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Rifabutin-induced cystoid macular oedema

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Rifabutin is a semi-synthetic antimycobacterial agent mainly used in the treatment of *Mycobacterium avium-complex* (MAC) in AIDS patients. Rifabutin-induced anterior uveitis has been reported previously. We report the case of a rifabutin-induced cystoid macular oedema (CMO) in an immunocompetent patient with pulmonary MAC infection. As far as we know, CMO secondary to rifabutin therapy has not been described previously.

Introduction

Rifabutin is a semi-synthetic spiro-piperidyl-rifamycin S derivative of rifamycin. This drug is used classically in the treatment of *Mycobacterium avium-complex* (MAC) infections in AIDS patients. Classical therapy consists of a combination of clarithromycin 500 mg twice a day, ethambutol 15–25 mg/kg/day and rifabutin 300 mg twice a day. Numerous cases of rifabutin-induced anterior uveitis, with or without hypopyon, associated with various degrees of vitritis, have been reported since 1990, the vast majority of cases being AIDS patients.[1–7] However, Frank *et al.*[8] reported a case of uveitis associated with rifabutin therapy in a 52-year-old human immunodeficiency virus-negative (HIV-negative) woman with MAC pulmonary infection. Jewelewicz *et al.*[9] reported the case of a bilateral rifabutin-associated uveitis in a non-AIDS immunosuppressed 8-year-old boy who had undergone bilateral lung transplant and had MAC pulmonary infection treated with rifabutin and clarithromycin. Another recent report mentioned three additional cases in HIV-negative immunocompetent individuals.[10] This side effect seems to be dose dependent and rapidly resolves after topical corticosteroid therapy and rifabutin therapy discontinuation.[3,4] Discontinuation of rifabutin also seems to prevent uveitis recurrence.[3]

Patient and methods

We report the case of a 56-year-old HIV-negative woman who had chronic obstructive pulmonary disease (COPD) and bronchial asthma. She was treated with topical inhaled corticosteroids, β_2-agonists and leucotriens antagonists. From April to May 1997, oral corticosteroid therapy had to be initiated because of COPD decompensation. She was also undergoing a nine-month therapy of rifabutin 150 mg twice a day, clarithromycin 500 mg twice a day and ethambutol 400 mg twice a day to treat a MAC pulmonary infection. The diagnosis was based on the presence of a left apical infiltrate on chest X-ray, a positive pulmonary biopsy and positive cultures of sputum and bronchio-alveolar washing. She had a rapid decrease in visual acuity in her right eye, which was associated with photophobia in September 1998.

Results

Her visual acuity was 5/20 in her right eye. She had a 1.1 mm hypopyon that was associated with severe anterior uveitis. Rifabutin was discontinued; an hourly therapy of 1% prednisolone acetate and mydriatics three times a day was introduced. One day later, the hypopyon had disappeared and fundus examination revealed the presence of peripheral opacities (snowballs). One week later, her visual acuity was 20/200 in her right eye and cystoid macular oedema (CMO) could be confirmed by fluorescein angiography and optical coherence tomography (OCT). A posterior sub-Tenon's triamcinolone injection (40 mg) was carried out, along with topical diclofenac and oral acetazolamide. Topical prednisolone was rapidly tapered. Five weeks later, anterior segment and vitreous examination were within normal limits and posterior pole examination showed a complete resolution of CMO. Final visual acuity was 20/20. From November 1998 until June 1999, the patient received a new treatment against MAC infection, consisting of rifampicin, azithromycin and ethambutol, without relapse of any ocular inflammation.

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Discussion

Our patient presented with a unilateral acute anterior uveitis and hypopyon, associated with vitritis and CMO. The delay between initiation of rifabutin therapy and onset of uveitis is variable, ranging from 2 weeks to >7 months,[1–5] and being 9 months in our patient. Intraocular inflammation resolution and normal visual acuity recovery have been observed within 6 days to 10 weeks of topical steroid treatment and discontinuation of rifabutin. In our patient, clinical recovery was observed 5 weeks after rifabutin discontinuation and adequate therapy.

Most authors comment on the increased risk of rifabutin-induced uveitis in cases of concomitant treatment with clarithromycin, which was the case in our patient.[1,4–6,9–11] Simultaneous fluconazole treatment also increases the risk. This phenomenon can be explained by the elevation of serum levels of rifabutin seen with concomitant treatment with macrolides and/or azole derivatives. Both of these classes of drugs, in particular azole derivatives, could inhibit hepatic metabolism of rifabutin via the P450 cytochrome system.[1,6] Shafran *et al.*[5] conducted a prospective randomized study including 119 patients, 50 of whom were on a regimen of rifabutin, clarithromycin and ethambutol; 23 of these 59 patients presented with uveitis, which developed at an average of 65 days after initiation of this treatment.[5] Our patient was treated with the same three drugs.

The pathogenetic mechanisms of rifabutin-induced uveitis in MAC-infected patients have not yet been elicited. Jacobs *et al.*[4] concluded from their study that a MAC bacteraemia is unlikely to induce uveitis *per se*, because MAC uveitis (without rifabutin) is seldom seen, and because an anterior chamber tap failed to show any microorganism on direct microscopic examination or on culture. Some authors think that uveitis could be a result of the formation of anti-rifabutin antibodies or of immunoglobulins directed against a rifabutin–protein complex (serum or tissue protein), similarly to what is already known with rifampicin.[12] However, rifabutin *in vivo* does not alter cellular immunity nor does it decrease the number of circulating CD4 lymphocytes.[7] Saran *et al.*[1] deduced from their observations that rifabutin-induced uveitis is probably not T-lymphocyte dependent, since it has been seen in AIDS patients in the vast majority of cases.

The striking feature in our case was the onset of CMO on day 7, the patient being already treated with topical corticosteroids and mydriatics. To our knowledge, no case of CMO has been described previously in association with rifabutin, and our patient did not have any predisposing factor for CMO (diabetes mellitus, antecedents of central retinal vein occlusion, previous ocular surgery, previous uveitis). The clinical outcome was favourable after a single posterior sub-Tenon's triamcinolone injection of 40 mg, topical diclofenac and oral acetazolamide.

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