2. Adjunctive therapy with methotrexate for presumed syphilitic uveitis: A report of three cases

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Abstract. Purpose: To report 3 cases with presumed syphilitic uveitis showing partial response to intravenous penicillin treated with oral methotrexate. Procedures: Interventional retrospective case series.

Intravenous penicillin was initiated at 24 million U/day for 10 days. 4 weeks after cessation of intravenous penicillin oral methotrexate 15-20 mg/week was administered for 6 months. Treatment efficacy was assessed by best-corrected visual acuity (BCVA), fundus fluorescein angiography and optical coherence tomography. Results: 3 patients (4 eyes) showing partial response to intravenous penicillin had complete resolution of posterior segment manifestations in 3 months with oral MTX.

BCVA improved in 4 eyes. During the follow-up of 4-15 months after cessation of MTX, no relapse occurred. Conclusions: As a great imitator, syphilis should be considered in all patients with uveitis.
Methotrexate might have an adjunctive role in patients with presumed syphilitic uveitis for suppressing inflammation and preventing recurrences.

Message of the paper: We believe our report provides the first example of adjunctive therapy of methotrexate for presumed syphilitic uveitis.

Introduction

Syphilis is a systemic disease caused by the spirochete Treponema pallidum[1]. It is known as “the great imitator” due to its wide variety of clinical presentations, including ocular disorders[2]. There has been a recent increase in the rate of syphilis infection in Turkey especially among women in poor settings [3]. This article focuses on the varied clinical presentations of the presumed syphilitic uveitis in human immunodeficiency virus (HIV) negative cases. The diagnosis was based on positive serum fluorescent treponemal antibody absorption (FTA-ABS) and positive serum treponema pallidum hemagglutination assay (TPHA). Ophthalmologic findings of the 3 cases mimick the presenting features of multiple evanescent white dot syndrome (MEWDS), branch retinal vein occlusion (BRVO), and Irvine-Gass respectively.

Case 1:

A 31-year-old woman had BCVA of 20/60 OD, 20/60 OS, and non-granulomatous iridocyclitis OU. Fundus examinations OU disclosed ½+ vitreous haze and cells associated with creamy-yellow superficial retinal accumulations and optic disc congestion (Figure 1,2). Fundus fluorescein

Figure 1. Color fundus photo of the right eye of Case 1. Note creamy-yellow superficial retinal accumulations and optic disc congestion.
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Figure 2. Color fundus photo of the left eye of Case 1. Note creamy-yellow superficial retinal accumulations and optic disc congestion.

Figure 3. Fundus fluorescein angiography arterial phase of the right eye of Case 1. Note increased choroidal fluorescence.

angiography (FFA) arterial phase OD disclosed increased choroidal fluorescence (Figure 3), and venous phase OD revealed increased staining at the optic disc and bifurcations of the vessels (Figure 4). FFA venous phase OS disclosed increased choroidal fluorescence associated with staining at the optic disc and bifurcations of the vessels (Figure 5). Her visual acuity improved to 20/30 OU 4 weeks after IV PCN therapy with persistence of
Figure 4. Fundus fluorescein angiography venous phase of the right eye of Case 1. Note increased staining at the bifurcations of the vessels associated with staining of the optic disc.

Figure 5. Fundus fluorescein angiography venous phase of the left eye of Case 1. Note increased choroidal fluorescence associated with staining at the optic disc and bifurcations of the vessels.
choroidal hyperfluorescence OU. Oral MTX 15 mg/week was initiated. FFA revealed decrease in choroidal hyperfluorescence OU at the third month of MTX therapy, (Figure 6,7) and her BCVA improved to 20/20 OU. The patient was followed for 15 months after cessation of MTX without recurrences.

**Figure 6.** Fundus fluorescein angiography arterial phase of the right eye of Case 1 at the third month of methotrexate therapy. Note decreased choroidal hyperfluorescence and resolution of progressive staining.

**Figure 7.** Fundus fluorescein angiography arteriovenous phase of the left eye of Case 1 at the third month of methotrexate therapy. Note decreased choroidal hyperfluorescence and resolution of progressive staining.
Case 2:

A 50-year-old man had BCVA of 20/20 OD, 20/200 OS. Anterior segments OU were unremarkable.

Right fundus was normal. Left fundus revealed 1+ vitreous haze and cells associated with intraretinal hemorrhages, vessel sheathing extending from the optic disc along the inferotemporal arcade (Figure 8). FFA arteriovenous phase OS revealed absence of arterial filling inferotemporally associated with vascular occlusions and aneurysmal changes (Figure 9). FFA

Figure 8. Color fundus photo of the left eye of Case 2. Note vitreous and intraretinal hemorrhages, vessel sheathing extending from the optic disc along the inferotemporal arcade.

Figure 9. Fundus fluorescein angiography arteriovenous phase of the left eye of Case 2. Note absence of arterial filling inferotemporally associated with vascular occlusions and aneurysmal changes.
late phase OS disclosed venous staining, leakage and areas of non-perfusion (Figure 10). The patient showed partial resolution of FFA findings without improvement in left visual acuity 4 weeks after IV PCN therapy. Oral MTX 20 mg/week was initiated. BCVA OS improved to 20/40 at the third month of MTX therapy with resolution of vitritis, intraretinal hemorrhages and persistence of arterial sheathing inferotemporally (Figure 11). The patient was followed for 12 months after cessation of MTX without recurrences.

**Figure 10.** Fundus fluorescein angiography late phase of the left eye of Case 2. Note venous staining, leakage and areas of non-perfusion.

**Figure 11.** Color fundus photo of the left eye of Case 2 at the third month of methotrexate therapy. Note resolution of vitreous haze, intraretinal hemorrhages and persistence of arterial sheathing inferotemporally.
Case 3:

A 52-year-old woman had BCVA of 20/20 OD, 20/400 OS, and non-granulomatous iridocyclitis OS.

Fundus examination OS disclosed 1+ vitreous haze and cells with macular edema. Spectralis OCT revealed cystoid macular edema with a foveal thickness of 693 µm associated with pigment epithelial detachment (PED) and epiretinal membrane (ERM) formation (Figure 12). She received IV PCN with resolution of vitreous haze and cells but no improvement of OCT findings. Oral MTX 17.5 mg/week was initiated. Left visual acuity improved to 20/30 at the third month of MTX therapy with regression of foveal thickness to 389 µm and resolution of PED but persistence of ERM (Figure 13).

Figure 12. Spectralis optical coherence tomography of the left eye of Case 3. Note cystoid macular edema, pigment epithelial detachment and epiretinal membrane formation.

Figure 13. Spectralis optical coherence tomography of the left eye of Case 3 at the third month of methotrexate therapy. Note regression of cystoid macular edema and resolution of pigment epithelial detachment but persistence of epiretinal membrane.
The patient was followed for 4 months after cessation of MTX without recurrences.

**Discussion**

Methotrexate (MTX), a dihydrofolic acid analogue, shows anti-proliferative and anti-inflammatory effects[4]. The anti-proliferative effect of MTX is related to inhibition of purine and pyrimidine synthesis [4]. The extent of Treponema pallidum (TP) attachment to cells is directly proportional with cellular DNA synthesis [5]. The anti-proliferative effect of MTX decreases TP adherence to cells [5]. The anti-inflammatory effect of MTX is related to inhibition of the adenosine deaminase which mediates conversion of adenosine to inosine [4]. MTX increases the cellular level of adenosine, a potent endogenous anti-inflammatory mediator [4]. Corticosteroids (CS) are universally used as the first-line immunosuppressants (ISs) for inducing comparatively rapid remission and for bridging to long-term maintenance therapy using other ISs until they take effect [6]. However, the effects of CS on the immune system is non-specific and involve several important pathways such as reducing the distribution and trafficking of leukocytes, blockage of various T-cell/macrophage functions, and decreasing the maturation of dendritic cells, as well as its potential side-effects of inducing acute syphilitic meningitis and acute syphilitic posterior placoid chorioretinitis in patients with syphilis [7,8].

Approximately 9% of treatment failures with IV PCN have been reported in patients with syphilitic uveitis [9]. Our 3 cases showed partial resolution of posterior segment manifestations, however they did not recover full vision after IV PCN therapy. We consider to initiate MTX for its specific anti-inflammatory and long-term maintenance effects after the specific therapy with IV PCN. All the cases showed resolution of posterior segment manifestations at the 3rd month of MTX therapy, and no recurrences in their 4-15 months of follow-up after cessation of MTX therapy.

Case 1 showed having similar ophthalmologic findings to MEWDS which is defined as a unilateral, self-limiting inflammatory disease that afflicts young women more than men [10]. However, case 1 had bilateral involvement and the course of the disease is non-self limiting. The posterior segment manifestation of Case 2 was compatible with syphilitic phlebitis which is reported to simulate BRVO [11]. Case 3 had macular edema mimicking Irvin Gass Syndrome which was defined as cystoid macular edema after cataract surgery [12]. However, case 3 was not pseudophakic. She had vitritis associated with CME, large disturbance of pigment...
epithelium associated with PED. As a great imitator, syphilis should be considered in all patients with uveitis. Methotrexate might have an adjunctive role in patients with presumed syphilitic uveitis for suppressing inflammation and preventing recurrences.

References