Thieme

# Bilateral Severe Panuveitis Occurring during Cancer Immunotherapy with Dabrafenib and Trametinib Therapy Due to Toxoplasmosis Reactivation

# Bilaterale schwere Panuveitis während einer Krebsimmuntherapie mit Dabrafenib und Trametinib aufgrund einer okulären Toxoplasmose-Reaktivierung

## Background

The development of cancer immunotherapy with small molecule kinase inhibitors such as BRAF inhibitors (BRAFi) or MEK inhibitors (MEKi) and immune checkpoint inhibitors allowed a major advance in the treatment of cancer. BRAF and MEK are effectors in the mitogen-activated protein kinase pathway (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway involved in cell proliferation, which is modified in cancer cells [1]. Therefore, small molecule kinase inhibitors inhibit cancer cell proliferation but also have an immune-stimulating tumor microenvironment [1]. BRAFi and MEKi in BRAF-mutant tumors could lead to an immune stimulatory microenvironment by enhancing the expression of immune stimulatory molecules and cytokines, as well as decreasing the expression of immunosuppressive molecules (such as IL-1A, IL-6, IL-8, IL-10) and reducing the number of regulatory immune cells (such as Tregs and MDSCs) [1]. They are mainly used for advanced cutaneous melanoma but also for other cancers such as non-small cell lung cancer.

Another strategy is to act on immune checkpoints that normally play a role in immune tolerance. Cytotoxic T lymphocyte antigen 4 (CTLA-4)–CD28 and programmed cell death 1 (PD-1)–programmed cell death 1 ligand 1 (PD-L1) are cell surface receptors that have an inhibitory effect on T cell response and therefore promote immune tolerance [1, 2]. Cancer cells take advantage of this mechanism to create a tolerant microenvironment for tumor cell proliferation. Therefore, immune checkpoint inhibitors target CTLA-4–CD28 and PD-1–PD-L1 axes to reestablish antitumor immunity [2]. They are used in advanced-stage melanoma and for solid organ tumors such as small cell lung cancer and non-small cell lung cancer, or renal cell carcinoma [2]. These revolutionary treatments lead to a higher response rate against cancer, especially with combined targeted therapy, but on the other hand, they can be associated with immune-related adverse events (irAEs). While these adverse events must be taken into consideration, other causes of ocular inflammation should also be ruled out.

## History and Signs

A 57-year-old woman presented a bilateral significant loss of vision that occurred 3 weeks previously. She was referred to Jules-Gonin Eye Hospital in August three years ago. A metastatic pulmonary adenocarcinoma (cTX cN0 cM1a stage IV) with peritoneal carcinomatosis was diagnosed 7 years previously. She had multiple complications such as intestinal obstruction secondary to malignant adhesions, ureteral compression, bilateral ovarian metastasis, and hepatic lesions. Several treatments were implemented, including chemotherapy with cisplatin, pemetrexed, followed by vemurafenib (BRAF inhibitor). These treatments were followed by carboplatin and gemcitabine, which was then followed by dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).

The treatment also required pressurized intraperitoneal aerosol chemotherapy (PIPAC) and surgery, and she received carboplatin, paclitaxel, bevacizumab, and atezolizumab (anti-PDL-1) at the end of 2018. Unfortunately, the cancer continued to progress, and dabrafenib and trametinib were reintroduced 1 year prior to the consultation.

Her best visual acuity was limited to counting fingers in the right eye (RE) and to 0.25 in the left eye (LE). She presented with 2+ anterior chamber cell grade in the right eye (RE) and 1+ in the left eye (LE) with retrocorneal precipitates in both eyes (OU). The intraocular pressure was normal OU. Funduscopy revealed a vitreous haze of 3+ in the RE and 2+ in the LE, and bilateral yellow foci were present in OU with choroidal folds (▶ **Fig. 1**). Fluorescein and indocyanine green (ICG) angiography showed multiple foci with hypofluorescent lesions at early and late phases. Large ocular hypocyanescent lesions correspond to toxoplasmic retinochoroiditis lesions. There was a presence of severe vitritis (vitrous haze). Satellite dark dots are shown in ▶ **Figs. 2** and **3** (arrows) [3].

## Therapy and Outcome

Laboratory workup revealed a positive serology for toxoplasmosis. (IgG > 300 UI/mL and IgM positive at 0.85 with a high avidity of 0.8). An anterior chamber polymerase chain reaction (PCR) for *T. gondii* was negative, as well as the cultures for bacteria, fungus, and the other PCRs for HSV1, 2, CMV, VZV, *Pneumocystis jirovecii, Mycobacterium tuberculosis*, a panfungal PCR essay, and a specific PCR for *Candida* spp. A diagnostic vitrectomy confirmed a positive vitreous PCR for *T. gondii* with 300 copies/mL. The other vitreous analyses were negative for malignant tumor cells, negative for bacteria, fungus, yeast, and Nocardia culture. A complete healing of the ocular lesions was observed after 1 month of antiparasitic therapy with sulfadiazine 1 g 4×/day and pyrimethamine with a loading dose at 100 mg then 50 mg/day. Because of intolerance to these antibiotics, the therapy was switched to Bactrim forte 3×/day. Dabrafenib and tra-





Klin Monatsbl Augenheilkd 2023; 240 | © 2023. Thieme. All rights reserved.

metinib were maintained. Final visual acuity was 0.8 (RE) and 0.63 (LE). Unfortunately, due to the advanced stage of the cancer, the patient died in June 2021.

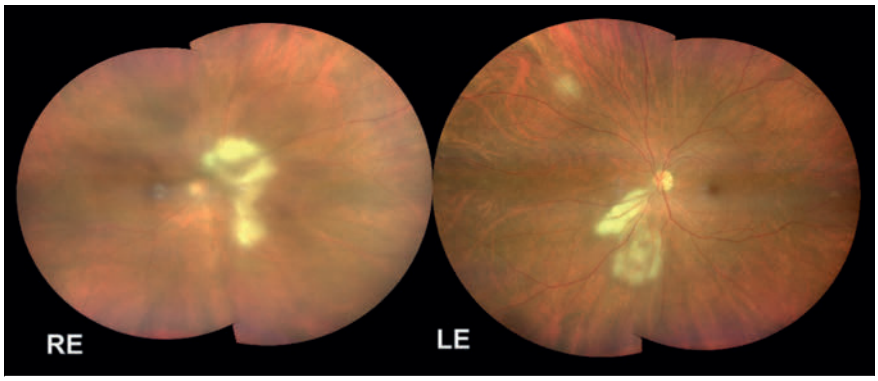
## Discussion

The irAEs are broad and can affect a multitude of organs such as pneumonitis, encephalitis, myocarditis, hepatitis, colitis, and many others [2]. The ocular irAEs remain rare and have been reported in 1% of patients [1,4]. The most encountered ocular irEAs are uveitis and sicca syndrome [2]. Iridocyclitis, paracentral acute middle maculopathy retinal vasculitis, multifocal choroiditis, and Vogt-Koyanagi-Harada (VKH)-like panuveitis, central serous-like chorioretinopathy, and orbital inflammation have been described [2,4,5]. Anterior uveitis is more frequent [4,5], but all types of uveitis can be encountered, from anterior uveitis to panuveitis. VKH-like disease has been reported in melanoma patients as a result of cross reactivity between tumor antigens and normal choroidal melanocytes [2,6]. Consequently, these patients present uveitis with choroidal involvement, serous retinal detachment, and auditory, meningeal, and skin damage.

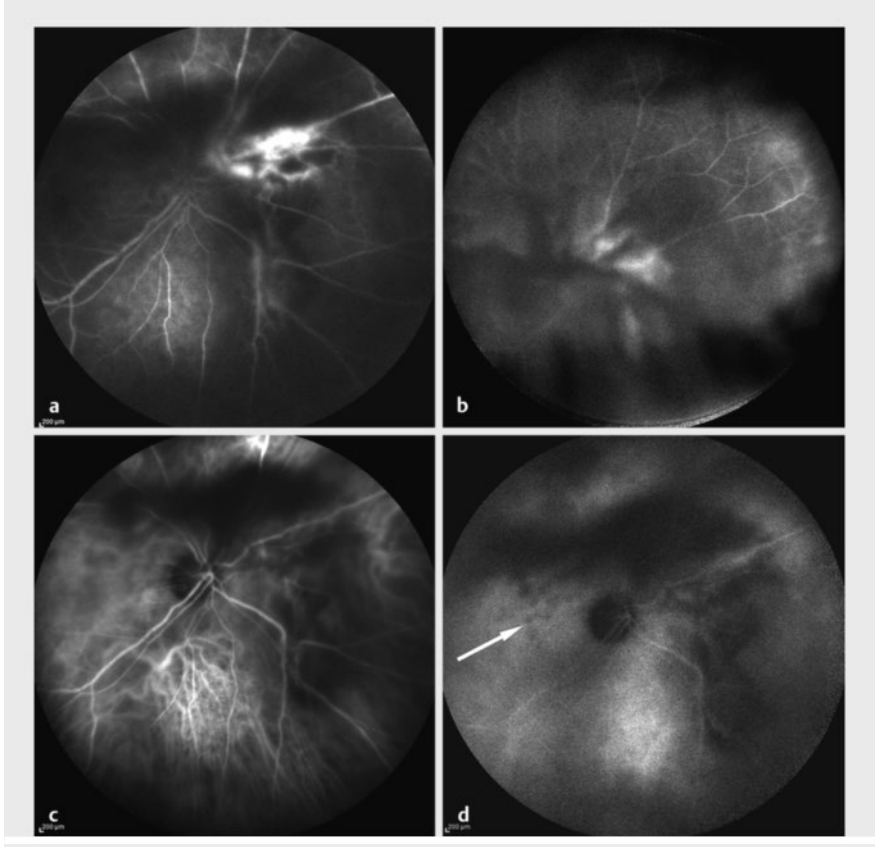
However, severe ocular inflammation during small molecule kinase inhibitors or checkpoint inhibitor therapy is not always an irAE but may occur as a secondary infectious complication [7].

Patients with cancer are at a higher risk of developing an opportunistic infection due to immunosuppression. The cancer itself, but also the cancer therapy, participates in the immunosuppression [8]. The advanced stage of systemic carcinoma in our case is a factor favoring the onset of ocular toxoplasmosis. The prevalence of *T. gondii* appears to be higher in patients with solid organ tumors and with hematological malignancies. For this reason, several studies recommend screening for toxoplasmosis in cancer patients [8].

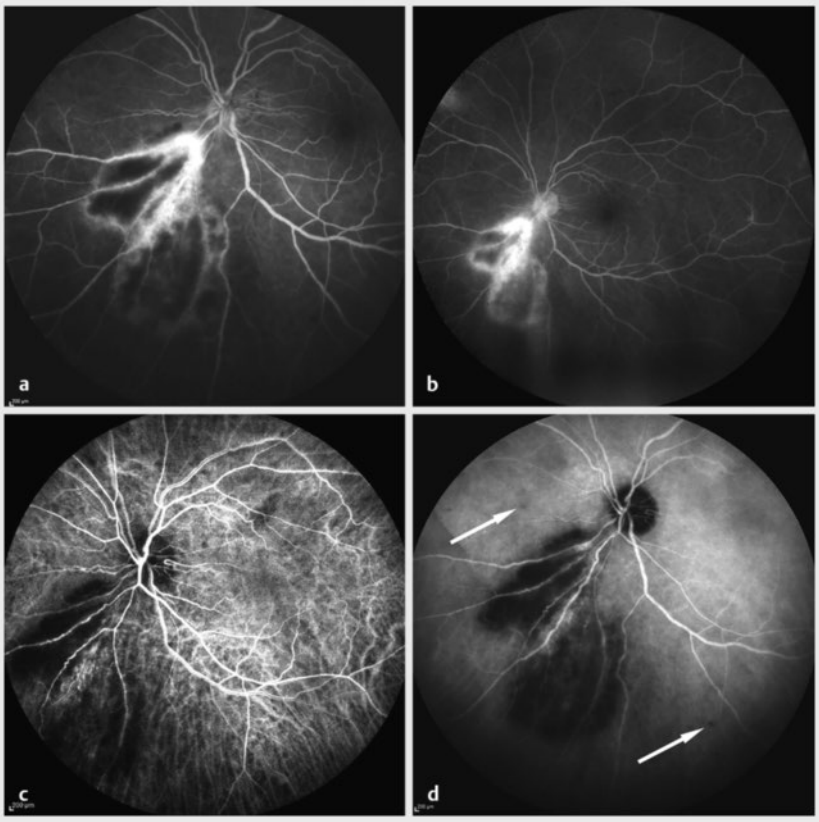
Immune checkpoints inhibitors enhance the risk of infection, such as the reactivation of tuberculosis, particularly with the PD-1/PD-L1 blockade. Indeed, they promote hyperinflammatory dysregulated immunity and therefore contribute to the development of the infection [7,9]. Several studies showed that mice with PD1 deletion appear to have significantly increased proinflammatory cytokines, resulting in excessive inflammation, and therefore uncontrolled bacterial growth [9]. A boost of T helper cell TH1 function is another possible explanation and can be compared to the immune reconstitution inflammatory syndrome (IRIS) in HIV




▶ **Fig. 1** Fundus photography at presentation, with bilateral yellow lesions due to toxoplasmic retinochoroiditis and panuveitis.




▶ **Fig. 2** Right eye fluorescein (**a** Fluorescein at 1 min; **b** Fluorescein at 7 min) and ICG angiography (**c** ICG at 1 min; **d** ICG at 10 min) showing the multiple foci with hypofluorescent lesions at early and late phases. Larges ocular hypocyanescent lesions correspond to toxoplasmic retinochoroiditis lesions. Note the presence of vitreous haze and satellite dark dots shown with the arrow.




▶ **Fig. 3** Left eye fluorescein (**a** Fluorescein at 1 min; **b** Fluorescein at 5 min) and ICG angiography (**c** ICG at 23 sec; **d** ICG at 9 min) showing the multiple foci with hypofluorescent lesions at early and late times phases. The two major lesions correspond to ocular retinochoroiditis lesions. Satellite dark dots are shown on the image by arrows.

patients [10]. The same reasoning can be applied to *T. gondii* infections. PD-1-deficient mice seem to be more susceptible to *T. gondii* infection because of reduced adequate immunity. PD-1–deficient mice have an increased production of IL-10 by CD4+ and CD8+ T cells, which has a counter-regulatory role by provoking a decrease in IL-12 production. This mechanism favors the toxoplasmosis reactivation [11].

However, other studies must be conducted because of divergent results. Indeed, some studies have noted that enhancement of the T cell by PD-1/PD-L1 blockage can lead to pathogen elimination [10]. Indeed, chronic infection induces CD8+ T cell exhaustion via the PD1–PDL-1 pathway. By restoring the CD8+ T cell response, anti-PDL-1 treatment helps control toxoplasma reactivation [12].

Naranjo criteria were not fulfilled for a side effect of a drug reaction in this case report [13]. The diagnosis of ocular toxoplasma is based on clinical findings. The high avidity of the ELISA test is in favor of a late toxoplasmic infection. PCR of aqueous humor or vitreous can be necessary to confirm the diagnosis. PCR of aqueous humor is positive in only 38 % of ocular toxoplasmic retinochoroiditis [14]. In the vitreous, PCR testing for toxoplasmosis is positive in 27 to 67 % of patients [15]. The rate of sensitivity depends on several factors, such as the immune status of the patient, the size of the lesion, or the delay between onset of ocular symptoms and sampling [16, 17]. Washout from the aqueous humor and capturing in the formed vitreous gel can also be an explanation. This analysis can be helpful particularly in immunocompromised patients with atypical ocular features or in oncologic disease that may be associated with negative *Toxoplasma* serology in immunocompromised patients [18, 19]. Simultaneous bilateral toxoplasmic retinochoroiditis reactivation remains exceptional, which justified the vitrectomy to confirm the diagnosis in this case [20, 21].

The exclusion of an opportunistic infection such as a fungal infection or endogenous ocular Nocardia infection is also mandatory in oncologic patients [22, 23].

Severe ocular inflammation occurring during targeted therapy or checkpoint inhibitor therapy is not always an irAE but may occur as a secondary infectious complication. Vitrectomy could be necessary to avoid a delay in the diagnosis as well as an unnecessary interruption of the cancer immunotherapy. A negative PCR for toxoplasmosis in the aqueous humor samples cannot rule out an ocular toxoplasmosis but may correspond to a false negative test (PCR is positive in only 38 % of ocular toxoplasmic retinochoroiditis). Checkpoint inhibitors may also produce a reactivation of infectious disease controlled by cellular immunity such as tuberculosis. An accurate diagnosis based on pathogen identification is mandatory in oncologic disease to avoid the stopping of oncologic therapies (checkpoint inhibitors, BRAFi inhibitors, and MEKi) or to avoid introduction of anti-infectious agents that are non-indicated. Early unnecessary discontinuation of oncology medication may lead to cancer relapse and initiation of unnecessary anti-infectious drugs may lead to severe side effects.

## Acknowledgement

This work was collected through the online JIR-cohort E-CRF (CER-VD PB 2016-00868) with the support of the AURIS Foundation, W & E. Grand d'Hauteville Foundation, Ingvar Kamprad Fund, Fleurette Wagemakers Foundation, Kononchuk Family Grant, Blatter Family Grant, and Rhumatismes-Enfants-Suisse Foundation. Acknowledgement to Professor Solange Peters (oncology department Centre hospitalier universitaire vaudois CHUV) and the team of the infectious disease department CHUV is given.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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Klin Monatsbl Augenheilkd 2023; 240: 574–577
**DOI** 10.1055/a-2004-5731
**ISSN** 0023-2165

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany