Drug induced uveitis

Margherita Meniconi, M.D.

Introduction

Disodium Pamidronate, a Calcium regulating agent, was described by Macarol and Frauenfelder [1] and other authors [2-5] to induce ocular inflammation.
We will report a case of uveitis induced by the same substance in a patient treated for hypercalcemia secondary to multiple myeloma.

Case presentation

Anamnesis:
A 66-year-old white male was referred for severe iritis OD resistant to conventional therapy. The patient was recently diagnosed with multiple myeloma with secondary anemia, hypercalcemia and renal insufficiency. Other past history showed a status post splenectomy after trauma and arterial hypertension. The patient was treated for hypercalcemia with IV fluids initially and subsequently IV disodium pamidronate 7 days before referral. Two days after the infusion of IV pamidronate the patient complained about pain and photophobia OD. He was referred to an ophthalmologist who diagnosed him with iritis and treated him with Pred forte q 15 minutes while awake OD. Despite the intensive topical therapy, the patient's ocular inflammation persisted prompting his referral to MEEI. Upon presentation, the patient denied prior episodes of ocular inflammation. He stated that he had enjoyed excellent spectacle corrected vision all of his life.
ROS: The patient experienced fever, chill and malaise. He had a history of multiple respiratory tract infections, sinusitis, cold sores, enlarged prostate and lower back pain.
PMH: FH: noncontributory

1. s/p splenectomy from trauma
2. Hypertension
3. s/p partial thyroidectomy for hyperthyroidism
4. recent diagnosis of multiple myeloma

Med.: SH: retired; tobacco (-), EtOH (-)

1. Zestril 10 mg qd
2. Hytrin 5 mg qd
3. Asa 81 mg qd
4. Albuterol 4 puffs qd
5. Pulmicort 2 puffs bid
6. Procrit im
7. IV Sodium Pamidronate

Allergies: nihil
Physical Examination:
The patient had visual acuity of sc. 20/400 OD, with pinhole 20/100 and 20/25 OS. No APD, normal pupils. Mild ptosis OD, no proptosis. The ocular movements were full and painless. Confrontational visual fields were full bilaterally. Intraocular pressures were 16 and 12, OD and OS respectively. Slit lamp examination OD revealed 2+ injection and chemosis of the superior conjunctiva, corneal edema with Descemet's folds, and 1+ cells in the anterior chamber. Iris within normal limits, lens mild nuclear sclerosis. Slit lamp exam OS of anterior and posterior segment was normal except for mild cataract. The corneal edema didn't allow accurate assessment of the fundus of the right eye. We obtained ultrasonography,OD, that showed a dilated sup. ophthalmic vein, a diffuse thickening of the choroid and no cells in the vitreous.

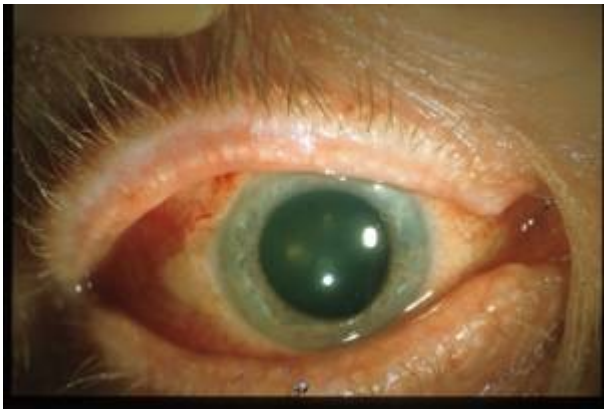
Figure 1. Overview of right eye: treatment already started, important injection and chemosis of conjunctiva

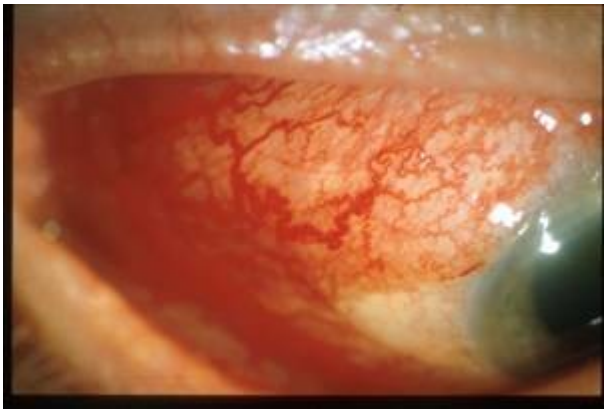
Figure 2. Chemosis and inflammation of superior part of conjunctiva, edema of cornea already in remission.

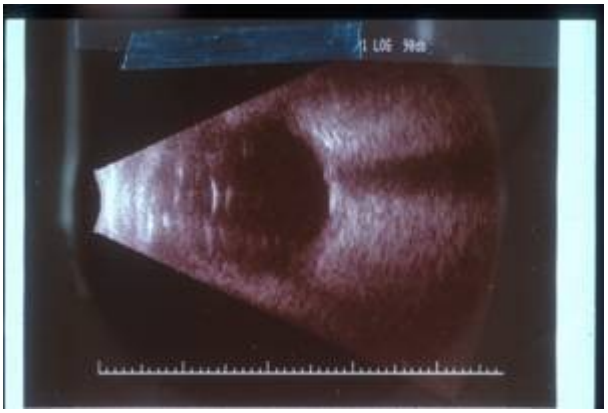
Figure 3. B-scan OD: thickening of choroidea, dilatation of superior ophthalmic vein, no cells in the vitreous

In summary this was the first episode of unilateral uveitis in an elderly white man with a reduced competence of immunity because of multiple myeloma and status post splenectomy. He presented the uveitis two days after an infusion of a calcium regulating agent with constitutional symptoms such as chill, fever and general malaise.

The differential diagnosis was:
Endogenous endophthalmitis with or without endocarditis
Medication induced uveitis
Myeloma associated uveitis
Autoimmune associated uveitis
HLA-B27 associated uveitis
In order to rule out an infectious origin we performed an anterior chamber tap. Immediate Gram stains and subsequent cultures were negative.
There were no signs of phlebitis at the site of the PICC line. We could not find any signs of bacteremia (Osler nodes, splinter hemorrhages of the fingernails or Roths spots at the fellow eye). Auscultation of the heart was

normal and excluded significant valvular heart disease. Blood analysis showed very high erythrocytes sedimentation rate (90mm/h) with CRP 2.5 mg/dl and normal white blood count (6.2x1000/mm3), anemia at 10.2 g/dl and normal thrombocytes. Blood cultures were all negatives.
In order to rule out a connective tissue disease related uveitis we did an extensive laboratory work up which came out normal or negative.
HLA B27 was negative.
Myeloma associated uveitis is extremely rare [6] .
Disodium Pamidronate is clearly reported as a possible cause of uveitis ([1-5, 7, 8]).
In summary the diagnosis of drug induced uveitis was the most likely.

Treatment and Patient course:
The patient was treated with IV Solumedrol I gm IV qd x 3 days along with Pred forte 1% every hour while awake.
The evolution was favorable: VA OD came from 20/400 to 20/100 in one day, 20/60 by day three and 20/30 two weeks later with complete resolution of corneal edema and inflammation.
Intraocular pressures returned to be symmetric.

Discussion
Description of the Drug:
Disodium Palmidronate is part of the biphosphonates:
Biphosphonates is a group of medication with a chemical structure analog of pyrophosphate. Disodium Pamidronate is a phosphonic acid (3-aminoethyl-1-hydroxypropylidene) bis-, disodium salt, pentahydrate or aminohydroxypopylidene biphophonate (ADP).
Biphosphonates are calcium regulating agents by virtue of inhibiting bone resorption.
Secondary hypercalcemia can be caused by humoral stimulation of bone resorption (PTH related protein secreting tumors) or due to excessive bone resorption by invasion of bone directly by malignancies (metastases and multiple myeloma). The second group is the target of the biphosphonates. Other indications of biphosphonates are osteoporosis and Paget's disease. The following mechanisms are thought to play a role: adsorption to calcium phosphate crystals (hydroxyapatite) and blocking its dissolution, inhibition of osteoclaste activity (shown in vitro models) and absence of inhibition of bone formation and mineralization in animal studies.

Medication induced Uveitis:
Most reports of medication induced uveitis are clinical observations which lack histopathologic proof.
Naranjo et al [9] . proposed in 1981 the following criteria for the diagnosis of adverse drug reaction:
1) The adverse reaction should be frequently described
2) Recovery after withdrawal of the drug
3) Exclusion of other causes
4) Proportionality between dosage and severity of side effect
5) Objective evidence (not only subjective complains)
6) Class effect
7) Positive rechallenge
Moorthy et al. [10] showed that it is rare that suspicious cases for drug related uveitis fulfill all seven proposed criteria and concluded that when fulfilling at least five criteria the probability of a cause-effect is very high.

Side effects of Disodium Pamidronate:
The general side effects of Disodium Pamidronat were published by Gallacher et al [11] in 1989 as retrospective study of 95 patients who received intravenous infusions of pamidronate for malignancy associated hypercalcemia, Paget's disease and osteoporosis. They described that all patients experienced pyrexia within 48 hours post-infusion ranging from 37.2 to 38.3 C, in some patient occurred rigor or general malaise.
Siris [2] described in 1993 the case of a woman treated for secondary hypercalcemia from Paget's disease. Interestingly the woman was treated in the early 1990s with a non-nitrogen containing biphophonate (etidronate disodium: salt of (1-hydroxyethylidene) diphosphonic acid, compare structural formula with pamidronate disodium) and didn't have any ocular side effect. Then with the introduction of newer substances she experienced bilateral iritis. There was a rechallenge, receiving two times substances of the same class, risedronate and pamidronate, followed by bilateral iritis, reversible after interruption of the treatment or respectively one month after a single iv dose administration.
The common element in both uveitogenic substances is a nitrogen group, which is lacking in the very first product administrated in the early nineties.
Marcarol and Fraunfelder [13] published in 1994 the ocular adverse reaction from 23 cases collected by the Ciba-Geigy Central Epidemiology and Drug Safety Center.
By half of the patients occurred a transient conjunctivitis with onset 6-48h post infusion.

Approximately a forth to a third of the patients (seven cases) had ant. uveitis, six of them bilaterally. The severity varied from minimal to mild to very severe forms requiring hospitalization, all with onset 24-48h post infusion.
A seventh (3 cases) of the patients had unilateral episcleritis/scleritis with onset 1-6d post-infusion. Several of the patients had a positive rechallenge confirming the cause of the problem.
In 1999 Mbekeani et al. [12] puplished three cases of alendronate-associatied anterior scleritis and posterior scleritis with possible orbital involvement. Alendronate is also an amino-biphosphonate with chemical formula (4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt trihydrate (compare structural formula below) It is 100-500 times more potent and is administrated by mouth in the prevention of osteoporosis in postmenopausal women.
Other cases and side effects have been published [3, 4, 14, 15] .
By comparison of the structural formula, one might speculate if that the aminoethygroup of this pyrophosphate may be responsible for the biological activity in induction of uveitis, scleritis.
Novartis has launched a new Calcium regulating agent, zoledronic acide, chemically very similar to palmidronate disodium but having an imidazole group instead of the aminoethyl group. In the product information (see internet www. Zometa.com) conjunctivitis has been described as very uncommon ocular adverse effect. It will be interesting to follow if any intraocular inflammations or scleritis will be reported or not. If not so, this would be of practical consequences in as much as the treatment could be changed on an other substance of the same class in a patient like our.

Criteria for Diagnosis in our Case:
The diagnosis of medication-induced-uveitis was given in our case by the nature (point 5 of Naranjos criteria) and time correlated event described in the literature (point 1) and by the exclusion of other origins (point 3). A short powerful anti-inflammatory treatment was initiated because of the severity of the inflammation and resistance to intensive topical treatment. Prompt responsiveness to the treatment and complete resolution of the inflammation resulted, further arguing for confirming the diagnosis (point 2). In our case we fulfill four of the seven proposed criteria.
Criteria 4, 6 and 7 indirectly ask for a re-exposure to the drug. Rechallenge would be the only way of prove the diagnosis but would be unethical if intended.
In our case the time passed between administration of the substance and ocular inflammation was short and particularly helpful. But we must be aware that there are substances inducing ocular inflammation months later (for ex. Rifabutin [16]). So suspicion should arise when tapering of steroid recurrences of inflammation occur and the patient takes a medication introduced in the past months.

Conclusion
The practical consequences of this case are (as many formulated before):
ÒThe treatment is the recognition of the drug related event itselfÓ.
The role of the ophthalmologist in the pluri-disciplinary approach of a patient like this, is to think of the possibility of a toxic (iatrogenic) event and to recommend the interruption of the current medication.
The outcome of inflammation has in general good prognosis with the unique condition of withdrawal of the causing agent (reversibility).
The second consequence is that similar substances (class effect) should be avoided if possible in order to avoid recurrence. So the quality of life of the patient is considerably conserved, especially precious if life expectancy is limited such as in malignancy related diseases.
The third consequence is that there is no indication for other treatment such as immunosuppressant or anti-infectious agents.

Go to Review Question

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