

Peripheral Retinal Ischemia in a Patient Undergoing Systemic Gemcitabine, Trastuzumab, and Carboplatin Combination Therapy for Breast Cancer

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ABSTRACT

We report a case of peripheral retinal ischemia in a 43-year-old woman receiving long-term systemic chemotherapy with gemcitabine, trastuzumab, and carboplatin for breast cancer. The patient presented with blurred vision in the right eye. Fundus examination revealed bilateral peripheral retinal neovascularization and hemorrhages. Optical coherence tomography demonstrated bilateral thinning of the middle retinal layers, and fluorescein angiography showed extensive peripheral retinal nonperfusion and neovascularization in both eyes. After excluding hematological, biochemical, and inflammatory causes of retinal ischemia, the retinal findings were attributed to drug-induced retinal ischemia. Panretinal photocoagulation was performed, resulting in stabilization of the retinal findings. This case highlights the importance of regular ophthalmic monitoring in patients receiving combination chemotherapy for breast cancer.

Keywords: Gemcitabine, trastuzumab, carboplatin, retinal ischemia, peripheral retinal neovascularization.

INTRODUCTION

The retina is a highly specialized neural tissue, and the blood–retinal barrier plays a critical role in regulating the exchange between systemic circulation and retinal tissue. Despite this regulatory function, the retina’s high metabolic demand makes it vulnerable to the toxic effects of systemic medications. Drug-induced retinal toxicity can present as dysfunction of the retinal pigment epithelium and photoreceptors, vascular damage, ganglion cell or optic nerve damage, cystoid macular edema, crystalline retinopathy, uveitis, changes in color vision, and alterations in electroretinography, as well as other miscellaneous effects.¹

Retinal toxicity has been well documented with several systemic medications such as tamoxifen, a selective estrogen receptor modulator widely used in breast cancer treatment, which may result in crystalline maculopathy

and retinal pigment epithelial changes, particularly with long-term exposure.² In addition, brolocizumab, an exciting new medication to add to the potential therapies to treat macular neovascularisation, has been reported to cause a severe occlusive retinal vasculitis.³ Furthermore, potentially life-saving anti-cancer treatments such as Mitogen-Activated Extracellular Signal-Regulated Kinase (MEK) inhibitors⁴, Fibroblast Growth Factor Receptor (FGFR) inhibitors⁵, and ulixertinib⁶ have also been reported to cause retinopathies. With the increasing use of systemic chemotherapy and targeted therapies in breast cancer, retinal toxicity has emerged as a rare but clinically significant adverse effect.

This report discusses a patient diagnosed with breast cancer who experienced retinal neovascularization and retinal hemorrhages after undergoing a targeted combination therapy involving gemcitabine, trastuzumab, and carboplatin.

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It was also aimed to address the ocular toxicity of these three drugs based on the findings of this patient. While there have been reports of macular ischemia associated with these medications, the occurrence of peripheral retinal ischemia in this case is quite rare.

CASE REPORT

A 43-year-old woman presented with blurred vision in her right eye, which had been occurring for the past two months. She was diagnosed with breast cancer three years ago and has been receiving a highly active chemotherapy regimen, including intravenous trastuzumab, gemcitabine, and carboplatin, for that duration. At presentation, the best-corrected visual acuity was 0.3 logMAR in the right eye and 0.0 logMAR in the left eye. Anterior segment examination was unremarkable, and intraocular pressures were 15 mmHg bilaterally. Pupillary responses and extraocular motility were also normal. The fundus examination revealed bilateral peripheral neovascularization. In the right eye, there was a retinal hemorrhage superior to the optic disc and a subhyaloid hemorrhage located inferior to the optic disc. Additionally, in the left eye, a retinal hemorrhage was observed nasal to the optic disc. (Figure 1) Optical coherence tomography (OCT) revealed bilateral thinning of the middle retinal layers, along with subhyaloid hemorrhage in front of the optic disc in the right eye. (Figure 2) Fluorescein angiography revealed areas of retinal ischemia and the presence of retinal neovascularization in both eyes. (Figure 3) Although retinal vasculitis was considered in the differential diagnosis, it was ruled out based on clinical and angiographic findings. Fundus examination revealed no perivascular sheathing, intraocular inflammatory signs, or vitritis. Fluorescein angiography did not demonstrate vascular wall staining or leakage, supporting an ischemic rather than inflammatory etiology. To explore possible alternative causes of retinal ischemia, a thorough evaluation of hematological and biochemical factors was conducted. This included a complete blood count, coagulation profile (which consists of prothrombin time, activated partial thromboplastin time, and international normalized ratio), inflammatory markers (such as erythrocyte sedimentation rate and C-reactive protein), and a basic metabolic panel, all of which were found to be within normal limits. These tests were performed to rule out hematologic disorders, systemic inflammatory or vasculitic processes, and hypercoagulable states that could explain the retinal ab-

normalities. Electrophysiological testing was not performed, as the patient's clinical findings and multimodal imaging results, including optical coherence tomography and fluorescein angiography, were considered sufficient to establish the diagnosis and guide management. In addition, the patient's general medical condition and ongoing intensive chemotherapy limited the feasibility of further functional testing. The diagnosis of chemotherapy-related retinal toxicity was established based on a combination of clinical observations, laboratory results, and imaging findings. After a thorough review of the patient's medical history and clinical findings, a clear temporal relationship was identified between long-term exposure to systemic gemcitabine, trastuzumab, and carboplatin and the onset of visual symptoms.

The bilateral and relatively symmetric involvement of the peripheral retina, together with fluorescein angiographic evidence of extensive non-perfusion and neovascularization, suggested a systemic cause rather than a localized vascular event. Alternative causes of retinal ischemia in a cancer patient, including diabetic retinopathy, retinal vein occlusion, paraneoplastic retinopathy, radiation retinopathy, metastatic retinal infiltration, and systemic vasculitic or hypercoagulable conditions, were carefully considered and excluded based on medical history, laboratory evaluation, and clinical findings. In the absence of other identifiable causes and in accordance with previously reported chemotherapy-related ischemic retinal changes, the retinal damage was attributed to drug-related toxicity.

Panretinal laser photocoagulation therapy was administered to the ischemic areas in both eyes. Three months after the laser treatment, the visual acuity was measured at 0.1 logMAR in the right eye and 0.0 logMAR in the left eye. A fundus examination revealed the presence of laser scars. Additionally, the subhyaloid hemorrhage located inferior of the optic disc had resolved and its position had descended. (Figure 4) Optical coherence tomography performed at the last follow-up visit demonstrated persistent thinning of the inner retinal layers without progression, with no evidence of significant macular edema or additional structural deterioration. A residual hemorrhage over the optic disc in the right eye was also noted. (Figure 5) No changes to chemotherapy were possible due to the patient's medical condition, and the patient was monitored closely.

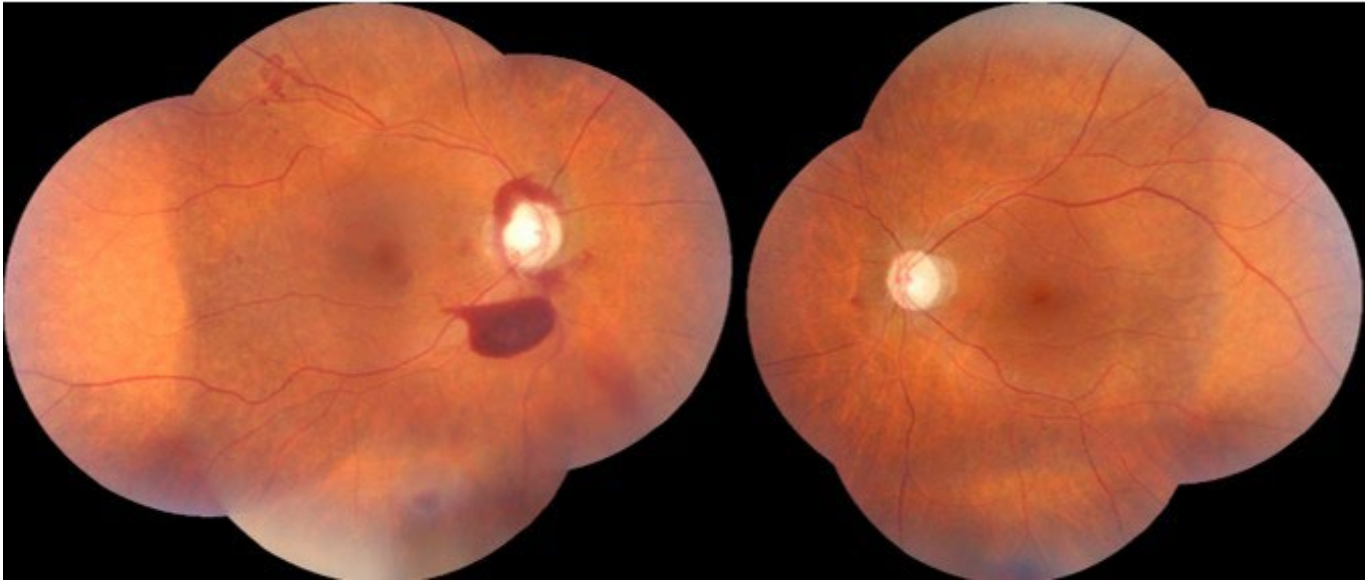


Figure 1: Right and left eye fundus photo. In the right eye, subhyaloid hemorrhages were observed superior and inferior to the optic disc, and a neovascular else was seen superior to the macula.

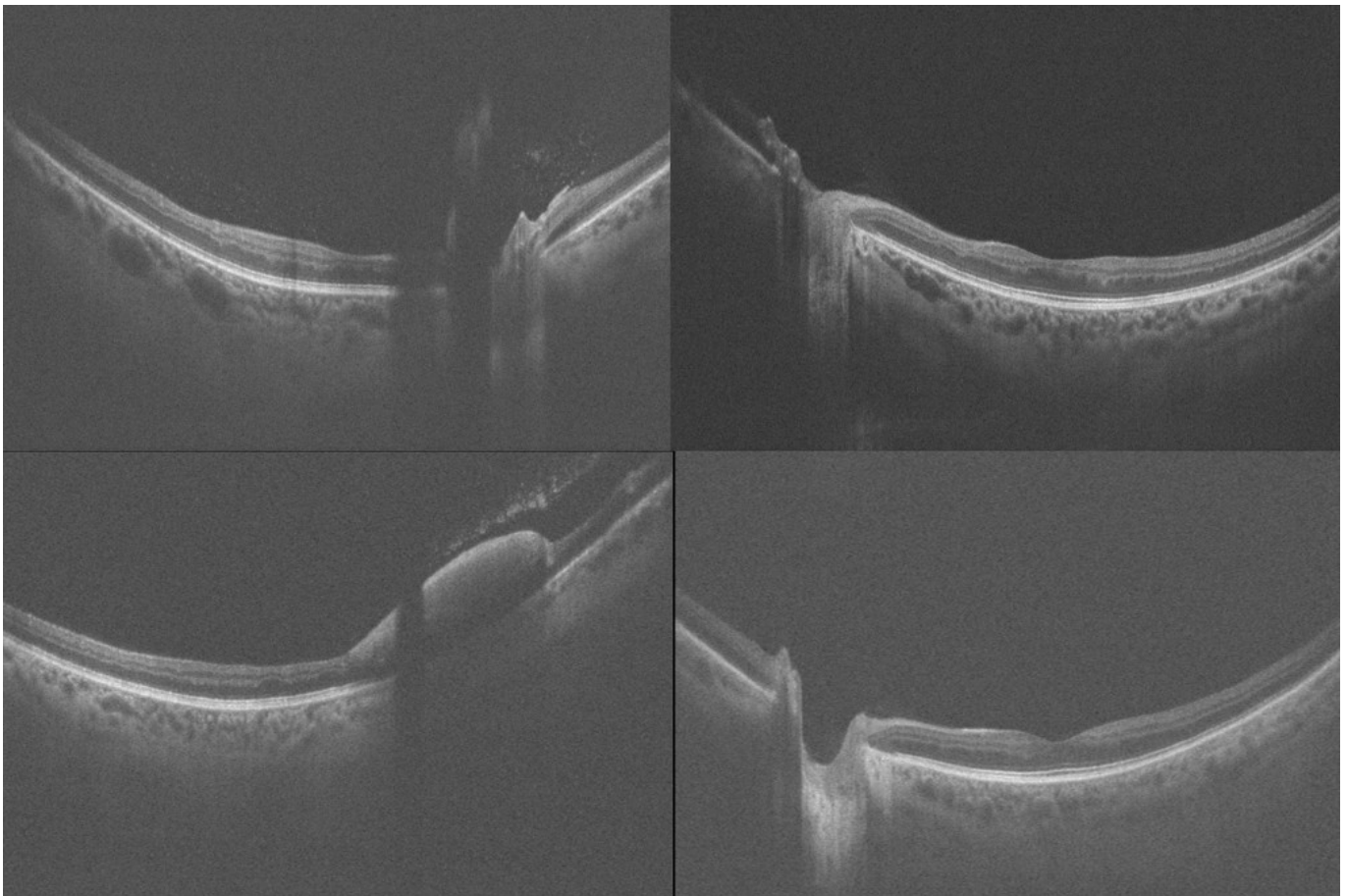


Figure 2: Bilateral OCT. Bilateral thinning of the middle retinal layers was observed, along with subhyaloid hemorrhage anterior to the optic disc in the right eye.

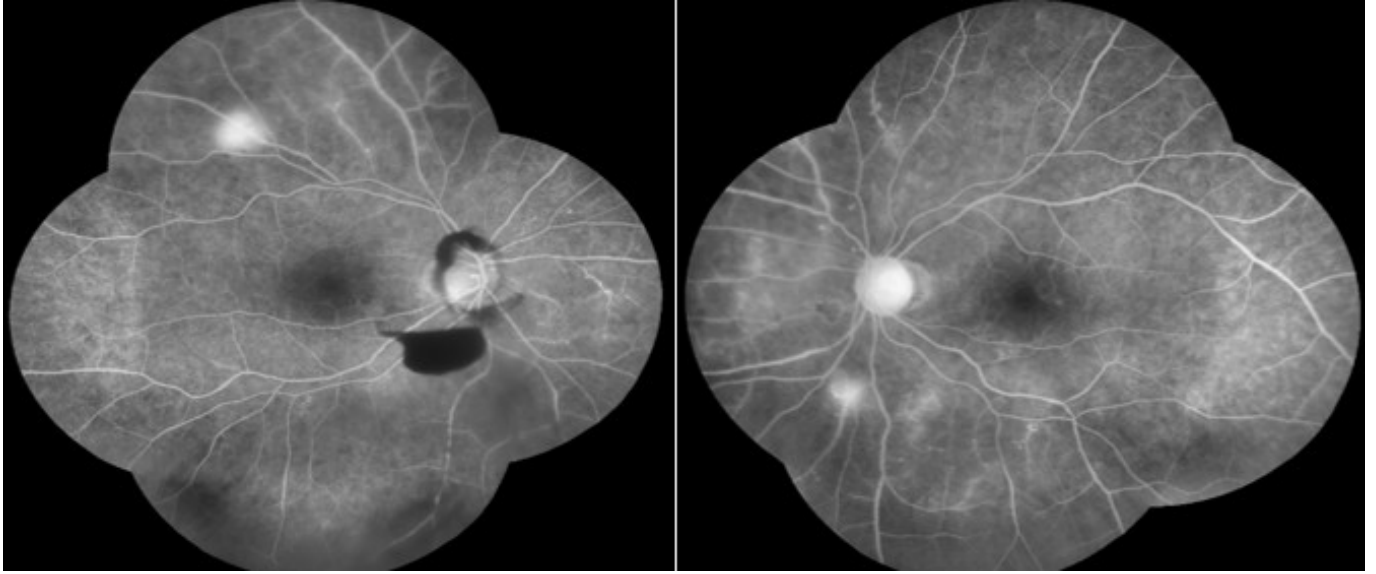


Figure 3: *Bilateral fluorescein angiography. In the fluorescein angiography of both eyes, areas of retinal ischemia and capillary leakage were observed.*



Figure 4: *Right and left eye fundus photo after the treatment. Bilateral laser scars were observed, and the subhyaloid hemorrhage in the right eye had resolved.*

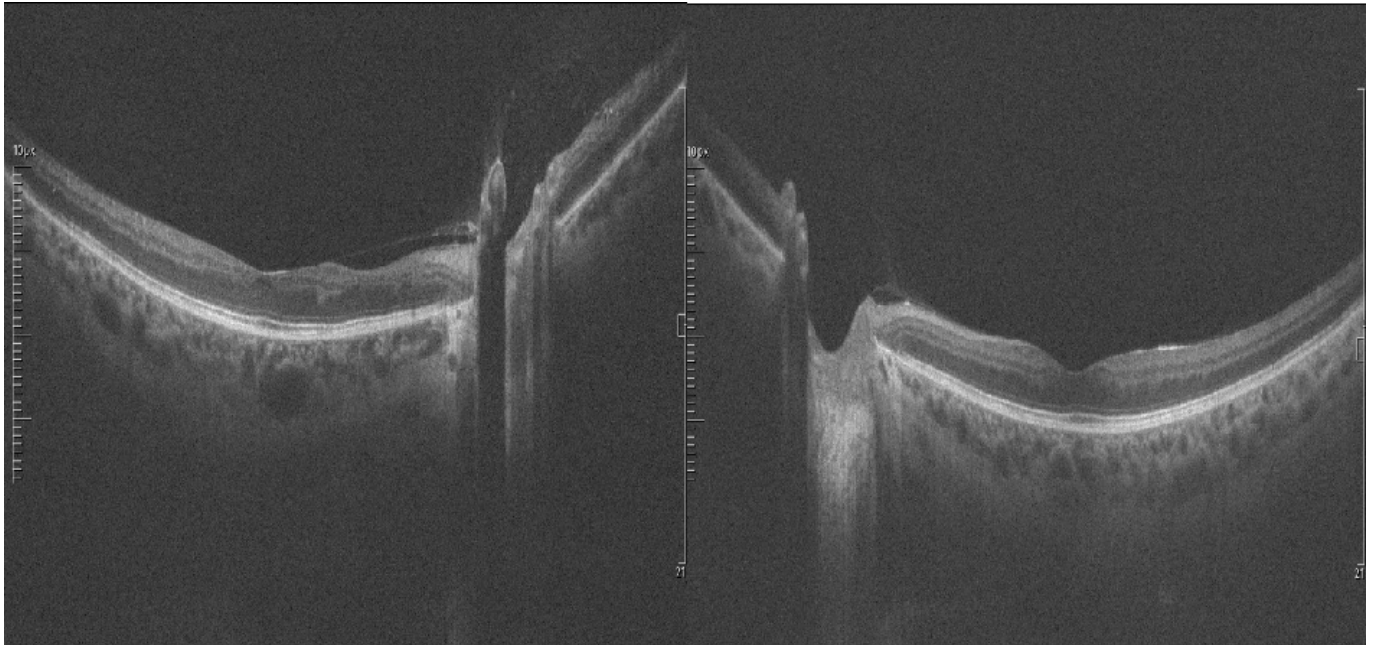


Figure 5. Bilateral OCT after treatment. OCT images demonstrate thinning of the middle retinal layers in both eyes. In the right eye, OCT reveals a hemorrhage over the optic disc.

DISCUSSION

In this report, we describe a patient receiving long-term systemic gemcitabine, trastuzumab, and carboplatin therapy for breast cancer who developed bilateral peripheral retinal ischemia with neovascularization and hemorrhage. Ocular adverse effects associated with anticancer therapies are diverse and may involve both the anterior segment structures and the retinal tissue. Although most reported retinal toxicities predominantly affect the macular region, the presence of peripheral-onset retinal non-perfusion in our patient represents a notable and relatively uncommon finding.

Systemic chemotherapy has been shown to induce retinal microvascular alterations. Optical coherence tomography angiography studies have demonstrated reduced retinal capillary density following chemotherapy, supporting microvascular compromise as an underlying mechanism of ischemic retinal damage.⁷ The predominant involvement of the peripheral retina may be explained by regional differences in retinal vascular architecture and perfusion reserve. Compared with the macular region, the peripheral retina is characterized by lower capillary density and limited autoregulatory capacity, rendering it more susceptible to systemic microvascular stress and ischemic injury.⁸ Under

conditions of chemotherapy-related endothelial dysfunction and disrupted angiogenic signaling, these vulnerable peripheral vascular networks may be compromised earlier, resulting in areas of retinal non-perfusion followed by neovascularization.⁹ Accordingly, peripheral retinal ischemia may constitute an early or insufficiently recognized manifestation of chemotherapy-induced microvascular toxicity. The hemorrhage over the optic disc and the thinning of the inner retinal layers in our patient may be attributed to chemotherapy-induced microangiopathy, endothelial dysfunction, and ischemic neurotoxicity. The optic nerve head is supplied by a dense yet vulnerable microvascular network derived primarily from the posterior ciliary circulation, which has limited autoregulatory capacity. Disruption of endothelial integrity and capillary perfusion may lead to localized ischemia, increased vascular fragility, and subsequent disc hemorrhage.

In parallel, chronic retinal ischemia can cause selective damage to the inner retinal layers, which are highly metabolically active and dependent on the retinal circulation. Prolonged hypoperfusion may trigger apoptosis of retinal ganglion cells and inner nuclear layer neurons, resulting in measurable thinning on optical coherence tomography. This ischemia-related inner retinal thinning has been previ-

ously described in various microvascular retinal disorders and is consistent with the OCT findings observed in our patient. The pathophysiological mechanisms underlying chemotherapy-related retinal ischemia are not fully understood; however, disrupted angiogenic signaling and endothelial dysfunction are thought to play central roles. Trastuzumab (Herceptin), a widely used monoclonal antibody in HER2-positive breast cancer, binds to HER2 receptors and inhibits downstream signaling pathways involved in cell proliferation and survival.¹⁰ Beyond its oncologic effects, increasing attention has been directed toward its potential vascular and ocular adverse effects. Canino et al. reported in their review of ocular toxicities associated with HER2-targeted therapies that, despite trastuzumab not being a direct anti-VEGF agent, inhibition of the HER2 signaling pathway can lead to indirect downregulation of VEGF, plasminogen activator inhibitor-1 (PAI-1), and tumor necrosis factor-alpha (TNF- α), which may impair endothelial cell survival and contribute to retinal microvascular compromise and ischemic changes through indirect anti-angiogenic mechanisms.¹¹

Previous reports have largely focused on macular involvement in chemotherapy-related retinal toxicity. Saleh et al. described bilateral ischemic maculopathy characterized by macular edema, retinal hemorrhages, and hard exudates observed at the fundus oculi. They also noted leakage from non-perfused foveolar capillaries, cystoid macular edema on retinal fluorescein angiography, increased retinal thickness, cystic changes, and serous detachment of the central retina on OCT.¹² In our patient, unlike Saleh's findings, the signs of peripheral ischemia were more pronounced, and OCT revealed thinning of the middle retinal layers. Prolonged ischemia may have contributed to retinal thinning, similar to what is seen in microvascular obstruction.

Gemcitabine is a nucleoside analogue approved for the treatment of various malignancies and is generally associated with a relatively mild toxicity profile, with thrombocytopenia and leukopenia being the most common hematologic adverse effects. Ocular toxicity related to gemcitabine is rare; however, a limited number of cases of retinal occlusive vasculopathy and retinal hemorrhages have been reported, typically characterized by cotton wool spots on funduscopic examination and vascular leakage on fluorescein angiography.^{13,14} Banach and Williams were the

first to describe bilateral ocular involvement in the form of Purtscher-like retinopathy and necrotizing vasculitis associated with gemcitabine therapy, which was accompanied by elevated erythrocyte sedimentation rate and increased antinuclear antibody levels.¹³ As in our patient, bilateral retinal involvement was observed; however, unlike their case, such laboratory abnormalities were not present in our patient. While retinal findings were reported to be reversible after discontinuation of gemcitabine in previous reports, including that of Tran et al., modification or cessation of chemotherapy was not feasible in our case due to the patient's underlying medical condition.¹⁴

Carboplatin is a platinum analogue chemotherapeutic agent structurally similar to cisplatin. Although ocular adverse effects related to carboplatin are not well defined, *in vitro* studies have demonstrated that platinum analogues can induce platelet activation and promote thrombotic complications, providing a plausible mechanism for ischemic vascular injury.¹⁵ Clinically, ocular side effects are rare; however, macular edema, bilateral metamorphopsia, and bilateral optic disc swelling have been reported.¹⁶ In addition, a case of bilateral ischemic retinopathy associated with combination therapy of carboplatin and paclitaxel has been described, in which panretinal photocoagulation was performed without subsequent improvement in visual acuity.¹⁷ However, in our patient, hematologic and coagulation parameters were within normal limits, and there was no history of thrombotic complications, suggesting that overt systemic thrombosis was unlikely to represent the sole mechanism underlying the retinal ischemic findings.

CONCLUSION

Although many drugs are linked to retinal toxicity, the retina is not typically the primary target, and the blood-retinal barrier provides strong protection against systemic drug exposure. As with any clinical decision, it is essential to balance the benefits of treatment with potential risks. Intravenous chemotherapy-induced retinal toxicity is a rare but significant adverse event that can lead to decreased visual function. This case report provides further evidence of retinal toxicity, reviewing its clinical and optical coherence tomography findings. Early detection and regular ophthalmic monitoring are crucial to ensuring effective cancer treatment while minimizing chemotherapy-related ocular complications.

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