Case study

Docetaxel-induced bilateral cystoid macular edema seems not cumulative dose dependent: A case report.

Abstract:

Docetaxel and paclitaxel are taxanes. They are widely used chemotherapeutic agents that have been shown to be effective for various types of solid malignancies. Docetaxel-related bilateral toxic cystoid macular edema (T-CME) has been reported as a rare and unusual adverse reaction. We report the case of a 43-year-old woman, followed for breast cancer, under treatment with Docetaxel 150mg, Perjeta (pertuzumab) 420mg and Trastuzumab (Herceptin®) 360mg, administered every three weeks. Three days after her second course of chemotherapy (300mg cumulative dose of Docetaxel), she reported a decrease in her visual acuity secondary to bilateral toxic cystoid macular edema objectified by spectral domain optical coherence tomography SD-OCT. Fluorescein angiography showed the same aspect encountered in CME during degenerative retinopathy. The treatment was not interrupted by his oncologist with four other cycles before stopping the Docetaxel and then moving on to chemotherapy cycles based only on, Perjeta 420 and Herceptin 360mg every 3 weeks. Three months after stopping Docetaxel, the evolution was spontaneously favorable, with total resorption of the T-CME.
Several studies suggest that a cumulative dose seems necessary for the onset of the toxic effect of this drug. To our knowledge, we report the first case of Docetaxel-induced T-CME occurring within less than 1 month, with a very low cumulative dose. This suggests that no cumulative dose is needed for macular edema to appear.

Key Words:cystoid macular edema, docetaxel, ocular toxicity, chemotherapy.

Introduction:

Taxanes as cytotoxic drugs have been commonly used in chemotherapy for over 20 years. The mechanism of action of taxanes is based on inhibition of the mitotic spindle. They bind to beta-tubulin subunits of microtubules, inhibit depolymerization and cause mitotic arrest of cells **[1]**. Docetaxel, one of the taxanes, was obtained from a non-cytotoxic precursor called Taxus baccata, approved for medical use in 1995 **[2]**. This drug is used for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, head and neck cancer and stomach cancer **[3-4-7]**.
Cystoid macular edema (CME) is a rare complication caused by Docetaxel. The exact mechanism is unclear, and the best treatment is to stop this causative agent.
To our knowledge, we report here the first case of bilateral T-CME, induced by this drug occurring in less than 1 month after its administration with a cumulative dose of only 300mg.

Case Report:

We report the case of a woman with no history of high blood pressure, diabetes, ocular or systemic inflammatory disease, followed for breast cancer. The patient has already received 3 cycles of chemotherapy, every three weeks based on Docetaxel 150mg, Perjeta (Pertuzumab) 420mg and Trastuzumab (Herceptin®) 360mg. Three days after her second course of chemotherapy, she reported a decrease in her visual acuity and was referred by her attending physician for an ophthalmological opinion.
On the ophthalmological examination, the best corrected visual acuity was 20/200 in both eyes. Slit-lamp anterior segment examination and intraocular pressure were normal in both eyes. Fundus examination revealed a loss of foveal reflex in both eyes with no evidence of hyalitis or associated retinal vasculitis. Spectral domain optical coherence tomography (SD-OCT) demonstrated bilateral macular edema (foveolar cystic cavities with macular thickening of 447um in the left eye and 434um in the right eye) (**figure 1**).
Fluorescein angiography showed normal filling of the choroidal and retinal vessels and an unremarkable parafoveal capillary network and no fluorescein leakage on the late angiograms phases (**figure 2**).
A toxic maculopathy, related to either Herceptin or Docetaxel, was mentioned and her oncologist was notified.
However, the treatment was not interrupted, with four more cycles before stoppingDocetaxel, and then switching to chemotherapy cycles based only on Perjeta 420 and Herceptin 360mg every 3 weeks.
One month after stopping Docetaxel**,**visual acuity beganto improve to reach 20/20 in both eyes at the third month. Macular control SD-OCT shows total resorption of the macular edema without sequelae (**figure 3**).
The good clinical and tomographic improvement after discontinuation of Docetaxel, allowed us to retain the macular toxicity effect of this product in this patient.

Discussion:

Docetaxel is one of the taxanes that inhibit mitosis in cancer cells. Neutropenia, peripheral sensory neuropathy, muscle pain, arthralgia and alopecia are the most common systemic side effects of taxanes **[5]**. Cardiovascular complications include

fluid retention (especially during Docetaxel treatment), arrhythmias or heart failure **[6]**. Ophthalmologic side effects of taxane chemotherapy are less common or not reported as frequently as they should be. They include cataract **[7]**, obstruction of lacrimal punctum and/or ducts; excessive lacrimation (epiphora), Meibomian gland dysfunction, blepharitis, Chalazion **[7]**, optic neuropathies; papilledema and cystoid macular edema **[3-4-7-8]**.

Toxic cystoid macular edema (T-CME) is a rare side effect of taxanes, with an approximately incidence of 0.3 and 0.5% **[4-7].** The first case of CME linked to the use of Docetaxel was reported in 2003 by Teitelbaum and Tresley **[9].** It was angiographically silent and partially reversible after stopping treatment. Since then, 57 cases of T-CME linked to taxanes (Paclitaxel) have been reported in the literature in the form of cases or small case-series **[7].** It is bilateral in more than 92% of cases **[7-9].** In their recent literature review, Ya-Ting Ye & al **[7]**, the average time to onset of macular edema after taking the drug was 4.25 months. However, in another review, it is 9.3 months with a range: from 1.5 to 42 months **[10].**

For some authors, a 3-month therapy is sufficient to induce T-CME **[8]**, and others **[11-12]**, suggest that a cumulative dose seems responsible for the toxic effects of this therapy. Indeed, when a cumulative dose of Docetaxel reached 200 mg/m2, a significant decrease in the colloid osmotic pressure values of plasma (Plasma COP) and interstitial fluid (Interstitial COP), hemoglobin, hematocrit, albumin and total proteins decrease significantly **[14]**. These authors suggested that an increase in plasma volume was followed by an accentuation of fluid filtration towards the interstitial medium **[12].** The cumulative dose of Docetaxel needed for this side effect is 300–400 mg/m2 and increases with additional corticosteroid therapy to 746 mg/m2 **[12].**

For our patient, the macular syndrome appeared three days after the second course of Docetaxel chemotherapy, which corresponds to 24 days after starting this medication with a cumulative dose of only 300mg (120 mg/m2). This leaves us to suggest that taxanes toxicity can appear early and does not depend on cumulative dose. To our knowledge, our patient is the first case reported in the literature with a time to onset of macular edema not exceeding one month.

Fluorescein angiography has an important contribution in the diagnosis, showing a normal filling of the choroidal and retinal vessels and an intact parafoveal capillary network **[12-3-7-11].** Late images show no significant leaks. This appearance resembles that of macular edema encountered in degenerative pathologies such as Goldmann-Favre syndrome, certain types of retinitis pigmentosa, phototoxicity, and the use of drugs such as niacin **[13].** It eliminates other causes of CME with diffusion of fluorescein such as diabetes, age-related macular degeneration (AMD), Irvine-Gass syndrome, uveitis, central vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) and the use of drugs such as thiazolidinediones, tamoxifen, topical medications: epinephrine, prostaglandins E2, timolol **[3-9]**.

SD-OCT images show larger hyporeflective cysts located in the outer nuclear layer and smaller cysts in the inner nuclear layer, with an intact outer retinal layer. The involvement is focal and symmetrical, centered around the fovea **[8-15].** These same SD-OCT results were found in our patient. Theabsence of hyperreflective plaques associated with exudation seen in central retinal vein occlusion and diabetes edema, does not establish the outcome of vascular degeneration or vascular occlusion **[10].** The study by Joel M. Perez & al **[15]** is the first to publish the results of A-OCT in the case of T-CME. She reports no flow disturbance in a normal foveal avascular area supporting the hypothesis that this is not a vascular-mediated phenomenon.

To date, the exact pathophysiological mechanism underlying taxane maculopathy remains unclear **[8].** Several possible mechanisms have been advocated, and the most accepted one is retinal pigment epithelium (RPE) dysfunction, causing fluid accumulation in the retinal layers **[7-8].**
Acetazolamide, prednisolone, triamcinolone, dorzolamide and intravitreal injection of anti-Vascular endothelial growth factor (anti-VGEF) **[10-15]**, have been used in the treatment of these T-CME, however, none of these products has proven effective. In most reported cases, resorption of macular edema occurs spontaneously after discontinuation of taxanes without any ocular treatment within 1.5 weeks to 6 months) **[10-14-15].**

Conclusion:

Toxic cystoid macular edema (T-CME) is a rare complication caused by Docetaxel. The exact mechanism is unclear, and the best treatment is to stop this causative agent.
Several studies suggest that a cumulative dose seems necessary for the onset of the toxic effect of this drug. To our knowledge, we report the first case of Docetaxel-induced T-CME occurring within less than 1 month, with a very low cumulative dose of 300mg only (120 mg/m2). This suggests that no cumulative dose is needed for macular edema to appear.

Figures:

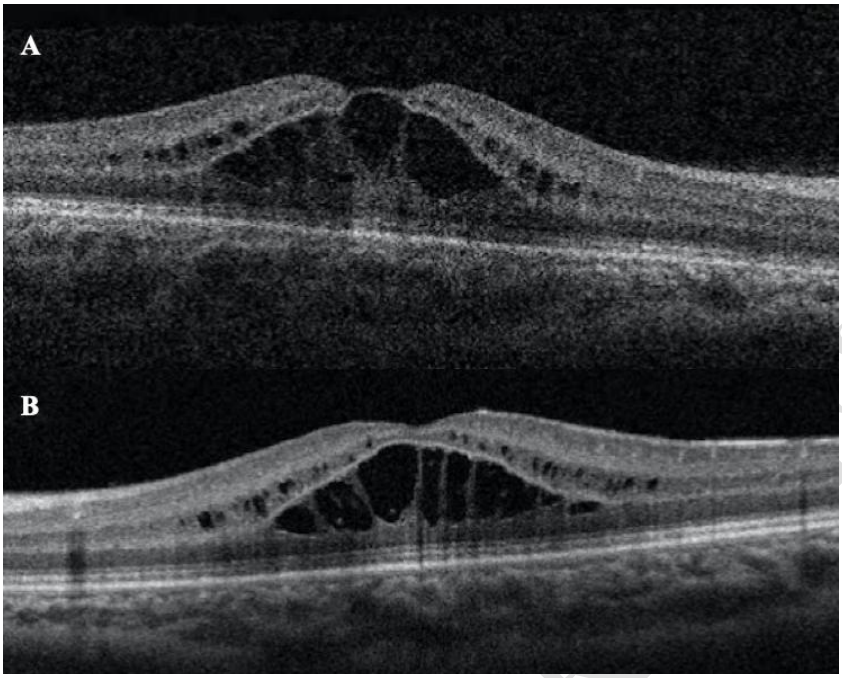

Figure 1 (A: Right eye, B: Left eye): Spectral domain optical coherence tomography (SD-OCT) demonstrating bilateral macular edema with foveolar cystic cavities.

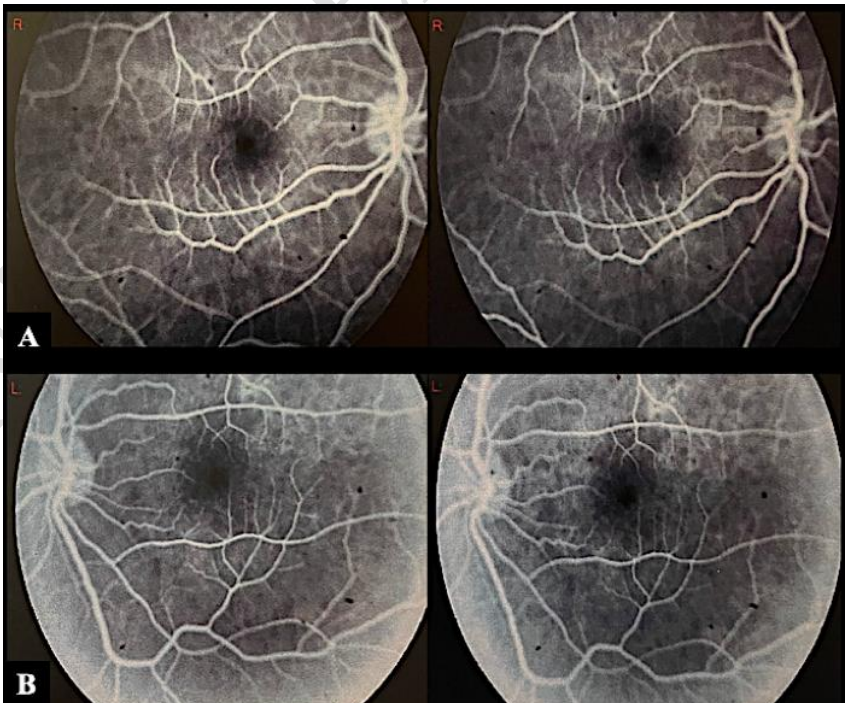

Figure 2 (A: Right eye, B: Left eye): Fluorescein angiography photography showing normal filling of the choroidal and retinal vessels, an unremarkable parafoveal capillary network and no fluorescein leakage on the late angiograms phases.

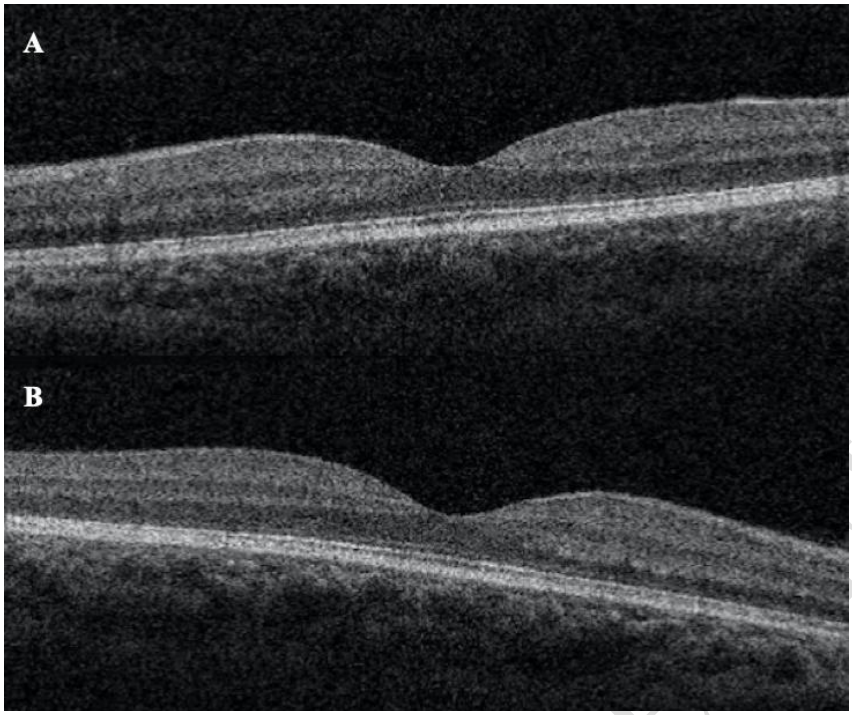

Figure 3 (A: Right eye, B: Left eye): Macular control with SD-OCT (3months after stopping Docetaxel) showing total resorption of the macular edema without sequelae.

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