Oftalmologia - Vol. 37: pp.211-215

Comunicações Curtas e Casos Clínicos

Vision loss and subretinal yellow deposits following cytostatic therapy for early-stage breast cancer: a case report

Arnaldo Dias Santos[1], Vanessa Lemos[1], Joana Ferreira[2], João P. Cunha[3], João Branco[3]
[1]Interno do Internato Complementar de Oftalmologia
[2]Assistente Hospitalar de Oftalmologia
[3]Assistente Hospitalar Graduado de Oftalmologia
Serviço de Oftalmologia do Centro Hospitalar de Lisboa Central - Director de Serviço: Dr. Miguel Trigo

RESUMO

Introdução/Objectivo: Relatar um caso de toxicidade ocular a dois esquemas de quimioterapia aprovados para tratamento do cancro da mama de estadio precoce: doxorrubicina (Adriamicina®) e ciclofosfamida – protocolo AC – e combinação carboplatina-docetaxel.
Material e Métodos: Doente do sexo feminino, 39 anos, com o diagnóstico de carcinoma ductal invasivo da mama estadio I, que se apresentou com queixas de diminuição bilateral e indolor da acuidade visual, dois dias após o primeiro ciclo intravenoso de doxorrubicina e ciclofosfamida.
Resultados: A melhor acuidade visual corrigida (MAVC) era de 20/100 bilateralmente e a fundoscopia demonstrou lesões retinianas amarelo-pérola no polo posterior e média periferia bilaterais, com hipertrofia do epitélio pigmentar da retina (EPR) no olho direito (OD). Tais lesões eram hiperfluorescentes na angiografia fluoresceínica e apresentavam-se como depósitos tipo drusen sob o EPR na tomografia de coerência óptica (OCT). O estudo electrofisiológico revelou disfunção macular e disfunção difusa das células bipolares e fotorreceptores, sendo estas alterações mais pronunciadas em OD. A perimetria de Goldmann, teste de visão cromática e OCT do nervo óptico foram normais. 72 horas após o tratamento, a MAVC melhorou espontaneamente para 20/25 em OD e 20/20 no olho esquerdo (OE). Documentou-se uma redução semelhante na MAVC após novo ciclo AC, bem como após um ciclo de 2ª linha de carboplatina e docetaxel, com recuperação espontânea após cada um dos ciclos. O restante exame objectivo manteve-se inalterado.
Conclusão: Este caso representa a primeira descrição de uma potencial reacção idiossincrásica ao protocolo AC e à combinação carboplatina-docetaxel, aprovados para o tratamento do cancro da mama.

Palavras-chave
Cancro da mama, quimioterapia, retinotoxicidade.

ABSTRACT

Introduction/Objective: To report a case of ocular toxicity related to two chemotherapeutic regimens approved for early-stage breast cancer: doxorubicin (Adriamycin®) and cyclophosphamide – AC protocol; carboplatin and docetaxel combination.

Material and Methods: We report a case of a 39-year-old woman with stage I ductal invasive breast cancer, who presented with bilateral painless reduced visual acuity two days after the first administration of intravenous doxorubicin and cyclophosphamide.
Results: The best corrected visual acuity (BCVA) was 20/100 in both eyes and the fundoscopy revealed pearly-yellow lesions in the posterior pole and mid-peripheral retina bilaterally, with retinal pigment epithelium hypertrophy in the right eye (RE). These lesions were hyperfluorescent on fluorescein angiography and appeared as drusen-like deposits under the retinal pigment epithelium in the optical coherence tomography (OCT). The electrophysiological study revealed a diffuse dysfunction of bipolar cells and photoreceptors and macular dysfunction, more pronounced in the RE. Goldmann visual field testing, color vision and optic nerve OCT were normal. 72 hours after the treatment, her BCVA improved spontaneously to 20/25 in the RE and 20/20 in the left eye (LE). A similar drop in BCVA was observed after a second cycle of AC protocol and after second-line cycle of carboplatin and docetaxel, with subsequent recover. The remaining observation remained remarkably similar.
Discussion: This can be the first report of a rare idiosyncratic reaction to AC protocol and carboplatin-docetaxel chemotherapeutic regimens, approved for early-stage breast cancer.

Key-words
Breast cancer, chemotherapy, retinotoxicity.

INTRODUCTION

Breast cancer is the second most common type of cancer in women[1], after skin cancer, with approximately 230,480 new cases of invasive breast cancer diagnosed every year in the USA[2]. Although it remains the second leading cause of cancer-caused death in women worldwide[1], the death rate related to this malignancy has been decreasing during the past two decades[3]. This trend is due mainly to better screening programs and advances in treatment[4]. However, in parallel with the advent of new cancer drugs and combination regimens, many chemotherapy-associated ophthalmic complications have been reported, most of which are reversible if detected early enough.

The purpose of this work is to report a case of retinal toxicity to two commonly used chemotherapeutic regimens for early-stage breast cancer: doxorubicin-cyclophosphamide (AC protocol) and carboplatin-docetaxel combination.

CASE REPORT

A 39-year-old Caucasian woman presented with bilateral, painless decreased visual acuity. She had been diagnosed with stage I ductal invasive breast cancer and had underdone conservative surgery one month prior and had completed the first cycle of an AC regimen two days earlier. This chemotherapeutic protocol consists of intravenous doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 given every three weeks for 4 cycles[5]. The patient had no history of ocular pathology, and the family history was also unremarkable.

On examination, the best corrected visual acuity (BCVA) was 20/100 in both eyes, with normal pupillary reflexes. The anterior segment examination was normal. Fundus examination revealed bilateral pearly-yellow lesions in the posterior pole and midperipheral retina, with some degree of perifoveal retinal pigment epithelium hypertrophy in the right eye (RE). Macular involvement was more significant in the RE (fig. 1). Goldmann visual field testing and Farnsworth-Munsell 100 color assessment were normal. A flash electroretinogram (ERG) revealed a diffuse dysfunction of bipolar cells and photoreceptors. Pattern ERG revealed bilateral macular dysfunction, more pronounced in the RE, and VEP demonstrated an increased P100 latency with a normal amplitude. Fluorescein angiography revealed hyperfluorescent spot lesions in the previously described locations, which remained stable throughout the exam, without staining or leakage. Spectral domain optical coherence tomography (SD-OCT) showed multiple macular drusen-like deposits under the retinal pigment epithelium (fig. 2). The optic nerve SD-OCT was normal.

Seventy-two hours after the first observation, the patient's BCVA improved spontaneously to 20/25 in the RE and 20/20 in the LE. The remaining ophthalmologic

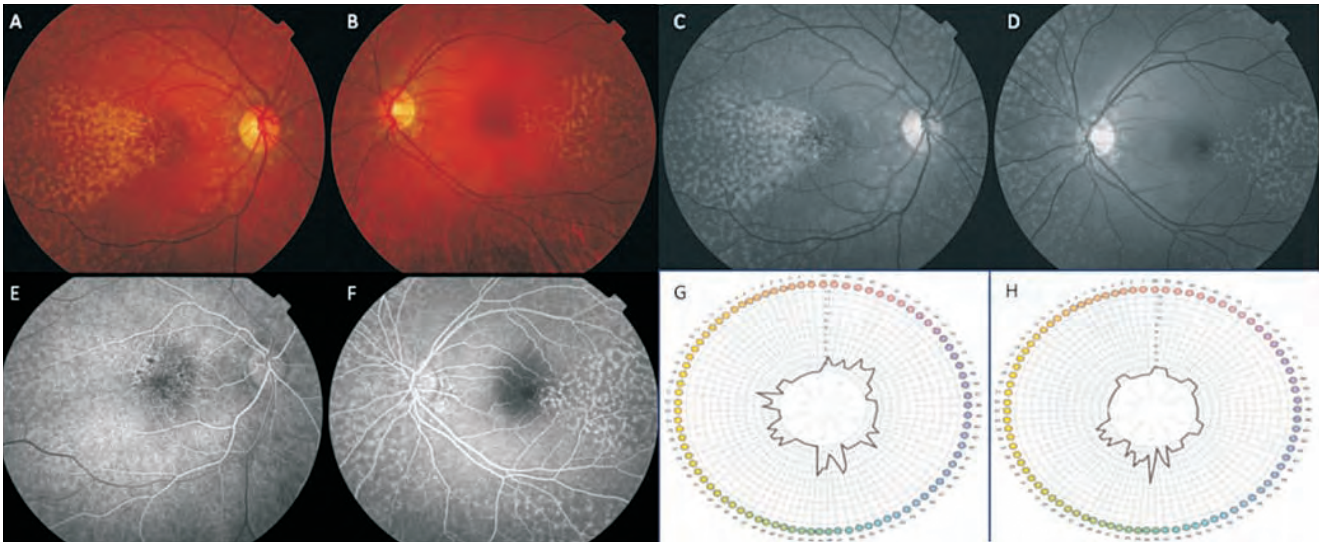

Fig. 1 | (A) Right eye (RE) retinography showing multiple pearly-yellow dots in the macular region and midperipheral retina; it also showed areas of retinal pigment epithelium hypertrophy around the fovea. (B) Left eye (LE) retinography showed lesions similar to those seen in the right eye but the macular involment was less prominent. (C and D) Red-free fundus images of RE and LE. (E) Fluorescein angiogram (FA) of the RE showed hyperfluorescent lesions without significant staining or leakage (arteriovenous phase). (F) FA of the LE showed hyperfluorescent lesions without significant staining or leakage (venous phase). (G and H) Farnsworth-Munsell 100 test showing no colour vision defects bilaterally.

exam results remained unchanged. Her visual acuity remained stable until another chemotherapeutic cycle was performed three weeks later, after which her VA dropped to 20/100 bilaterally. Subsequent recovery of visual acuity was observed again 72 hours after completing the cycle, but there was no change in the OCT, angiography and retinography results.

After multidisciplinary discussion, the therapeutic protocol was changed to docetaxel and carboplatin combination. This chemotherapeutic regimen consists of intravenous docetaxel 75 mg/m^2 and carboplatin (AUC 5) administered every three weeks for six cycles6. However, 48 hours after the first administration, we documented another painless, bilateral decrease in visual acuity. The fundoscopy and ophthalmic examination findings remained the same. Three days after the treatment, her visual acuity returned to 20/25 in the RE and 20/20 in the LE (fig. 3). All adjuvant chemotherapy was stopped, and the patient is now asymptomatic and under strict oncologic and ophthalmologic surveillance.

DISCUSSION

Despite its small size, the eye is the center of intense biochemical activity, requiring a disproportionately high blood supply. Consequently, next to the liver, it is the

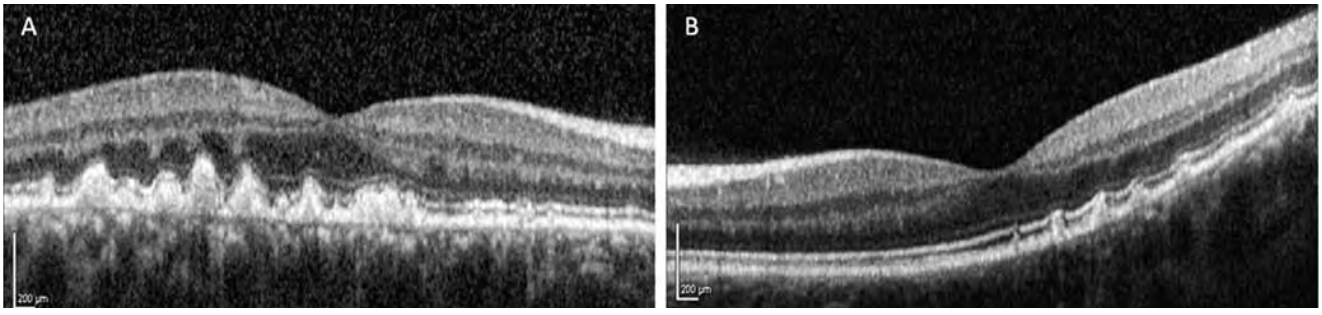

Fig. 2 | Right eye (A) and left eye (B) spectral domain optical coherence tomography showing multiple macular drusen-like deposits under the retinal pigment epithelium, more prominent in the right eye.

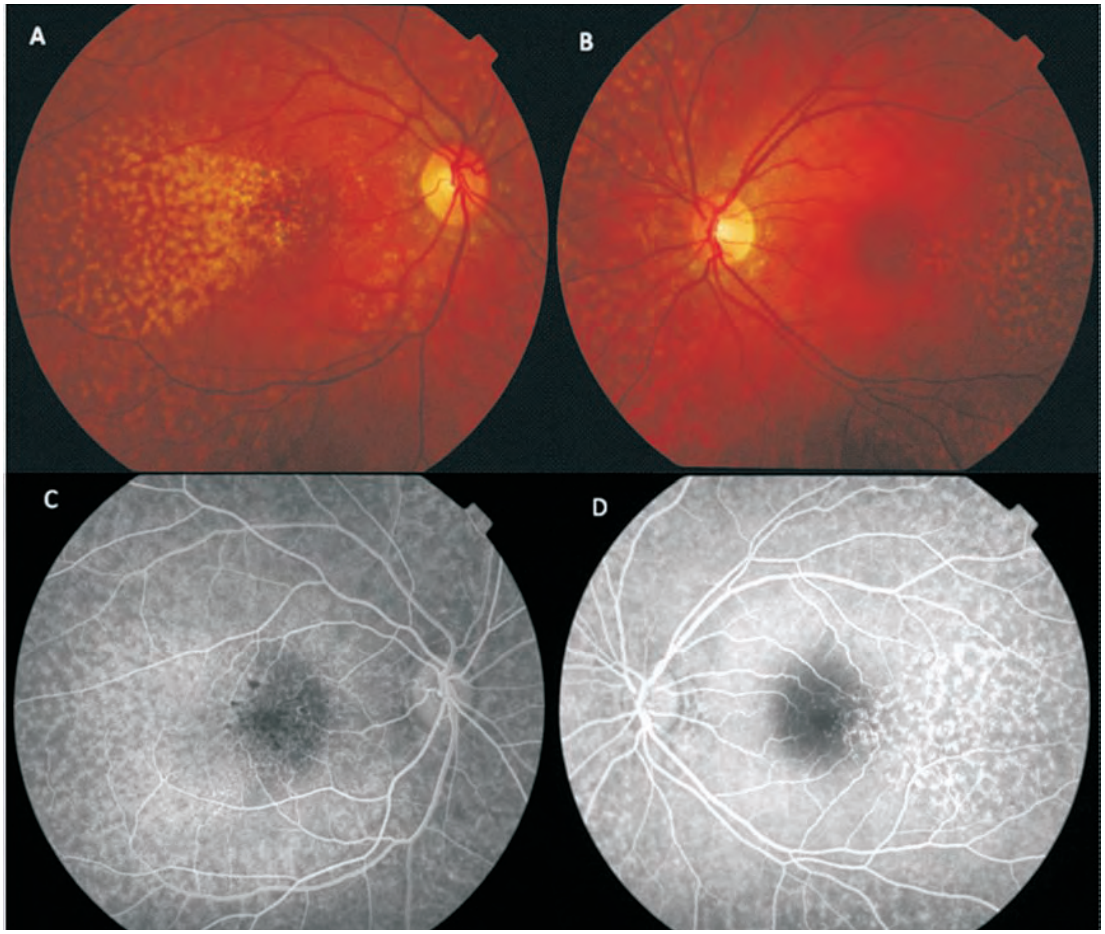

Fig. 3 | Retinography (A and B) and venous phase FA (C and D) three days after the administration of TC chemotherapeutic regimen.

second most common organ to manifest symptoms of systemic drug toxicity[7].

The authors conducted a literature review to investigate which of the drugs administered to this patient could cause a drop in visual acuity. Doxorubicin (Adriamycin®) and Cyclophosphamide (Cytoxan®) are the basis of the AC chemotherapeutic protocol8. Doxorubicin is an antibiotic that damages DNA by promoting its uncoiling and generating free radicals[9]. Severe, reversible acute maculopathy has been reported in two cases following doxorubicin, desferrioxamine and iron sorbitol citrate administration in patients pretreated with cisplatin[10]. Cyclophosphamide is a nitrogen mustard derivative that acts as an alkylating agent to interfere with DNA replication and RNA transcription9. Reversible blurred vision lasting for 60 minutes to two weeks has been documented in children who received maximum doses of this drug11. This adverse effect may be due to endothelial toxicity affecting the optic nerve and the retina's blood supply.

Docetaxel (Taxotere®) and Carboplatin (Paraplatin®) constitute the second line TC chemotherapeutic regimen administered to this patient. Docetaxel is a taxane that stabilizes microtubules, thereby inhibiting mitosis[12]. Its most frequent adverse ocular effect is epiphora due to canalicular stenosis[9]. There have also been some case reports of taxane-associated cystoid macular edema[13,14], which was not observed in this clinical case. Carboplatin is an alkylating agent that inhibits DNA replication and fragmentation, leading to cell death[9]. Intravenous administration of this drug can also cause ocular toxicity associated with maculopathy, optic neuropathy, choroidoretinitis and optic neuritis, all of which are usually reversible[15-17].

Based on this literature review, we concluded that both chemotherapeutic regimens administered to the patient had the potential to cause a sudden, reversible drop in visual acuity, possibly as a result of endothelial toxicity. However, our case is the first to document exuberant fundoscopic and electrophysiological alterations immediately after

the initiation of early-stage breast cancer treatment. Unlike the visual acuity, the retinal changes did not recover and remained stable thereafter. Therefore, one must keep in mind the possibility that this patient could have some type of hereditary retinal dystrophy, like fundus flavimaculatus or Doyne honeycomb retinal dystrophy, despite the fact that her direct relatives were healthy. These dystrophic changes might render her more susceptible to the cytotoxic effects of these drugs.

This case report may represent the first description of a rare idiosyncratic retinotoxic reaction to cytostatic therapy for early-stage breast cancer.

REFERENCES

1. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics. CA Cancer J Clin. 2011;61(6):409-18.
2. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics. The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61:212-236.
3. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W et al., editors. SEER cancer statistics review, 1975-2007. Bethesda: National Cancer Institute; 2010.
4. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353:1784-1792.
5. Fisher B, Brown AM, Dimitrov NV, Poisson R, Redmond C, Margolese RG, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol. 1990 Sep;8(9):1483-96.
6. Mavroudis D, Alexopoulos A, Malamos N, Ardavanis A, Kandylis C, Stavrinidis E, et al. Salvage treatment of metastatic breast cancer with docetaxel and carboplatin. A multicenter phase II trial. Oncology. 2003; 64(3):207-12.
7. Tripathi RC, Tripathi BJ. The eye. In: Riddell H, ed. Proceedings, Pathology of drug-induced and toxic diseases. London: Churchill Livingstone, 1986:377.
8. Eisner A, Luoh SW. Breast Cancer Medications and Vision: Effects of treatments for early-stage disease. Curr Eye Res. 2011;36(10):867–885.
9. Schmid KE, Kornek GV, Scheithauer W, Binder S. Update on ocular complications of systemic cancer chemotherapy. Surv Ophthalmol. 2006;51(1):19-40.
10. Voest EE, Neijt JP, Keunen JE, Dekker AW, van Asbeck BS, Nortier JW, et al. Phase I study using desferrioxamine and iron sorbitol citrate in an attempt to modulate the iron status of tumor cells to enhance doxorubicin activity. Cancer Chemother Pharmacol. 1993;31:357-62.
11. Kende G, Sirkin SR, Thomas PR, Freeman AI. Blurring of vision: a previously undescribed complication of cyclophosphamide therapy. Cancer 1979;44:69-71.
12. Risinger AL, Giles FJ, Mooberry SL. Microtubule dynamics as a target in oncology. Cancer Treat Rev. 2009;35:255–261.
13. Murphy CG, Walsh JB, Hudis CA, Lake D, Theodoulou M. Cystoid macular edema secondary to nab-paclitaxel therapy. J Clin Oncol. 2010;28:e684–e687.
14. Smith SV, Benz MS, Brown DM. Cystoid macular edema secondary to albumin-bound paclitaxel therapy. Arch Ophthalmol. 2008; 126:1605–1606.
15. Lauer AK, Wobig JL, Shults WT, Neuwelt EA, Wilson MW. Severe ocular and orbital toxicity after intracarotid etoposide phosphate and carboplatin therapy. Am J Ophthalmol. 1999; 127: 230-3.
16. O'Brien ME, Tonge K, Blake P, Moskovic E, Wiltshaw E. Blindness associated with high-dose carboplatin. Lancet 1992;339:558.
17. Rankin EM, Pitts JF. Ophthalmic toxicity during carboplatin therapy. Ann Oncol. 1993;4:337-8.

Este trabalho foi apresentado como poster no 55º Congresso da Sociedade Portuguesa de Oftalmologia e no Congresso da Sociedade Europeia de Oftalmologia, em 2013.

Os autores não têm interesses comerciais a declarar.

CONTACTO

Hospital de Santo António dos Capuchos, Serviço de Oftalmologia, Alameda de Santo António dos Capuchos, 1169-050 Lisboa.
E-mail: arnaldomiguelsantos@gmail.com
Telefone: 00351 919273677