Bilateral Ocular Myositis Associated with Whipple's Disease

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Key Words

Whipple's disease · Ocular myositis · Extraocular muscle · Immune reconstitution inflammatory syndrome

Abstract

Purpose: To describe the clinical features of a Caucasian female patient with a history of treated gastrointestinal Whipple's disease (WD) who developed new-onset diplopia, with a description of the histopathological features of the extraocular muscle biopsies. **Methods:** A previously fit 38-year-old Caucasian female presented with acute-onset diplopia after being on a sustained medication regime for biopsy-proven gastrointestinal WD. A magnetic resonance imaging scan of her orbits with gadolinium revealed diffuse enhancement of the bellies of the extraocular muscles bilaterally, particularly the medial rectus, superior rectus, and superior oblique muscles, consistent with an infiltrative myositis. She underwent unilateral extraocular muscle biopsies. **Results:** The extraocular muscle biopsies contained macrophages between the muscle fibres. These contained periodic acid-Schiff-positive cytoplasmic granules. Immunohistochemistry with an antibody raised to *Tropheryma whipplei* showed positive staining of the same macrophages. Transmission electron microscopy confirmed

the presence of effete *T. whipplei* cell membranes in lysosomes. **Conclusion:** This case describes bilateral WD-associated extraocular muscle myositis. The exact mechanism for this unusual presentation is unclear, but both a WD-associated immune reconstitution inflammatory syndrome and treatment failure are possibilities, with a good response observed to antibiotic therapy and adjunctive corticosteroids.

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Introduction

Whipple's disease (WD) is a rare infectious disease caused by the organism *Tropheryma whipplei* [1], usually affecting middle-aged white males. The multisystemic effects of WD are well described, with weight loss and diarrhoea predominating, as well as arthritis and arthralgia. Fifteen percent of WD cases do not display classic signs, and therefore WD can be a diagnostic challenge and is often mistakenly diagnosed as another multisystemic disorder such as inflammatory arthropathy [2]. Occasionally central nervous system (CNS) and ophthalmic complications are observed [3]. Here we report the first description of bilateral ocular myositis associated with WD.

Case Report

A previously fit 38-year-old Caucasian female presented with intermittent fevers, arthralgia affecting the hands and feet, rash, and fatigue. She subsequently developed abdominal pain, diarrhoea, and weight loss. Investigations for infective, malignant, metabolic, and inflammatory causes did not clearly identify an aetiological diagnosis, and directed investigations for HIV and other blood-borne viruses were also negative. A presumptive diagnosis of adult-onset Still's disease was subsequently made. Sequential immunosuppressive therapy with azathioprine and methotrexate in combination with oral corticosteroids resulted in no significant improvement. The interleukin-6 receptor antagonist tocilizumab also had a limited effect on her symptoms, but it did normalise her C-reactive protein (CRP) level from 100 to <5 mg/l. The arthralgia eventually settled with repeated courses of pulsed intravenous methylprednisolone, but the diarrhoea and abdominal pain persisted. Cross-sectional computerised tomography imaging revealed hepatic enlargement with sinusoidal dilatation. Due to ongoing gastrointestinal symptoms, oesophagogastroduodenoscopy was performed and showed no gross abnormalities. A duodenal biopsy revealed periodic acid-Schiff (PAS)-positive macrophages, and an ensuing polymerase chain reaction (PCR) was also positive for *T. whipplei*. The diagnosis of WD was made 8 years after her initial presentation.

To treat the WD, a 2-week course of intravenous ceftriaxone (2 g/day) was given, followed by maintenance phase oral co-trimoxazole (960 mg twice daily). The immunosuppressive therapy was weaned to leave the patient on 5 mg of oral prednisolone. Around this time, the patient was admitted to intensive care with a severe community-acquired pneumonia, further complicated by impaired consciousness. To investigate the possibility of WD affecting her CNS, magnetic resonance imaging (MRI) of the brain was performed, which demonstrated left frontal white matter changes. Cerebrospinal fluid cell counts and biochemistry were unremarkable (red cells: 0/μl; white cells: 1/μl; glucose: 5.5 mmol/l; protein: 0.28 g/dl). A subsequent cerebrospinal fluid PCR for *T. whipplei* was negative on two occasions. A further two courses of intravenous ceftriaxone were given (2 g/day for 2 weeks), followed by a switch to oral co-trimoxazole. Although respiratory and CNS function improved, over the subsequent 4 weeks the patient developed new diplopia on left lateral gaze and displayed a persistently raised inflammatory response, with ongoing pyrexia (>38°C), leucocytosis ($18.5 \times 10^9/l$), and elevated CRP (278 mg/l). MRI of her orbits with gadolinium revealed diffuse enhancement of the bellies of all the extraocular muscles bilaterally, particularly the medial rectus, superior rectus, and superior oblique muscles (fig. 1a), consistent with an infiltrative myositis.

A biopsy of the superior and lateral rectus extraocular muscles showed CD68-positive macrophages (fig. 2a) and occasional CD3-positive T cells (not shown) between the muscle fibres. The inflammatory cells were not actively destroying the myocytes. A PAS stain showed a distribution of staining identical to the CD68, revealing macrophages with densely packed cytoplasmic pink globules (fig. 2b). Immunohistochemistry performed by a reference laboratory in Marseilles, France, showed positive staining of the macrophages with an antibody to *T. whipplei*, with a pattern identical to the PAS stain (fig. 2c). Transmission electron microscopy of the sample retrieved from the formalin-fixed paraffin-processed tissue showed collapsed and concertinaed cell walls of *T. whipplei*

Fig. 1. a Baseline T1-weighted fat-saturated post-gadolinium coronal MRI of the orbits, showing enlargement of the extraocular muscles (large arrows), with stranding and enhancement within the retrobulbar fat (small arrow), particularly on the left. **b** Follow-up MRI of the orbits 8 months after initiation of the therapy, showing improvement of the stranding and enhancement within the retrobulbar fat, with persistent but improved muscle enlargement.

Fig. 2. **a** CD68 immunohistochemistry showing collections of macrophages between the myocytes (arrows). **b** PAS stain showing collections of macrophages between the myocytes, as well as cytoplasmic pink/purple globules (arrows). **c** *T. whipplei* immunohistochemistry showing a positive brown signal (arrow) within the macrophages. **d** Transmission electron micrograph of a macrophage containing material within the lysosomes (arrows). Original magnification $\times 2,600$. **e** Transmission electron micrograph of a higher power of plate **d**, showing *T. whipplei* collapsed and concertinaed cell walls (arrow). Original magnification $\times 20,000$.

within the lysosomes of the macrophages (fig. 2d, e). No viable bacteria were identified. Overall, the light microscopic, immunohistochemical, and ultrastructural features were those of a *T. whipplei*-associated myositis of the extraocular muscles. A PCR for *T. whipplei* on the ocular muscle biopsy was negative.

Transthoracic and transoesophageal echocardiography revealed a vegetation on the aortic valve with mild aortic regurgitation and diffuse thickening of the pulmonary valve consistent with WD endocarditis.

The patient completed a further 6-week course of intravenous ceftriaxone, subsequently commencing a planned minimum of 18 months of oral doxycycline (200 mg/day) and hydroxychloroquine (300 mg/day). However, the ocular symptoms persisted until the institution of a 2-week course of oral prednisolone (40 mg/day), which brought rapid symptomatic improvement. This was then tapered down (reduced by 10 mg every 1–2 weeks) to a 7.5 mg/day maintenance dose. Eight months after the initiation of doxycycline and hydroxychloroquine, the symptomatic improvement was maintained with complete resolution of CRP and weight recovery. Repeat MRI 8 months (fig. 1b) after initiation of the maintenance therapy demonstrated a definite reduction in the enhancement within the retro-orbital fat, with no mass or pathological enhancement, although persistent (but reduced) enlargement of the extraocular muscles.

Discussion

WD is a multisystemic disorder which presents with a wide spectrum of symptoms, leading to a challenge in diagnosis. Extragastrointestinal manifestations of WD, although uncommon, can encompass cardiovascular, musculoskeletal, and central and peripheral nervous system involvement. Ocular involvement and myositis are rare manifestations of WD, with only 2 previous cases of unilateral ocular myositis described in the literature [4, 5]. Generalised myositis has, however, been reported as a result of WD in other cases [6]. Extraocular muscles significantly differ from other muscle types, predominantly due to their function in the tight control of eye movements. It has therefore been postulated that susceptibility to certain diseases may be increased, but the pathogenic mechanism for this remains unclear [7].

Other patterns of ocular involvement have been described with WD, similar to many infectious diseases [8]. Numerous reported secondary manifestations of eye disease in WD include uveitis, retinitis, papilloedema, and optic atrophy [9–11]. Although classically manifesting alongside gastrointestinal symptoms, WD can sometimes present with purely ophthalmic involvement, posing a challenge to diagnosis [12–14]. It is thought that ocular involvement is usually a neurological manifestation, but this may not apply to extraocular muscle involvement [7, 15].

Our patient had a firm diagnosis of WD following PAS-positive macrophages demonstrated on duodenal biopsy and confirmed with positive PCR, with CNS and ophthalmic muscle involvement suspected after the initial diagnosis. MRI of the orbits demonstrated inflammation of the extraorbital muscles. The subsequent biopsy of these muscles revealed a tight correlation of the pattern of CD68-positive macrophages on each of high-strength microscopy, PAS staining, and immunohistochemistry. Electron microscopy further demonstrated effete *T. whipplei* bacterium cell wall components within the lysosomes of macrophages.

The lack of complete clinical remission after initial antimicrobial therapy in our case may have been due to treatment failure or relapse of disease. Fourteen days of ceftriaxone (2 g/day) or meropenem (1 g 3 times/day) followed by 12 months of oral co-trimoxazole (160/800 mg/day) has been shown to be effective at achieving cure at 3 years. A randomised controlled trial showed that remission was maintained in all patients (n = 18 with ceftriaxone; n = 20 with meropenem), except for 2 patients who died from unrelated causes [16]. A case series of ocular WD treatment concluded that co-trimoxazole and rifampicin continued for at least 1 year was effective in 7 out of 11 cases, although an intravenous induction phase was not included in the management [15]. However, more recent data suggest that doxycycline and hydroxychloroquine may be superior to co-trimoxazole in difficult-to-treat or relapsed cases [17].

An alternative possibility is that myositis was a late presentation of the disease [4, 5], occurring as part of an immune reconstitution inflammatory syndrome (IRIS). In a large proportion of WD-associated IRIS cases, however, patients had complete resolution of the symptoms before a late recurrence of inflammation, in contrast to this case [18]. IRIS has been described as a recognised complication of WD with a rate of up to 10%, and is sometimes interpreted as undertreatment or recurrent disease [18, 19]. IRIS has historically been a term most often encountered in the setting of HIV, occurring after initiation of highly active antiretroviral treatment. This treatment induces an inflammatory reaction due to a dysregulated immune response to either subclinical or incompletely treated opportunistic infections following immune reconstitution. The immunopathogenesis in WD may be different, with IRIS occurring due to rapid weaning of immunosuppression initiated for presumed inflammatory conditions prior to a definitive diagnosis of WD being made [19]. IRIS can occur in WD patients who have previously received antibiotic and/or immunosup-

pression treatment, with subsequent new deterioration occurring in a setting where specimens are *T. whipplei* PCR negative. In our case, the PCR on fresh and paraffin-fixed extraocular muscle tissue was indeed negative [19]. The ocular myositis in our case may be due to IRIS rather than untreated WD, because of a lack of resolution of the ocular symptoms despite systemic symptomatic and biochemical improvement with appropriate antibiotic therapy, as well as the presence of an inflammatory infiltrate on ocular biopsy with effete bacterial cell walls, rather than intact organisms. Most WD-associated IRIS cases, however, tend to show a more generalised inflammatory picture, and treatment failures on co-trimoxazole are well recognised. It is noteworthy that both previously described cases of ocular myositis occurred after over 1 year of antibiotic therapy for WD [4, 5], with one case requiring corticosteroids in addition to further antibiotic therapy to achieve resolution [4]. The use of steroids, however, in WD-associated IRIS has a limited evidence base, in contrast to steroid use in tuberculosis-associated IRIS [20].

In conclusion, we describe the first case of WD-associated bilateral extraocular myositis with a detailed demonstration of associated histopathological features. The

exact mechanism for this unusual presentation is unclear, but both a WD-associated IRIS and treatment failure are possibilities, with a good response observed to optimised antibiotic therapy and adjunctive corticosteroids.

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Statement of Ethics

The subject has given informed consent for this case report. The study was performed in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors declare no conflicts of interest or financial interests.

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