

Title of the manuscript: Choroidal thickening with serous retinal detachment in immune checkpoint inhibitor-induced uveitis: a case report

1) Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

For the last sentence in "Introduction", [Another article describes bilateral intermediate uveitis with hot discs on angiography and 6/6 visual acuity associated with dabrafenib and trametinib therapy (10).], please explain what is "hot" disc.

Authors' response: In the revised document, sentence was replaced with (Another article of a patient on dabrafenib and trametinib therapy described a bilateral intermediate uveitis with late optic disc fluorescein leakage on angiography and 6/6 visual acuity.). This sentence avoids the term "hot disc" with the use of "optic disc fluorescein leakage on angiography" instead.

Please mention Figure 2C is left or right eye.

Authors' response: LE has been added, please see the revised document.

The authors pointed out that this case can actually be a flare up of herpetic uveitis when the patient is immunocompromised with the BRAF/MEK inhibitors despite on prophylactic dose of oral acyclovir.

Authors' response: This has been added to the discussion to clarify why herpetic uveitis flare up is very unlikely:

"Because the patient had keratouveitis in the past and due to the immunosuppression with BRAF/MEK inhibitors, we started the treatment with oral acyclovir empirically at presentation. Although non-specific anterior uveitis and vitritis could be a sign of herpetic related panuveitis, multimodal imaging of the chorioretina excluded HSV involvement. In acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN), which are inflammatory conditions due to the VZV and HSV, necrotizing retinitis and occlusive arteritis are characteristic signs (12), which were not present in our patient. On the other hand, severe multiple subretinal serous retinal detachments and thick choroid, which were present in our patient, are not present in ARN and PORN. Serum testing for herpesvirus antibodies was not performed because it does not add any value in the diagnosis of ARN or PORN (12)."

Language Quality: Grade B (Minor language polishing)

Authors' response: English language polishing has been done by an English native speaker.

2) Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: It is an interesting case report.

Authors' response: No revision needed according to this reviewer.

3) Science editor:

Language Quality: Grade B (Minor language polishing)

Authors' response: English language polishing has been done by an English native speaker.

Scientific Quality: Grade C (Good)

The manuscript elaborated a case of Choroidal thickening with serous retinal detachment in uveitis induced by BRAF / MEK inhibitors. The manuscript is well written and can be helpful for the readers to ameliorate the diagnostic and therapeutic approach for this scenario.

Are relevant autoimmune antibodies detected in laboratory tests?

Authors' response: This has been added to the Laboratory examinations section in the revised document:

"Of all, only Toxoplasma gondii IgG antibodies were positive (66,40 IU/ml). Serum testing, aqueous, and vitreous humor samples were not obtained. "

And this to the discussion:

"Serum testing for herpesvirus antibodies was not performed because it does not add any value in the diagnosis of ARN or PORN (12). Of all blood tests, only Toxoplasma gondii IgG antibodies were positive. In adults, IgG antibodies against Toxoplasma gondii can be detected from 22.5% to more than 80% of population (13). Due to low diagnostic value of Toxoplasma gondii IgG antibodies and no other clinical signs suggesting ocular toxoplasmosis, this diagnosis was excluded. "

There is too little discussion. The authors can consider the adverse reactions of BRAF / MEK inhibitors and the pathogenesis of related uveitis.

Authors' response: Discussion has been extended and we considered the pathogenesis of the BRAF/MEK uveitis as well.

This has been added to the revised discussion:

" Because the patient had keratouveitis in the past and due to the immunosuppression with BRAF/MEK inhibitors, we started the treatment with oral acyclovir empirically at presentation. Although non-specific anterior uveitis and vitritis could be a sign of herpetic related panuveitis, multimodal imaging of the chorioretina excluded HSV involvement. In acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN), which are inflammatory conditions due to the VZV and HSV, necrotizing retinitis and occlusive arteritis are characteristic signs (12), which were not present in our patient. On the other hand, severe multiple subretinal serous retinal detachments and thick choroid, which were present in our patient, are not present in ARN and PORN. Serum testing for herpesvirus antibodies was not performed because it does not add any value in the diagnosis of ARN or PORN (12). Of all blood tests, only Toxoplasma gondii IgG antibodies were positive. In adults, IgG antibodies against Toxoplasma gondii can be detected from 22.5% to more than 80% of population (13). Due to low diagnostic value of Toxoplasma gondii IgG antibodies and no other clinical signs suggesting ocular toxoplasmosis, this diagnosis was excluded. "

And

"The mechanism behind BRAF/MEK inhibitors induced panuveitis, which clinically closely resembles the Vogt-Koyanagi-Harada (VKH) disease (15), remains unclear. In the VKH disease pathogenesis, CD4+ and CD8+ cells (T cells) target melanocytic antigens in choroid and RPE, which impair the outer blood retinal barrier (16). BRAF/MEK inhibitors interfere with MAPK pathway, which is involved in the T-cell receptor signalling pathway (17). This interference could lead to similar changes in choroid and RPE as observed in VKH disease (15). "

Thank you for helping us to improve this case report.

Best wishes,

Peter Kiraly