular inflammation and white retinal lesions, particularly in the context of persistent fever, leukopenia, thrombocytopenia and elevated transaminase levels, should be worked up for rickettsial infection. This includes a thorough history and exam, and serologic testing during the acute and convalescent phase. The gold standard for diagnosis is seroconversion defined as ≥4-fold rise in serologic IgM and IgG antibodies to *R. typhi* during the convalescent phase detected by immunofluorescence assay (IFA),[14] which may take 2–3 weeks as seen in the first case herein. Polymerase chain reaction (PCR) assays of anterior chamber fluid to identify the pathogen could also be considered, but to our knowledge are not widely available.[15] Epidemiological risk factors such as recent travel to tropical or subtropical regions, particularly Texas, California, and Hawaii, and exposure to vector fleas in rodents, cats, or opossums should also raise suspicion for *R. typhi* infection.

Other infectious etiologies such as herpes simplex virus (HSV), Epstein-Barr virus (EBV), syphilis, and tuberculosis should be considered in the differential diagnosis. Non-infectious causes of uveitis, including sarcoidosis, Vogt-Koyanagi-Harada syndrome, multiple evanescent white dot syndrome (MEWDS), punctate inner choroidopathy (PIC), and birdshot choroidopathy should be considered as well. Murine typhus may be distinguished from these other disease processes by the location of its lesions in the inner retina,[10,16] as well as history and pertinent positive and negative exam findings. In some cases, serologic tests may show elevated titers of HSV or EBV (as in case 2) which may correspond to stress-induced reactivation of latent infection[17] and should be ruled out as the primary infection based on history and exam findings. In contrast to murine typhus, other diseases such as MEWDS or sarcoidosis typically present with pathology localized to the outer retina,[18,19] present often monocularly in the case of MEWDS, and may present with other striking systemic signs in the case of sarcoidosis. Although it is possible that elevated *R. typhi* antibody titers in our patients may be an incidental finding in the context of other etiologies such as post-infectious uveitis, this is less likely given the identical presentation in these two previously healthy patients, with transaminitis consistent with murine typhus, and with the onset of decreased vision correlating temporally with disease onset.

The current standard of care is empiric antibiotic treatment pending laboratory confirmation. The preferred antibiotic regimen is doxycycline (PO 100 mg BID, or IV for severe infection) for 3–7 days in children or continued for 2–3 days after resolution of symptoms in adults.[5,20,21] If tetracyclines cannot be tolerated such as in the setting of pregnancy, chloramphenicol and quinolones may be effective alternatives.[13,22] Topical and oral steroids may also be necessary to treat uveitic manifestations, as in the cases described herein. Systemic infection is generally clinically mild, although it can potentially cause severe complications and even death in 4% of those without appropriate antibiotics.[1] Ocular symptoms typically resolve within 3–10 weeks after the initial examination and the disease carries a good visual prognosis.[5] However, persistent visual loss has been reported due to ischemic optic neuropathy, branch retinal artery occlusion (BRAO), choroidal neovascularization, and cystoid macular edema.[23] Studies have shown doxycycline therapy to be associated with a shorter duration of febrile illness compared to other antibiotics,[22] however, the role of steroids on the course of ocular involvement requires further investigation.[24]

4. Conclusions

Rickettsia typhi is one of the many possible infectious agents that can cause uveitis. Heighted suspicion based on history can guide testing, particularly in patients in endemic areas presenting with persistent fevers, transaminitis, and unique posterior segment inflammation during summer and fall months. Prompt identification and initiation of targeted antibiotic therapy, with the consideration of adjunctive steroids after ruling out other infectious agents such as tuberculosis and syphilis, can shorten the course of the disease and in turn, lower the risk of severe complications.

Patient consent

Verbal consent to publish the cases was obtained from both patients.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

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References

1. Civen R, Ngo V. Murine typhus: an unrecognized suburban vector borne disease. *Clin Infect Dis*. 2008;46(6):913–918.
2. Ben-Zvi I, Meltzer E, Feld O, Bank I. A case of murine typhus associated with large vessel infarct of the spleen. *Am J Med Sci*. 2008;335(6):502–503.
3. Masalha R, Merkin-Zaborsky H, Matar M, Zirkin H, Wirguin I, Herishanu Y. Murine typhus presenting as subacute meningoencephalitis. *J Neurol*. 1998;245(10):665–668.
4. van der Vaart T, van Thiel P, Juffermans NP, et al. Severe murine typhus with pulmonary system involvement. *Emerg Infect Dis*. 2014;20(8):1375–1377.
5. Abroug N, Khochtali S, Kahloun R, Mahmoud A, Attia S, Khairallah M. Ocular manifestations of rickettsial disease. *Infect Dis Ther*. 2014;2(3):1.
6. California Department of Public Health. In: *Human Flea-Borne Typhus Cases in California*. Division of Communicable Disease Control; 2019, 2001-2018 https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.cdph.ca.gov%2FPrograms%2FCID%2FDCDC%2FCDPH%2520Document%2520Library%2FFlea-borneTyphusCaseCounts.pdf&data=02%7C01%7CA.Somasundaram%40elsevier.com%7C97b44b3130c84a7fe37608d821ff2deb%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637296727616732988&sdata=PwvVmKOxGTtwRHZffq6q0ix7Pl8SDq8W0B1DZCEwu0g%3D&reserved=0.
7. Brooks F, Fineberg R. Ocular manifestations of typhus fever. A review of the literature from 1867 to 1943. *Am J Ophthalmol*. 1951;34(4):605–608.
8. Zhang J, Pau D, Lee A. Postinfectious optic neuropathy in endemic typhus. *J Neuro Ophthalmol*. 2011;31(4):342–343.
9. Fehily S, Cross G, Fuller A. Bilateral conjunctivitis in a returned traveller. *PLoS Negl Trop Dis*. 2015;9(1), e0003351.
10. Khairallah M, Ben Yahia S, Toumi A, et al. Ocular manifestations associated with murine typhus. *Br J Ophthalmol*. 2009;93(7):938–942.
11. Meleth A, Sen H. Use of fundus autofluorescence in the diagnosis and management of uveitis. *Int Ophthalmol Clin*. 2012;52(4):45–54.
12. Ben-Ezra D, Forrester J. Fundal white dots: the spectrum of a similar pathological process. *Br J Ophthalmol*. 1995;79(9):856–860.
13. Tsioutis C, Zafeiri M, Avramopoulos A, Prousali E, Miligkos M, Karageorgos S. Clinical and laboratory characteristics, epidemiology, and outcomes of murine typhus: a systematic review. *Acta Trop*. 2017;166:16–24.
14. Paris D, Dumler J. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. *Curr Opin Infect Dis*. 2016;29(5):433–439.
15. Chronopoulos A, Roquelaure D, Souteyrand G, Seebach JD, Schutz JS, Thumann G. Aqueous humor polymerase chain reaction in uveitis - utility and safety. *BMC Ophthalmol*. 2016;16(1):189.
16. Lu T, Kuo B, Chung Y, Liu C. Murine typhus presenting with multiple white dots in the retina. *Scand J Infect Dis*. 1997;29(6):632–633.

17. Coskun O, Sener K, Kilic S, et al. Stress-related Epstein-Barr virus reactivation. *Clin Exp Med*. 2010;10(1):15–20.
18. Silva R, Albini T, Flynn HJ. Multiple evanescent white dot syndromes. *J Ophthalmic Inflamm Infect*. 2012;2(2):109–111.
19. Goldberg N, Jabs D, Busingye J. Optical coherence tomography imaging of presumed sarcoid retinal and optic nerve nodules. *Ocul Immunol Inflamm*. 2016;24(3):293–296.
20. Paras M, Hyle E, Foreman R, Coffey K. Case 14-2018: a 68-year-old woman with a rash, hyponatremia, and uveitis. *N Engl J Med*. 2018;378(19):1825–1833.
21. Botelho-Nevers E, Socolovschi C, Raoult D, Parola P. Treatment of Rickettsia spp. infections: a review. *Expert Rev Anti Infect Ther*. 2012;10(12):1425–1437.
22. Gikas A, Doukakis S, Pediaditis J, Kastanakis S, Manios A, Tselentis Y. Comparison of the effectiveness of five different antibiotic regimens on infection with Rickettsia typhi: therapeutic data from 87 cases. *Am J Trop Med Hyg*. 2004;70(5):576–579.
23. Kahloun R, Gargouri S, Abroug N, et al. Visual loss associated with rickettsial disease. *Ocul Immunol Inflamm*. 2014;22(5):373–378.
24. Khairallah M, Chee S, Rathinam S, Attia S, Nadella V. Novel infectious agents causing uveitis. *Int Ophthalmol*. 2010;30(5):465–483.