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BARTONELLA HENSELAE RELATED UNILATERAL ANTERIOR UVEITIS AND SUBSEQUENT MULTIFOCAL RETINITIS IN A CASE UNDER CERTOLIZUMAB TREATMENT

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ABSTRACT

Introduction: A case of ocular bartonellosis under anti-tumour necrosis factor treatment is described.

Case description: A 29-year-old woman with psoriasis who had been on certolizumab treatment was examined with a left visual deterioration following a fever bout, malaise, and placoid erythematous rashes on her neck. As there was acute anterior uveitis in her left eye, it was recommended to stop certolizumab treatment for a possible infectious aetiology. However, her physician elected to continue the certolizumab treatment. Ten days later, the patient noticed further visual decline despite the topical steroid treatment. This time, there were scattered yellow-white small retinitis foci at the left posterior pole. Infectious agents were searched and while *Bartonella henselae* antibodies were negative for immunoglobulin M, the immunoglobulin G titre was 1/80. Clinical findings were improved with the systemic treatment of oral trimethoprim-sulfamethoxazole (160/800 mg twice daily for six weeks) and azithromycin (500 mg once daily for two weeks).

Discussion: Though extremely rare, ocular bartonellosis should be kept in mind in patients on anti-tumour necrosis factor treatment as rapid and accurate diagnosis may end up with an excellent visual outcome and full recovery.

KEYWORDS

Bartonella henselae, cat-scratch disease, ocular bartonellosis, retinitis, immunosuppression

LEARNING POINTS

- Anti-tumour necrosis factor treatment is fraught with several ocular side effects including myositis, corneal infiltrates, scleritis, uveitis, optic neuritis, retinal vasculitis and ophthalmoplegia.
- When a new uveitis episode occurs in cases undergoing anti-tumour necrosis factor therapy, its cause poses a diagnostic challenge as it can have either an infectious or a non-infectious nature.
- Though very rare, ocular bartonellosis may also occur in immunocompromised individuals and a prompt diagnosis and appropriate treatment can lead to an excellent visual recovery.

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INTRODUCTION

Bartonella henselae is the causative agent for the cat-scratch disease[1]. Although Parinaud oculoglandular syndrome and neuroretinitis are the characteristic features, a wide array of ocular manifestations including both anterior and posterior segments may occur[2,3].

Certolizumab pegol is a PEGylated recombinant, humanised antibody. It targets the inflammatory cytokine tumour necrosis factor alpha (TNF-α) that plays a central role in the pathogenesis of psoriasis[4]. The initial dose of subcutaneous 400 mg administered at weeks 0, 2 and 4 is the recommended regimen. Subsequently, a maintenance dose of either 200 mg or 400 mg is given every two weeks depending on the severity of the condition in adult psoriasis[4].

Numerous ocular side effects of anti-TNF treatment such as uveitis, scleritis, optic neuritis, myositis, corneal infiltrates, retinal vasculitis and ophthalmoplegia have been reported[5,6]. We present a case of ocular bartonellosis (OB) in an immunocompromised patient who initially developed unilateral anterior iridocyclitis and subsequently acute multifocal retinitis. To the best of our knowledge, this is the first reported case of OB under anti-TNF treatment.

CASE DESCRIPTION

A 29-year-old woman on certolizumab treatment for psoriasis was examined with a left visual deterioration following a fever bout, malaise, and placoid erythematous rashes on her neck. She had received nine cycles of certolizumab treatment, with the last dose almost one week before our first examination. She did not experience any type of uveitis beforehand.

The best-corrected visual acuity (BCVA) was 10/10 in oculus dexter (OD) and 8/10 in oculus sinister (OS). Intraocular pressure was 14 mmHg bilaterally. While the right anterior segment was normal, there was ciliary injection and +2 anterior chamber cells in the left eye. Both fundi looked normal *(Fig. 1A and B)*. Fundus autofluorescence (FAF) imaging was unremarkable bilaterally *(Fig. 1C and D)*. A fluorescein angiogram (FA) revealed no abnormal findings in OD, while it showed subtle optic nerve head staining in OS *(Fig. 1E and F)*. Macular spectral-domain optical coherence tomography (OCT) was normal for both eyes *(Fig. 1G and H)*. Full systemic work-up including the infectious panel was planned; the patient was put on topical 8 × 1 prednisolone acetate 1% and 3 × 1 tropicamide 0.5% for the left eye. Discontinuation of the certolizumab treatment was recommended until the infectious aetiology was ruled out. Unfortunately, her physician kept the patient on certolizumab treatment.

Ten days later, the left optic disc appeared oedematous and there were scattered multiple yellow-white small retinitis foci throughout the posterior pole, and a retinitis area straddling the inferior optic disc border *(Fig. 2A)*. Those areas were hypoautofluorescent on FAF imaging *(Fig. 2B)*; retinitis foci looked hypofluorescent on repeat FA *(Fig. 2C and D)*. Inner retinal layers were hyperreflective, and hyperreflective precipitates were observed at the posterior vitreous area on spectral-domain OCT sections transversing through the retinitis foci *(Fig. 2E)* and peripapillary retinitis area *(Fig. 2F)*. There was no visual field loss in OS (Humphrey 30-2 Swedish interactive thresholding algorithm visual field test – *Fig. 2G*). Placoid erythematous rashes were evident on the patient's neck *(Fig. 2H)*. Though there was no history of exposure to cats, relevant tests for *B. henselae* were performed as the clinical appearance suggested OB. Enzyme-linked immunosorbent assay tests were negative for immunoglobulin M (IgM), and positive for IgG at a titre of 1/80. Cranio orbital magnetic resonance imaging was normal; chest X-ray and a computed tomography scan of the chest were unremarkable. Routine blood tests showed an increase in C-reactive protein (14.2 µm/l) and erythrocyte sedimentation rate (42 mm/h). Serology tests for other possible infectious aetiologies were negative, and a QuantiFERON-TB Gold test was also negative.

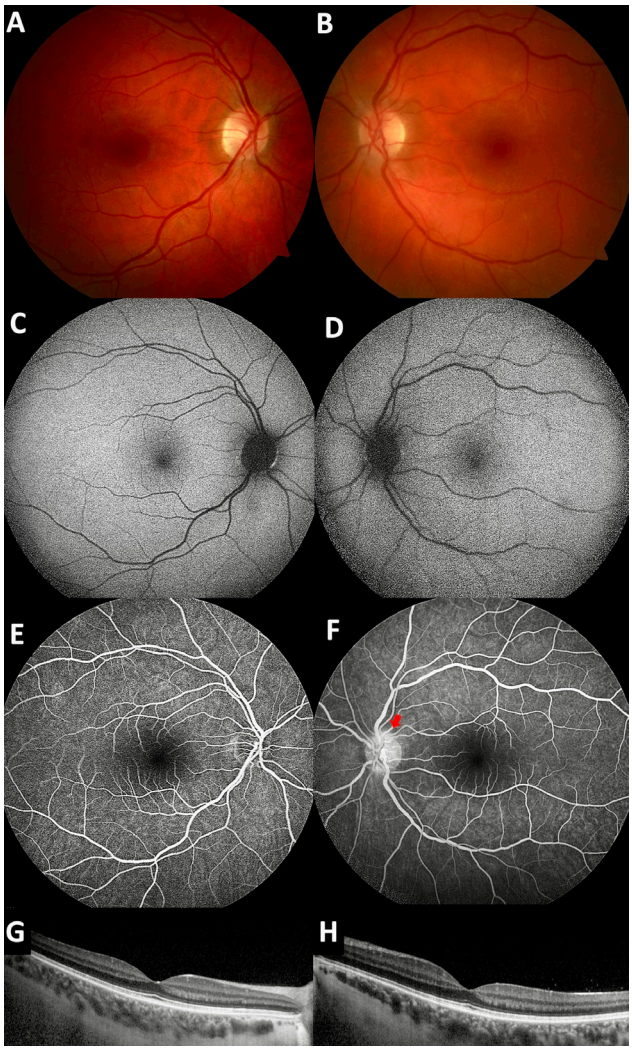

Figure 1. At the presentation. Colour fundus picture of the right eye (A) with an unremarkable appearance and the left eye (B) with a normal-looking posterior pole and very subtle optic disc margin blurriness. Normal fundus autofluorescence imaging findings bilaterally (C, D). Venous phase of fluorescein angiogram showing no abnormality in the right eye (E) and subtle optic disc staining at the left posterior pole (red arrow) (F). Spectral-domain optical coherence tomography delineating normal macular contour in both eyes (G, H).

The diagnosis of OB was established with the constellation of clinical findings and laboratory results. Oral trimethoprim-sulfamethoxazole (160/800 mg 2 × 1, for 40 days) and azithromycin (500 mg 1 × 1, for 15 days) were commenced. Systemic steroid treatment was not considered as the patient did not have any visual field disturbance. The serology tests were repeated two weeks later, and similar results were obtained.

On the sixth week of follow-up, the patient's BCVA was 10/10 in OS. Slit-lamp examination was unremarkable. Complete resolution of the retinitis foci and the optic disc oedema was achieved *(Fig. 3A)* and FAF imaging was unremarkable *(Fig. 3B)*. Placoid erythematous rashes on her neck had disappeared *(Fig. 3C)*.

DISCUSSION

A new uveitis episode poses a diagnostic dilemma in patients under anti-TNF therapy. Uveitis may occur either as a *de novo* case or as a recurrence related to inadequate treatment in these patients. Thus, a comprehensive differential diagnosis analysis should be carried out[7]. Sobolewska et al.[7] evaluated 16 patients on biologic agents who developed uveitis for the first time or experienced intraocular inflammation that was different in location or laterality from the previous inflammation. Eleven patients (69%) developed a first episode of uveitis, while five (31%) had recurrences. Seven patients (44%) exhibited alterations in their uveitis pattern, all of which were part of the well-known spectrum of ocular sarcoidosis. The authors emphasised the importance of differentiating uveitis recurrence related to the underlying disease and drug-induced uveitis. They suggested considering sarcoidosis as a potential cause of uveitis in patients receiving biologic agents.

OB may exhibit unusual signs in immunocompromised patients. Establishing the correct diagnosis could be challenging. Curi et al.[3] reported on three HIV-positive patients who had concurrent, serologically proven OB. All patients had exhibited subretinal yellowish lesions, accompanied by fluid accumulation and vascular alterations. An abnormal vascular network was observed on FA corresponding to these lesions. The authors emphasised that OB might cause an unusual vasoproliferative response in immunocompromised hosts.

Lee et al.[8] described two cases of OB following a renal transplant. The first case, a 45-year-old male, had experienced blurred vision in his right eye a decade after the transplant. There was bilateral optic disc oedema without any evidence of inflammation. *Bartonella henselae* IgM and IgG were tested positive; he was treated with doxycycline and azithromycin. The second patient, a 44-year-old male, had complained about floaters in his left eye, four years after the renal transplant. He had exhibited anterior uveitis, vitritis, evidence of old retinal choroiditis and a yellow, deep lesion in the temporal retina. He was initially treated with topical and oral corticosteroids for panuveitis since the laboratory work-up for infectious or non-infectious causes was negative. He had developed an exudative retinal detachment during the follow-up and had lost his left vision despite the vitreoretinal surgery. Subsequently, he developed a disseminated disease with brain and heart involvement. The diagnosis was established following the detection of *B. henselae* IgM and IgG antibodies. Even though he was treated with doxycycline, ceftriaxone and rifampin, his left visual acuity did not improve.

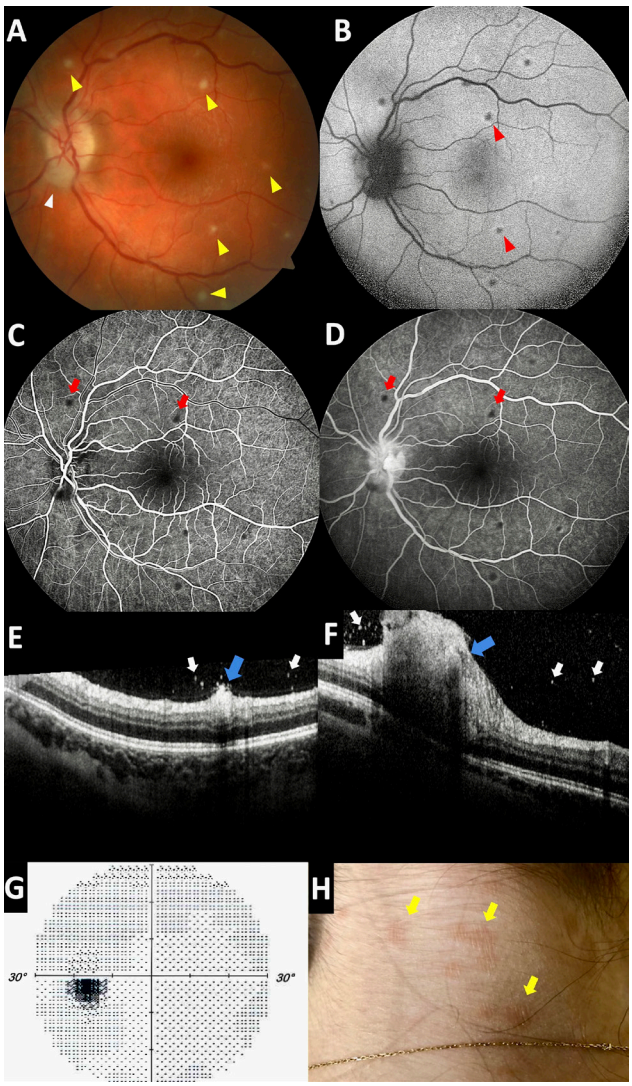

Figure 2. Ten days later, left eye. Colour fundus picture (A) showing peripapillary retinitis adjacent to the inferior optic disc border (white arrowhead) together with multiple small foci of yellow-white retinal infiltrates scattered throughout the posterior pole and mid-periphery (yellow arrowheads). Fundus autofluorescence imaging (B) revealing the hypoautofluorescent spots at the areas corresponding to the retinal infiltrates (red arrowheads). Early (C) and late (D) phases of fluorescein angiogram depicting the disc leakage and staining corresponding to the retinal infiltrates (red arrows). Spectral-domain optical coherence tomography transversing the small foci of retinitis (E) and the retinitis area located adjacent to the inferior optic disc border (F) delineating the focal areas of hyperreflectivity in the inner retinal layers (blue arrows), hyperreflective particles at the posterior vitreous area (white arrows). There was no pertinent visual field loss on the Humphrey 30-2 Swedish interactive thresholding algorithm visual field test of the left eye (G). Erythematous placoid rashes on the neck (H, yellow arrows).

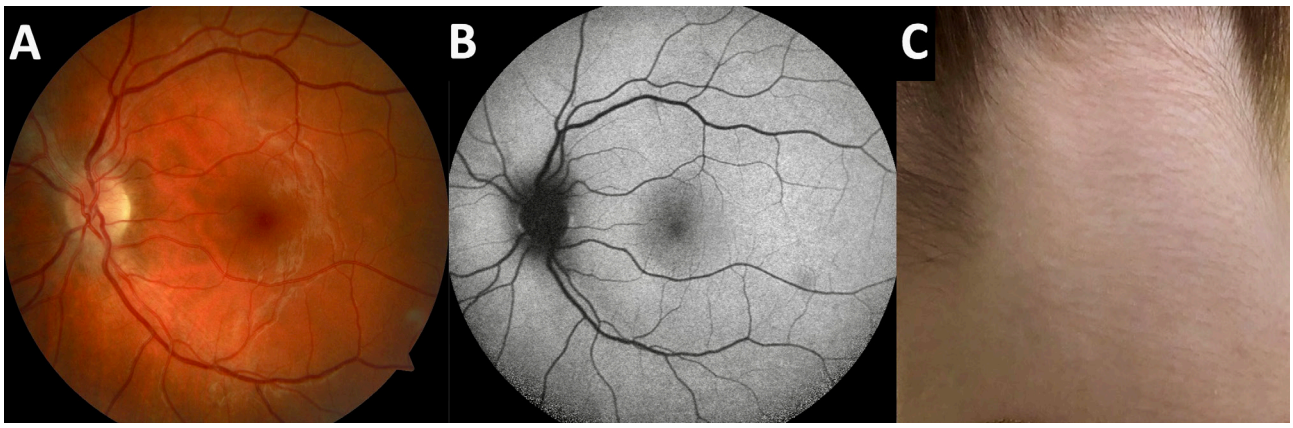

Figure 3. Four weeks after the presentation, left eye. Colour fundus picture (A) showing the resolution of the optic disc oedema and retinal infiltrates, and the disappearance of the hypoautofluorescent spots on fundus autofluorescence imaging (B). Normal-looking neck skin (C).

Irshad et al.[9] published details of a 15-year-old patient with OB who had chronic myeloid leukaemia and had undergone an allogeneic bone marrow transplant. She presented with a progressive visual loss in her right eye and right-sided neck swelling. Ophthalmological examination revealed oedema and hyperaemia of the optic disc surrounded by flame-shaped haemorrhages together with the late leakage around the optic disc and fluorescein pooling at the macula on FA. Histopathological examination of the specimen acquired from the neck revealed necrotising granulomatous lymphadenitis. Initial *B. henselae* IgG was positive at a titre of 1/128, whereas it was positive at a greater dilution of 1/512 a week later. The patient was treated with doxycycline and rifampin.

Wu et al.[10] reported a 57-year-old patient with OB and a history of IgA vasculitis who was on cyclophosphamide and rituximab, and had bilateral blurry vision. On fundoscopy, there were bilateral vitritis, optic disc oedema, scattered inner retinal and preretinal lesions throughout the posterior pole, vascular sheathing and well-circumscribed, preretinal white lesions along the retinal vessels in the inferior mid-periphery of the right eye. Serology tests and diagnostic vitrectomy yielded negative results for infectious aetiology. However, a brain biopsy revealed foci of necrosis accompanied by lymphohistiocytic inflammation, and a positive polymerase chain reaction for *B. henselae*. The diagnosis of bartonellosis was established, and the patient was treated with doxycycline and rifampin. Retinal lesions were regressed, and seroconversion was evident at 12 weeks from the presentation (IgG 1/256 from 1/128).

The diagnosis of OB relies on the assessment of clinical signs and related findings. A positive result for *B. henselae* IgM or a high IgG titre is considered sufficient to establish a diagnosis[11,12]. The present case had a positive IgG serology at a titre of 1/80. While we conducted a repeat serology test, it was possible that the antibody titre remained unchanged due to antibiotic treatment already being administered, or because the patient's immune response was influenced by certolizumab treatment.

Rifampicin, gentamicin, cotrimoxazole, ciprofloxacin, azithromycin and doxycycline have demonstrated effectiveness in managing Bartonella infections[13]. Severe inflammation affecting the optic nerve or macula can be successfully treated by combining antibiotics with corticosteroids. We did not consider systemic corticosteroid treatment for the present case, as there was no visual field loss. Prolonged treatment was also not considered as the clinical picture resolved totally.

In immunocompromised patients, the clinical manifestations may overlap and make the differential diagnosis challenging. It is imperative to consider both infectious and non-infectious aetiologies. To the best of our knowledge, the present case is the first reported case with OB under anti-TNF treatment. Although being uncommon, *B. henselae* infection may be seen in immunocompromised patients. Rapid diagnosis and treatment may prevent serious ocular or systemic complications.

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