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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

Introduction

Whipple's disease (WD) is a rare infectious disease caused by the organism *Tropheryma whipplei*[1], usually affecting middle-aged white males. The multi-system effects of WD are well described with weight loss and diarrhoea predominating, as well as arthritis and arthralgia. 15% of WD cases do not display classical signs and therefore WD can be a diagnostic challenge, often mistakenly diagnosed as other multi-system disorders such as inflammatory arthropathies[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, most likely caused by an immune reconstitution inflammatory response following weaning of immunosuppressive therapy.

Case Report

A previously fit 38-year-old female presented with intermittent fevers, arthralgia affecting 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 a presumptive diagnosis of Adult-onset Stills Disease was made. Sequential immunosuppressive therapy with azathioprine and then methotrexate, in combination with oral corticosteroids, bought no significant improvement. The interleukin-6 receptor antagonist, tocilizumab, also had limited effect on her symptoms, but did normalise her C-reactive protein (CRP) from 100 mg/L to <5 mg/L. The arthralgia eventually settled with repeated courses of pulsed intravenous methylprednisolone, but diarrhoea and abdominal pain persisted. Cross-sectional computerised tomography (CT) imaging revealed hepatic enlargement with sinusoidal dilatation. Due to ongoing gastrointestinal symptoms, oesophagogastroduodenoscopy (OGD) was performed and proved to be normal. Duodenal biopsy revealed PAS-positive macrophages and subsequent polymerase chain reaction (PCR) was also positive for *Tropheryma whipplei*. The diagnosis of WD was made 8 years after her initial presentation.

To treat the WD, a 2-week course of intravenous ceftriaxone (2g/day) was given, followed by maintenance phase oral co-trimoxazole (960mg twice daily). Immunosuppressive therapy weaned to leave the patient on 5mg 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 preformed, which demonstrated left frontal white matter changes. Cerebro-spinal fluid (CSF) cell counts and biochemistry were unremarkable (Red cells 0/µl; white cells 1/µl; Glucose 5.5 mmol/L; protein 0.28 g/dL). Subsequent CSF PCR for *T. whipplei* was negative on two occasions. A further 2 courses of intravenous ceftriaxone were given (2g/day x 2 weeks), followed by a switch to oral co-trimoxazole. Although the patient's respiratory and CNS function resolved, over the subsequent 4 weeks the patient developed new diplopia on left lateral gaze and displayed a persistently raised inflammatory response; with ongoing pyrexia (>38ºC), leucocytosis (18.5 x 10^9/L) and elevated CRP (278 mg/L). MRI of her orbits with gadolinium revealed diffuse enhancement of the bellies of the extra ocular muscles, particularly the medial rectus, superior rectus and superior oblique muscles (**Figures 1,2,3),** consistent with an infiltrative myositis.

A biopsy of extra-ocular muscle at low scanning power exhibited a fairly unremarkable architecture (**Figure X)**. At higher power, there were occasional inflammatory cells between the myocytes, comprising CD68 positive macrophages (Fig a) and occasional CD3 positive T-cells (as demonstrated by immunohistochemistry). The inflammatory cells were not actively destroying the myocytes. A periodic acid-Schiff (PAS) stain showed a distribution of staining identical to the CD68 pattern revealing macrophages with densely packed cytoplasmic pink globules (Fig b). Immunohistochemistry performed by the laboratory in Marseilles, France showed positive staining of the macrophages with an antibody to *Tropheryma whipplei,* with a pattern of staining identical to the PAS stain (Fig c). Transmission electron microscopy of the sample retrieved from the formalin fixed paraffin processed tissue showed unequivocal collapsed and concertinaed cell walls of *Tropheryma whipplei* within the lysosomes of macrophages (Fig d and e). No viable bacteria were identified. Overall the light microscopy, immunohistochemical and ultrastructural features were those of a *Tropheryma whipplei* associated myositis of the extra ocular muscles.

Trans-thoracic and trans-oesophageal 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 third 6-week course of intravenous ceftriaxone, then commenced a planned minimum 18 months of oral doxycyline (200mg/day) and hydroxychloroquine (300mg/day). The ocular symptoms persisted however, until institution of a 2-week course of oral prednisolone (40mg/day) brought rapid symptomatic improvement. This was then tapered down (reduced by 10mg every 1-2 weeks) to a 7.5mg/day maintenance dose. 8 months after initiation of doxycycline and hydroxychloroquine, symptomatic improvement was maintained with complete resolution of CRP and weight recovery to 60kg. Repeat MRI imaging at 8 months (Figure 4) after initiation of maintenance therapy demonstrated definite reduction in the enhancement within the retro orbital fat with no mass or pathological enhancement, although persistent (but reduced) enlargement of the extra ocular muscles.

Discussion

WD is a multi-system disorder which presents with a wide spectrum of symptoms, leading to a challenge in diagnosis. Extra-gastrointestinal 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 two previous cases of ocular myositis described in the literature[4 5]. Generalised myositis has, however, been reported as a result of WD in other cases[6]. Extra-ocular muscles differ from other muscle types significantly, predominantly due to their function in tight control of eye movements. It has been postulated therefore, 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, presenting a challenge to diagnosis[12-14]. It is thought that ocular involvement is usually a neurological manifestation, but this may not apply to extra-ocular muscle involvement[7 15].

The case described is a unique presentation of bilateral myositis of extra-ocular muscle. The patient had a firm diagnosis of WD following PAS-positive macrophages demonstrated on duodenal biopsy and confirmed with positive PCR, with CNS and ocular involvement suspected after initial diagnosis. Serial MRI orbits demonstrated progressive inflammation of extra-orbital 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 *Tropheryma whipplei* bacterium cell wall components within lysosomes of macrophages. This strong pattern of involvement has never previously been demonstrated in the limited cases of WD associated extra-ocular myositis in the literature.

The lack of complete clinical remission after initial antimicrobial therapy in our case may have been due to

treatment failure or relapse of disease. 14 days of ceftriaxone (2g/day) or meropenem (1g x 3 times/day) followed by 12-months of oral co-trimoxazole (160/800mg /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 and n=20 meropenem), except 2 patients who died from unrelated causes[16]. A case series of ocular WD treatment concluded co-trimoxazole and rifampicin continued for at least 1 year was effective in 7/11 cases, although an intravenous induction phase was not included in management[15]. However, more recent data suggest that doxycyline and hydroxychoroquine 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] and we postulate that this can occur as part of an immune reconstitution inflammatory syndrome (IRIS).

IRIS has been described as a recognised complication of WD with a rate of up to 10%, and is sometimes interpreted as under-treatment 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 anti-retroviral treatment (HAART). HAART induces an inflammatory reaction due to a dysregulated immune response to either sub-clinical or incompletely treated opportunistic infections following immune reconstitution. The immunopathogenesis in WD may be different, with IRIS occurring due to rapid weaning of immunosupression initiated for presumed inflammatory conditions prior to a definitive diagnosis of WD being made[19]. We suggest that the ocular myositis in our case is more likely to be due to IRIS than untreated WD because of a) lack of resolution of ocular symptoms despite systemic symptomatic and biochemical improvement with appropriate antibiotic therapy; and b) the presence of an inflammatory infiltrate on ocular biopsy with effete bacterial cell walls, rather than intact organisms. It is noteworthy that both the 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].

In conclusion we believe that the appearance of ocular features with initial definitive treatment for WD followed by the response to steroid treatment, in combination with the detailed imaging and histopathological description of myositis, present evidence of a first ever case of WD IRIS of the ocular muscles.

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Figure Legends

Imaging figures:

1. T2 weighted coronal image through the orbits.
2. T1 weighted coronal image through the orbits.
3. T1 weighted fat saturated post gadolinium coronal image through the orbits.
4. *Insert FU MRI image*

Histology figures:

a. CD68 immunohistochemistry showing collections of macrophages between the myocytes (arrows)

b. Periodic acid-Schiff (PAS) stain showing collections of macrophages between the myocytes, showing cytoplasmic pink/purple globules (arrows).
c. *Tropheryma whipplei* immunohistochemistry showing a positive brown signal between the mycocytes (arrows) within the macrophages.
d. Transmission electron micrograph of a macrophage containing material within its lysosomes. (arrows). Original magnification x2,600
e. Transmission electron micrograph of a higher power of plate d showing *Tropheryma whipplei* collapsed and concertinaed cell walls (arrow). Original magnification x20,000

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